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REVIEW ARTICLE

Noninvasive Neuromonitoring: Current Utility in Subarachnoid Hemorrhage, Traumatic Brain Injury, and Stroke

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Abstract Noninvasive neuromonitoring is increasingly being used to monitor the course of primary brain injury and limit secondary brain damage of patients in the neurocritical care unit. Proposed advantages over invasive neuromonitoring methods include a lower risk of infection and bleeding, no need for surgical installation, mobility and portability of some devices, and safety. The question, however, is whether noninvasive neuromonitoring is practical and trustworthy enough already. We searched the recent literature and reviewed English-language studies on noninvasive neuromonitoring in subarachnoid hemorrhage, traumatic brain injury, and ischemic and hemorrhagic stroke between the years 2010 and 2015. We found 88 studies that were eligible for review including the methods transcranial ultrasound, electroencephalography, evoked potentials, near-infrared spectroscopy, bispectral index, and pupillometry. Noninvasive neuromonitoring cannot yet completely replace invasive methods in most situations, but has great potential being complementarily integrated into multimodality monitoring, for guiding management, and for limiting the use of invasive devices and in-hospital transports for imaging.

Keywords Neuromonitoring · Noninvasive · Neurocritical care · Cerebrovascular disease · Traumatic brain injury

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Introduction

Various methods for cerebral monitoring at the bedside are applied in the neurointensive care unit (NICU) since it is often impossible to clinically evaluate patients due to their critical condition and/or sedation and because the safety of wake-up trials is questionable [1–3]. The more widespread methods of neuromonitoring (NM) and their utility for an integrated multimodality approach were recently assessed by a Neurocritical Care Society (NCS) expert group and a consensus published [4–6]. Detecting abnormalities in cerebral perfusion, oxygenation, chemistry, and function represents the main objective of NM in general to support measures for regeneration from the primary brain damage and to prevent secondary brain damage.

Among these NM methods, invasive methods are widely prioritized in severe brain injury and thought to be fairly accurate, reliable, and valid, although prospective data demonstrating their outcome-improving capacity are scarce. Invasive NM such as by probes and/or catheters to measure intracranial pressure (ICP), brain temperature (BT), brain oxygen tension ($PbtO_2$), neurochemistry via microdialysis (MD), cerebral blood flow (CBF), and jugular oxygen saturation ($SjvO_2$) has the plausibly acknowledged advantage of "getting closer to the pathology". However, disadvantages of invasive NM are that it is expensive, cannot easily be changed or readapted, may require neurosurgical assistance, often requires imaging to control the probe location, and, above all, carries a certain risk of bleeding and infection.

Noninvasive NM comprises both very traditional methods such as electroencephalography (EEG) and newer methods such as near-infrared spectroscopy (NIRS) and is being received with very variable degrees of trust among neurointensivists. Its general advantages beyond noninvasiveness

are safety, portability (of some devices), and often relatively low cost. Generally perceived disadvantages are distance from pathology, interference with other signal sources and other NICU equipment, at times stronger operator-dependency, occasionally reduced spatial resolution, and that it often gives more indirect or relative (trends) outputs rather than absolute parameter values.

However, subpopulations of NICU patients might be particularly suitable for noninvasive NM, such as patients who are treated in the emergency or prehospital setting, undergoing acute interventions (such as stroke thrombectomy), less severely affected (i.e., Glasgow Coma Scale 9–12, not yet sedated and intubated), and/or presenting with multilocular or diffuse pathology (i.e., SAH), conditions in which more global monitoring techniques would be desirable as an alternative or addition to local, probe-related NM. At present, however, this subgroup has not been well-defined by data from high-quality studies.

This review summarizes those methods of noninvasive neuromonitoring (NINM) that are currently being used and have been studied. It focuses entirely on noninvasive bedside methods that either allow continuous parameter assessment or can be repeated as often as desired and that are applied in the NICU, mainly to monitor the dynamics of the primary injury and to detect threatening secondary brain damage. We only investigated those conditions most frequently encountered on the NICU: subarachnoid hemorrhage (SAH), traumatic brain injury (TBI) and stroke [acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH)] in adults. The review does not cover imaging or methods used to confirm brain death or make prognoses after cardiac arrest, although NINM methods do play an important role in both conditions.

In addition to the primary impact of *SAH*, i.e., aneurysm rupture that may be associated with extreme ICP increases and early infarcts, hydrocephalus and rebleeding comprise early complications. Delayed complications include vasospasm, delayed cerebral ischemia (DCI), seizures, hyponatremia, myocardial injury or arrhythmias, and pulmonary edema. About 50% of patients with angiographic evidence of vasospasm develop DCI, resulting in further neurological deficits or death. However, DCI and vasospasm may occur independently as well [7–11]. NM is particularly directed at detecting vasospasm, DCI, and its sequelae.

Brain damage related to *TBI* is caused by the initial cerebral insult, but also by secondary complications such as ischemia, hypoxia, expanding hematoma, inadequate CBF, brain edema, intracranial hypertension, hydrocephalus, metabolic dysfunction, and seizures. NM is utilized to detect processes leading to cerebral edema, increases in ICP or decrease in cerebral perfusion pressure (CPP), as well as posttraumatic seizures [12–14].

The care focus in *ICH* is to prevent secondary hematoma expansion, edema, and their consequences. NM is mainly used to monitor for ICH growth, perihematomal edema, cerebral autoregulation and seizures [15–18].

Complications of *AIS* largely depend on timely recanalization, infarct location, infarct growth, and its ultimate size. In particular, edema development in large hemispheric and cerebellar infarction will significantly compromise outcome [19, 20]. NM is applied to monitor success and maintenance of recanalization, optimal penumbra conditions, the evolution of infarct edema and to trigger neurosurgical procedures.

In addition to detecting these more specific forms of secondary brain damage in each of these pathological conditions, NINM is intended to support overall physiologic homeostasis and stable cerebral hemodynamics and oxygenation, which may be achieved by measures such as certain ventilator settings, circulatory support, treatment of energy-consuming conditions such as fever or seizures, metabolic balancing, adequate nutrition, adjustments in analgesia and sedation, ICP treatment, and interventional/surgical procedures.

The objective of this review was to provide a—primarily descriptive—overview on noninvasive neuromonitoring recently applied and studied in the NICU. According to the PICOS approach, assessed were the *participants* NICU patients with SAH, TBI, and stroke (AIS and ICH); the *intervention* application of noninvasive neuromonitoring, possibly combined with any therapeutic intervention; the *comparisons* with invasive neuromonitoring/with imaging/with no monitoring; the *outcomes* (patho)physiologic parameter measurements or correlations/prognosis/mortality/function; and the *study designs* prospective (observational/case–control/randomized controlled)/retrospective/larger case series. We neither aimed for a systematic review in the strict sense, nor a meta-analysis.

Methods

Following the PICOS approach stated above, an electronic Medline (PubMed) search was performed using the following terms in varied combinations: "subarachnoid hemorrhage, aneurysmal subarachnoid hemorrhage, nontraumatic subarachnoid hemorrhage, traumatic brain injury, intracerebral hemorrhage, acute ischemic stroke, acute stroke, cerebral ischemia, neurocritical care, intensive care, critical care, noninvasive neuromonitoring, transcranial Doppler ultrasonography, transcranial color-coded sonography, electroencephalography, continuous EEG, quantitative EEG, evoked potentials, somatosensory-evoked potentials, brainstem auditory-evoked potentials, visual-evoked potentials, motor-evoked potentials, near-

infrared spectroscopy, bispectral index, bioimpedance, electrical impedance, pupillometry". We screened for clinical, human studies in adult patients published in the English language in the following designs: prospective randomized, or observational, or case–control designs, retrospective analyses, and case series. Since the recently published NCS consensus covered most of the past literature and the focus of this review was the current situation, studies were restricted to those published from January 2010 to July 2015 to avoid redundancy, with the exception of studies on evoked potentials and some very new emerging methods (search interval from 2000 to 2015) because of the very few available publications from the main time frame relating to them. The authors reviewed full texts and reference lists from relevant papers to identify further articles. Studies that did not contain information on our PICOS questions, were not original studies, or were case series of less than 10 participants were excluded.

Results

A total of 88 publications were included: 32 on transcranial ultrasonography (TCU), 16 on evoked potentials (EP), 11 on EEG, 11 on NIRS, 5 on bispectral index (BIS), 4 on bioimpedance, 2 on pupillometry, 1 on skull accelerometry, and 6 on multimodality NM comprising more than 1 noninvasive method. Study populations, design aspects, and main findings with statistical results of these studies are summarized in Table 1.

Transcranial Ultrasonography

Using TCU information can be obtained at high temporal resolution and low cost; the technique also offers portability, repeated assessment, and relatively easy interpretation. TCU also has certain limitations, such as intraoperator variability, need for considerable training, limited spatial resolution, and the difficulty to keep probes fixed should continuous recordings be desired. Moreover, transtemporal acoustic windows are inadequate in up to 20% of subjects since both bone and dura may interfere with insonation [14, 21, 32–34]. Transcranial Doppler (TCD) ultrasonography measures intravascular erythrocyte velocities in real time using high-frequency (2 MHz) acoustic waves. Since increased cerebral velocity can be caused either by global hyperdynamic flow or local reduction in vessel caliber, some authors propose using the Lindegaard ratio to distinguish these two conditions, comparing extracranial carotid and middle cerebral artery (MCA) velocities. In assessing vasospasm after SAH, flow velocities (FV) over 120 or 90 cm/s in the anterior or posterior circulation, respectively, increasing FV by over 50 cm/s in 24 h, or a Lindegaard ratio >3 are usually considered to indicate vasospasm [21–25]. By using transcranial color-coded duplex sonography (TCCS), blood flow in the parenchymal and vascular structures is color coded, which reduces insonation angle errors as compared with TCD. Both TCD and TCCS require experienced sonographers. Both TCD and TCCS are currently used in the NICU and seem to have similar accuracy; yet, TCCS may be more sensitive, for example, in identifying vasospasm [26–29].

Another aim of monitoring is to assess cerebral autoregulation or detect threatening anomalies in cerebral blood flow (CBF) by revealing cerebral hypo- and hyperperfusion. Since control examinations can be repeated frequently and threats such as midline shift (MLS) monitored by using TCU in the NICU [30, 31], this method may constitute an adjunct or even alternative to serial CT transports that are prone to complications in ventilated, unstable, critically ill patients.

Recommendations from the multimodality monitoring (MMM) consensus conference suggest that TCCS is superior to TCD, although the quality of evidence is low, and that TCU should be employed to predict DCI or vasospasm after SAH, using the Lindegaard ratio and/or comparing the MCA mean velocities of the two hemispheres [5]. Our current search identified 8 retrospective (n range 11–300) and 16 prospective (n range 18–124) studies on TCD and 8 prospective (n range 18–124) studies on TCCS (Table 1).

TCU has been used to evaluate cerebral autoregulation using specific, moving correlation coefficients. Mx and Mxa are calculated by mean FV in proportion to mean CPP or mean arterial blood pressure (MAP), respectively. Zero or negative Mx means that no or an inverse association is present between FV and CPP, suggesting active cerebrovascular responses to CPP changes and intact autoregulation. Positive Mx indicates impaired autoregulation, representing a passive vascular response to CPP [32, 35, 36]. Sx and Sxa are derived from systolic FV and mean CPP or MAP, respectively, while Dx and Dxa are based on diastolic FV and mean CPP or MAP, respectively. Mx and vasospasm in combination were associated with DCI after SAH [26]. Among these indices, Sx and Sxa showed the best correlation with outcome after TBI [37] and DCI after SAH [38]. Mx showed moderate agreement ($r = 0.58$) with the previously established pressure reactivity index (Prx) derived from invasive ICP monitoring, but discrepancies were found, particularly in cases of severe intracranial hypertension [39].

With TCU cerebral perfusion can be evaluated indirectly, by measuring FV and estimating the pulsatility

Table 1 Relevant current studies on noninvasive neuromonitoring and its application in the NICU (between 2010 and 2015[d])

Authors	Group	Patient number	Study design	Main findings
Transcranial Doppler ultrasonography (TCD/TCU)				
Miller et al. [54]	SAH	107	R	Time onset of vasospasm 5.5 days (±2.5). Sensitivity for DCI prediction 71% (NPV 48%)
Miller et al. [55]	SAH	29	R	Vasospasm detection in 71% of subjects, in 64% of these ipsilateral to the ruptured aneurysm. DCI in the same vessel territory in 86%, in the same hemisphere in 93%
Nakae et al. [56]	SAH	142	R	Better vasospasm correlation of the ratio of mean FV of the ipsilateral to the contralateral MCA than the absolute mean FV (DCI predictive value established by AUC 0.89 and 0.80, respectively)
Da Costa et al. [59]	SAH	18	P cc	Lower cerebrovascular reactivity index (ratio between MCA velocity changes and PCO_2 changes) in patients than controls ($p = 0.0001$)—no correlation with vasospasm or DCI
Calviere et al. [26]	SAH	30	P cc	Cerebral autoregulation deterioration in combination with vasospasm correlated with DCI ($p = 0.007$)
Paschoal et al. [61]	SAH	105	P obs	Cerebral embolization detected only in 4 patients
Gura et al. [45]	TBI	52	P obs	PI significantly correlated with ICP ($r = 0.57$, 0.53, 0.779 on days 1, 3, 5, respectively; $p < 0.0001$) and outcome (GOS) ($r = 0.58$, 0.53, 0.47 on days 1, 3, 5, respectively; $p < 0.01$)
Gura et al. [46]	TBI	47	P obs	Noninvasive eCPP results associated with invasively measured values ($r = 0.92$; $p < 0.001$)
Bouzat et al. [51]	TBI	98	P obs	PI (sensitivity 90%, specificity 91%; AUC 0.93—threshold 1.25) and diastolic FV (sensitivity 92%, specificity 76%; AUC 0.95—threshold 25 cm/s) predicted risk for secondary neurological deterioration
Reinstrup et al. [60]	TBI	27	P obs	Significant reduction in MCA mean FV associated with hypocapnia ($p \leq 0.05$)
Bouzat et al. [40]	TBI	11	R[a]	Asymmetry (ipsilaterally lower) of systolic FV >25% and ipsilateral PI ≤ 0.80 in patients with traumatic internal carotid artery dissection ($p < 0.01$)
Budohoski et al. [37]	TBI	300	R	Autoregulation indices Mx, Mxa, Sx, Sxa and Dx correlated with GOS and mortality at 6 months): Sx ($p = 0.00001$, AUC = 0.66; $p = 0.0003$, AUC = 0.65); Sxa ($p = 0.0005$, AUC = 0.61; $p = 0.02$, AUC = 0.64)
Budohoski et al. [39]	TBI	201	R	Moderate correlation of Mx with Prx ($r = 0.58$; $p < 0.001$)
Sorrentino et al. [32]	TBI	248	R	Prediction of unfavorable outcome (GOS) by Mx and Mxa ($p = 0.0033$; $p = 0.047$)—proposed cut-off value of Mx > 0.3 for impaired autoregulation (Mx < 0.05 for intact autoregulation)
Varsos et al. [35]	TBI	280	R	Correlation of Mx with low vasomotor tone of the cerebral arteries ($r = -0.14$; $p = 0.021$)
Fülesdi et al. [47]	ICH	20	P obs	RAP, eCPP and CBF indices more sensitively reflect cerebral circulation than FV ($p = 0.006$, $p = 0.002$, $p = 0.016$, respectively)—RAP correlating with hemorrhage volume at 2-week follow-up ($r = -0.44$, $p = 0.04$)
Regula et al. [58]	ICH	62	P obs	Increased FV suggestive of vasospasms in 37% of patients with ventricular involvement. Vasospasm correlated with DCI ($p = 0.046$)
Kiphuth et al. [57]	ICH	115	P obs	Increased FV suggestive of vasospasms in 5.7% of 53 patients with ventricular involvement, DCI in one patient
Nakagawa et al. [48]	ICH	21	P cc	CVRi and transfer gain (derived from MAP and mean FV oscillations analysis) higher in patient group than in controls ($p = 0.04$, $p < 0.004$, respectively)
Oeinck et al. [49]	ICH	26	P cc	Gain (FV variations in response to MAP) higher in patient group than in controls ($p \leq 0.000034$)—no correlation with outcome. Poorer individual phase (autoregulatory response speed) correlated with lower blood pressure, larger hematoma volume, and worse outcome (mRS at 90 days) ($p = 0.013$)
Reinhard et al. [36]	ICH	26	P cc	On day 3 and 5, Mx higher in patient group than in controls and associated with lower eCPP and GCS, ventricular hemorrhage, and worse outcome (mRS at 90 days) ($p = 0.013$)
Kiphuth et al. [44]	ICH	124	P obs	Prediction of outcome at 6 months (mRS) by PI ($p < 0.001$)—in 59 patients correlation with invasive ICP monitoring ($r = 0.712$)
Wang et al. [63]	ICH	48	P obs	Diastolic/mean FV reduction and PI increase in unaffected hemisphere associated with outcome (mRS at 90 days) ($p \leq 0.03$)—prediction of death at day 14 by PI (OR 1.64)

Table 1 continued

Authors	Group	Patient number	Study design	Main findings
Vicenzini et al. [50]	ICH	20	P obs	After mannitol bolus administration, mean FV increase in the ipsilateral MCA ($p = 0.004$), PI enhance in the contralateral hemisphere ($p = 0.001$)
Combined Transcranial Doppler–Near-infrared spectroscopy (TCD–NIRS)				
Budohoski et al. [38]	SAH	98	P obs	Prediction of DCI by Sxa (OR 7.46, PPV 0.62, NPV 0.89) and TOxa (OR 4.52, PPV 0.50, NPV 0.86)
Transcranial color-coded duplex sonography				
Wang et al. [28]	SAH	18	P obs	Sensitivity 86.7% and specificity 100% for detection of vasospasm (PPV 100%, NPV 66.7%). Sensitivity 88.9% and specificity 55.6% for detection of DCI (PPV 66.7%, NPV 83.3%)
Turek et al. [53]	SAH	92	P obs	Sensitivity 71% and specificity 88% (AUC = 0.83) for detection of angiographic vasospasm (peak systolic velocity threshold 98 cm/s)
Brandi et al. [33]	TBI	45	P obs	eICP and eCPP similar to invasively measured ICP and CPP values ($p < 0.001$)
Kiphuth et al. [30]	ICH	61	P obs	MLS $\geq$ 4.5–7.5 mm suggested conservative treatment failure. Sensitivity 69% and specificity 100% for prediction of fatal outcome at 6 months with MLS $\geq$ 12 mm (PPV 100%, NVP 74%)
Kiphuth et al. [44]	ICH	124	P obs	Correlation of PI with MLS ($r = 0.645$); PI predicted mortality at 6 months (PPV 93.8%, NPV 79.3%; $p < 0.001$)—in 85 patients
Prunet et al. [27]	TBI Stroke SAH	20	P obs[b]	TCCS- and TCD-derived PI results correlated well with each other ($r = 0.897$; $p < 0.0001$); good accuracy for both methods (AUC = 0.870, AUC = 0.901, respectively; $p = 0.69$)
Kiphuth et al. [31]	ICH SAH	26 11	P obs	Sensitivity 100% and specificity 83% for extraventricular/lumbar drainage reopening with ventricular width $\geq$5.5 mm (NPV 100%, PPV 81%)
Rajajee et al. [52]	TBI SAH AIS ICH	30 11 1 11	P obs	Sensitivity 96% and specificity 94% for detection of ICP > 20 mmHg by ONSD (PPV 84%, NPV 99%)—greatest accuracy with ONSD values $\geq$0.48 cm
Combined Transcranial color-coded duplex sonography–evoked potentials (TCCS–EP)				
Di Pasquale et al. [62]	SAH	16	R	Correlation of MCA resistance and cortical N20 amplitude interhemispheric ratio changes with reversibility of ischemic penumbra ($r = 0.78$, $p < 0.01$)—no correlation with irreversible ischemic damage
Evoked potentials (EP)				
Wachter et al. [83]	SAH	51	P obs	No correlation of SSEP, VEP, and BAEP values with outcome (GOS), except for median nerve SSEP on admission and VEP 2 weeks after admission ($p = 0.03$ and 0.01, respectively)
Ritz et al. [80]	SAH	90	R	Better prediction of outcome (GOS) by SSEP than by Hunt and Hess and WFNS scales. Bilateral cortical response absence always associated with death
Hughes et al. [77]	TBI	123	R	SSEP as good predictor of both recovery of consciousness after coma ($p = 0.02$) and time to emerge from coma ($p < 0.05$)
Amantini et al. [78]	TBI	60	P obs	Prediction of outcome (awakening from coma, disability) by SSEP (PPV 93.1%, NPV 41.9% and PPV 86.2%, NPV 87.1%, respectively) better than by EEG reactivity
Lew et al. [79]	TBI	22	P obs	SSEP bilateral absence as predictors of unfavorable outcome (death or persistent vegetative state)—specificity and PPV 100%
Houlden et al. [74]	TBI	81	P obs	Correlation of SSEP with functional and cognitive outcome (GOS, Barthel score, working memory, and information-processing speed) ($p < 0.05$)
Xu et al. [82]	TBI	58	P obs	SSEP predictors of outcome (brain death, persistent vegetative state, or minimally conscious state at 12 months) in long-term (30 days) unconscious patients (AUC = 0.89; $p < 0.001$)
Morgalla et al. [70]	TBI	100	R	Correlation of SSEP, but not BAEP, with long-term outcome (GOS at 3 years) ($p = 0.0366$)
Shiban et al. [86]	AIS	20	P obs	MEP and SSEP as good predictors of functional outcome (mRS, NIHSS at 90 days), (PPV 92%, NPV 71% and PPV 83%, NPV 66%, respectively), better than successful reperfusion – by TICI 2b/3 (PPV 75%, NPV 100%)

Table 1 continued

Authors	Group	Patient number	Study design	Main findings
Zhang et al. [71]	AIS	161	P obs	Pathologic SSEP, BAEP, and EEG patterns and lack of EEG reactivity as good predictors of poor outcome (GOS at 6 months) (sensitivity 92.4–97%)—bilateral absence of SSEP and BAEP wave V with highest specificity (100%; PPV 100%)
Su et al. [75]	AIS	100	P obs	Correlation of SSEP and BAEP with unfavorable outcome (mRS at 6 months) (prognostic accuracy 94.3–98.7%—$p < 0.01$)
Burghaus et al. [84]	AIS	30	R	Association of abnormal BAEP with malignant course of MHCI ($p < 0.05$)—no significant difference for SSEP between malignant or nonmalignant course
Haupt et al. [76]	AIS	111	P obs	SSEP and BAEPs findings on admission both correlated with outcome (GOS at 4 weeks) ($p < 0.01$)
	ICH	76		
	SAH	28		
Zhang et al. [72]	AIS	67	P obs	Absence of bilateral SSEP (N20/N60) predictor of unfavorable outcome (mRS at 6 months)—100% specificity, 31 and 49.3% sensitivity, resp.). Lesion-ipsilateral absence of N60 (sens. $\geq$ 97.2%)
	ICH	21		
Haupt et al. [81]	AIS	111	P obs	Correlation of SSEP with outcome (GOS at 4 weeks) ($p < 0.05$)
	ICH	76		Correlation of BAEP with outcome after supratentorial infarction/hemorrhage ($p < 0.05$)—not always confirmed association after infratentorial infarction/hemorrhage and SAH
	SAH	28		
Schwarz et al. [69]	AIS	20	P obs	MEP predictors of motor function at 3 months ($p < 0.0001$), better than clinical data (specificity 97 vs 21%; sensitivity 65 vs 94%) and correlated to radiologically confirmed brainstem lesions ($p < 0.0001$)
	ICH	6		
	TBI	2		
Combined somatosensory-evoked potentials–electroencephalography (SSEP–EEG)				
Bosco et al. [73]	SAH	51	P obs	Death more likely with of SSEP and EEG deterioration (32 and 24%, resp.)—correlation of SSEP-EEG worsening with outcome (GOS at 3 months) ($p \leq 0.001$ and $p \leq 0.012$, respectively), mortality ($p \leq 0.001$)
	ICH	15		In SAH patients, SSEP-EEG worsening preceded ICP increase in 31.4% of patients who developed vasospasm and DCI
				Nonconvulsive seizures with periodic discharges and rhythmic delta activity, SSEP amplitude instability, reduced/lost cortical SSEP detected earlier than TCD and angiographic evidence of vasospasm
Amantini et al. [87]	TBI	29	P obs	SSEP alterations preceded ICP increases in 30% (simultaneous with ICP increases in 38%)—SSEP changes better predictors of secondary brain damage than ICP (in the range 20-40 mmHg)
	ICH	14		
	SAH	20		Detection of nonconvulsive status epilepticus by cEEG in 3% of patients
	AIS	5		
Fossi et al. [68]	TBI	44	P obs	SSEP always measurable, also during EEG suppression
	ICH			Detection of nonconvulsive status epilepticus by cEEG in 9% of patients
Combined brainstem-evoked potentials–encephalography (BAEP–EEG)				
Burghaus et al. [85]	AIS	22	R	Abnormal BAEP and generalized slowing/slow delta patterns associated with malignant course of MHCI ($p = 0.04$)—highest significance at presence of both ($p = 0.02$)
Encephalography (EEG)				
Gollwitzer et al. [93]	SAH	12	P obs	Prediction of DCI by quantitative EEG in 6 patients (sensitivity 89% and specificity 77%, AUC = 0.66)
				In 4 cases, EEG anomalies preceded TCD-documented vasospasm and CT/MRI-detected DCI by 2.3 days
Rathakrishnan et al. [94]	SAH	12	P obs	In 3 cases, cEEG predicted DCI 24 h before the clinical deterioration and identified poor responders to DCI treatment sensitivity of 67 and 50% for the prediction of clinical outcome
O'Connor et al. [103]	SAH	69	R	cEEG recorded electrographic seizures in 8.6% of patients with no clinical suspicion of seizures, no correlation with poor outcome (mRS at discharge)
Lindgren et al. [105]	SAH	28	R	Nonconvulsive seizures detected in 7% of patients -one nonconvulsive status epilepticus
Crepeau et al. [104]	SAH	68	P obs	EEG abnormalities in 75% of cohort –19% periodic discharges, 26% rhythmic delta activity and 29% both patterns—and 5.9% had seizure pattern. No prediction of outcome (mRS at discharge) by certain patterns

Table 1 continued

Authors	Group	Patient number	Study design	Main findings
Claassen et al. [109]	SAH	53	P obs	53 patients with nonconvulsive seizures (among 479 SAH patients), partially associated with inflammatory serum biomarkers increases, correlated with poor outcome (mRS at 3 months) (OR 1.2)
Vespa et al. [102]	TBI	140	R	Detection of nonconvulsive seizures by cEEG in 23% of patients
Hartings et al. [100]	TBI	18	P obs	Detection of 455 spreading depolarizations, 41% associated with EEG depression—cEEG recorded 81% of spreading depolarizations confirmed by invasive electrocorticography
Ong et al. [106]	SAH ICH AIS	11 8 3	R	No correlation between periodic activity, focal slowing, or seizures and outcome (mortality/consciousness recovery). Prolonged periodic epileptiform discharge associated with stimulus-induced discharges ($p = 0.009$)
Steinbaugh et al. [107]	TBI SAH	46 6	P rand	Levetiracetam correlated better clinical outcome (Glasgow Outcomes Scale—EDRS at discharge, 3 and 6 months) than phenytoin. Severe generalized slowing predictive of worse outcomes ($p < 0.049$)
Szaflarski et al. [110]	TBI SAH	46 6	P rand	Levetiracetam was correlated with better clinical outcome (Glasgow Outcomes Scale—EDRS at discharge, 3 and 6 months) ($p < 0.042$) than phenytoin ($p < 0.043$)
Near-infrared spectroscopy (*NIRS*)				
Yousef et al. [119]	SAH	163	P obs	Cerebral desaturations ($cSO_2 < 50$) for at least 30 min related to 3.25 and 2.72 risk of DCI and poor outcome (mRS at 3 months), respectively (PPV 70%; NPV 63% and 80%, respectively)
Yokose et al. [128]	SAH	14	P cc	Sensitivity 100% and specificity 85.7% for detection of vasospasm as by DSA and TCD. Higher cSO_2 ($p = 0.048$), lower deoxy-hemoglobin ($p = 0.002$), no difference in total hemoglobin in patients vs controls
Zweifel et al. [122]	SAH	27	P obs	Strong correlation between NIRS-based autoregulation index and Mx ($r = 0.81$)
Budohoski et al. [38]	SAH	98	P obs	THx-independent predictor of DCI (PPV 54%, NPV = 88%)
Lewis et al. [124]	TBI	21	R	Fix correlated with Mx ($r = -0.89$, $p < 0.000001$)
Budohoski et al. [125]	TBI	42	R	After arterial pressure and ICP changes, NIRS reacted significantly earlier than $PbtO_2$ ($p < 0.001$)
Zweifel et al. [126]	TBI	40	P obs	Significant correlation between NIRS parameters and ICP values ($r = 0.56$, $p = 0.0002$). Significant agreement in the optimal CPP and ABP assessment using NIRS or ICP monitoring ($p < 0.05$)
Vilke et al. [129]	TBI	61	P obs	NIRS parameters better indicators of hospital mortality than GCS score, blood sugar, or hemoglobin levels ($p = 0.003$)—higher NIRS values in survivors ($p \leq 0.029$)
Dias et al. [127]	TBI	18	P obs	eCPP correlated with measured/calculated CPP ($r = 0.83$, $p < 0.0001$) Greater difference (>10 mmHg) between measured/calculated CPP and optimal CPP target associated with poorer outcome (GOS at 6 months) ($p = 0.04$). NIRS had lower bias than intraparenchymal monitoring probes (CBF thermal flow sensor, $PbtO_2$, and brain temperature sensors)
Diedler et al. [123]	TBI	37	R	Significant correlation between THx and ICP-derived coefficient when NIRS slow oscillations had powerful input signal and THx value agreement is present between right and left side ($r = 0.80$, $p < 0.01$)
Hametner et al. [121]	AIS	43	P obs	During endovascular recanalization, lower median AUC 10% below baseline correlated with reperfusion ($p = 0.009$). Lower interhemispheric difference and higher variability of predicted death at 90 days ($p = 0.037$) and poor outcome (mR) ($p = 0.032$), resp.
Bispectral Index (*BIS*)				
Duncan et al. [132]	SAH	31	P obs	Sensitivity of 95.4% and specificity of 58.1% for monitoring depth of anesthesia—concordance with clinically evaluated depth of anesthesia ($p < 0.01$)[c]
Cottenceau et al. [133]	TBI	24	P obs	Asymmetrical BIS values in 75% of burst-suppression induced by barbiturates
Cottenceau et al. [134]	TBI	11	P obs	Correlation between EEG and BIS ($r = 0.94$) Barbiturate infusion reflected by maintenance of BIS in range 6–15

Table 1 continued

Authors	Group	Patient number	Study design	Main findings
Flores et al. [136]	AIS	53	P obs	Inverse correlation between BIS score and NIHSS at discharge ($p < 0.001$) and between BIS score and infarct volume ($p = 0.031$)
				BIS value >81 independent predictor of clinical improvement (NIHSS score) ($p = 0.024$)
Riker et al. [135]	TBI	11	P obs	BIS values correlated with EEG suppression during pentobarbital infusions ($r = -0.99$; $p < 0.001$)
	ICH	1		
Bioimpedance				
Lou et al. [141]	MHCI	69	P obs	Positive EBI in 88.4% of patients. Significant difference between EBI values in malignant and nonmalignant progress ($p < 0.001$)
				At 24 h after onset, sensitivity 90.9% and specificity 87.2% for prediction of malignant MHCI course
He et al. [144]	AIS	107	P cc	Positive correlation between infarct side EBI values and infarction volume ($p < 0.05$). Perturbative index higher with infarction volume >20 ml
Liu et al. [142]	ICH	52	P cc	Positive correlation of hematoma side EBI values with perihematomal edema volume ($r = 0.88$, $p < 0.01$) and of hematoma side EBI values with infarction volume ($r = 0.85$, $p < 0.01$)
	AIS	33		
Liu et al. [143]	ICH	78	P cc	Positive correlation of hematoma side EBI values with perihematomal edema volume ($p < 0.01$) and of hematoma side EBI values with infarction volume ($p < 0.001$)—higher sensitivity with lesion volume >20 ml
	AIS	51		
Pupillometry				
Taylor et al. [155]	TBI	26	P cc	Constriction velocity reduction (<0.6 mm/s) with ICP > 20 mmHg and MLS > 3 mm or with brain swelling and ICP > 30 mmHg without MLS
	SAH	5		
Chen et al. [149]	TBI	66	P obs	Inverse correlation between pupil reactivity and ICP abnormality, NPI or nonreactive pupil associated with ICP peaks (>30.5 mmHg) ($p < 0.0046$)
	SAH	44		
	ICH	25		Pathological pupillary examination preceded the ICP peak by 15.9 h
Cranial accelerometry				
Smith et al. [156]	SAH	14	P obs	Sensitivity 81% for detection of TCD demonstrated vasospasm—PPV 55%, NPV 61%

Main results presented in the most uniform way possible, insofar as was available from the publications

SAH subarachnoid hemorrhage; *TBI* traumatic brain injury; *ICH* intracerebral hemorrhage; *AIS* acute ischemic stroke; *MHCI* malignant hemispheric cerebral infarction; *TCD* transcranial Doppler; *TCCS* transcranial color-coded duplex sonography; *NIRS* near-infrared spectroscopy; *DCI* delayed cerebral ischemia; *NPV* negative predictive value; *PPV* positive predictive value; *OR* odds ratio; PCO_2 end-tidal carbon dioxide partial pressure; *MCA* middle cerebral artery; *PI* pulsatility index; *ICP* intracranial pressure; *GOS* Glasgow Outcome Scale; *CPP* cerebral perfusion pressure; *eCPP* estimated CPP; *eICP* estimated intracranial pressure; *MAP* mean arterial pressure; *FV* flow velocities; *Mx* mean FV/CPP correlation index; *Mxa* mean FV/arterial blood pressure correlation index; *Sx* systolic FV/CPP correlation index; *Sxa* systolic FV/arterial blood pressure correlation index; *Dx* diastolic FV/CPP correlation index; *Prx* intracranial pressure reactivity index; *CVRi* cerebrovascular resistance index; *TOxa* tissue oxygen index/arterial blood pressure correlation coefficient; *RAP* resistance area product; *resp.* respectively; *CBF* cerebral blood flow; *mRS* modified Rankin scale; *MLS* midline shift; *ONSD* optic nerve sheath diameter; *EP* evoked potentials; *SSEP* somatosensory-evoked potential; *VEP* visual-evoked potential; *BAEP* brainstem auditory-evoked potentials; *MEP* motor-evoked potentials; *EEG* electroencephalography; *EDRS* Extended and Disability Rating Scale; *WFNS* World Federation of Neurosurgical Societies; *NIHSS* National Institutes of Health Stroke Scale; *fMRI* functional magnetic resonance imaging; *MRA* magnetic resonance angiography; *PET* positron emission tomography; *cEEG* continuous electroencephalography; *CT* computed tomography; *DSA* digital subtraction angiography; *Fix* ICP/CBF velocities association index; *GCS* Glasgow come scale; $PbtO_2$ brain tissue oxygenation; *THx* tissue oxygenation/arterial blood pressure association index; [HbO_2] oxy-hemoglobin concentration; [*HHb*] deoxy-hemoglobin concentration; [*oxCCO*] cytochrome c oxidase oxidation concentration; *DCS* diffuse correlation spectroscopy; *XeCT* xenon-enhanced computed tomography; *BIS* bispectral index; *EIS* electrical impedance spectroscopy; *EBI* electrical bioimpedance; *Npi* neurological pupil index; *AUC* area under ROC curve; *P* prospective; *obs* observational study; *cc* case–control; *rand* randomized; *R* retrospective

[a] Matched cohort study

[b] Head-to-head comparison

[c] During general anesthesia for the endovascular treatment, authors did not specify if measurements were extended to the ICU setting

[d] Exception: studies on EP not restricted to that time frame

index (PI = peak systolic FV − end diastolic FV/mean FV). Increased PI (>1.2–1.3), low diastolic FV, and peaked waveform suggest a reduced CBF, such as due to elevated ICP, low $PaCO_2$, or ischemia. As such, TCU has been employed to noninvasively estimate CPP and ICP [12, 14, 40–43]. Indeed, PI correlated well with invasive ICP monitoring [44, 45]. TCCS analysis showed similar results between estimated and real ICP or CPP values [33]. Estimated CPP (eCPP) correlated well with invasive CPP values [46]. Diagnostic accuracies were good and similar for TCD and TCCS [27].

Additional hemodynamic parameters based on TCD have been elaborated, such as eCPP (eCPP = [FVmean/(FVmean − FVdiast)] × [Blood Pressure mean − Blood Pressure diast]), resistance area product (RAP = Blood Pressure mean/FVmean), cerebral blood flow index (CBFI = eCPP/RAP), and dynamic cerebral autoregulation derived from the transfer function analysis of mean FV variations in response to MAP, obtaining two parameters. These parameters are phase (that represents the autoregulatory response speed) and gain (that expresses the damping effect of cerebral autoregulation); synchronous oscillations and high gains denote impaired dynamic cerebral autoregulation. The values were used to evaluate the cerebral circulation in patients with ICH; they correlated with hemorrhage volume at follow-up and were more sensitive than velocity measurement alone [36, 47–49].

TCD has also been utilized to investigate the effects of an osmotherapeutic mannitol bolus on MCA after ICH, showing FV increase in the ipsilateral MCA and PI increase in the contralateral hemisphere ($p \leq 0.004$), possibly reflecting preserved pulsatility in the nonaffected hemisphere [50]. Interestingly, TCD screening of TBI patients on admission revealed their risk of developing secondary neurological deterioration by PI ≥ 1.25 [14, 51] or traumatic internal carotid artery (ICA) dissection in patients with PI ≤ 0.80 [40].

Parenchymal TCCS can also be used to assess MLS by visualizing the third ventricle via its parallel hyperechogenic margins with surrounding hypoechogenic thalami, for example, after ICH. MLS ≥ 12 mm predicted mortality at 6 months and MLS ≥ 4.5–7.5 mm suggested that conservative treatment would fail [30]. TCCS helped monitor width changes of the lateral ventricles during extraventricular/lumbar drainage clamping as an alternative to repeated computed tomography (CT) scans in patients developing hydrocephalus following ICH (with subsequent intraventricular involvement) and SAH (sensitivity and positive predicted value 100%) [31]. Moreover, alterations in optic nerve sheath diameter (ONSD) can be estimated by optic nerve ultrasonography. This method displays the linear hypoechogenic structure of the optic nerve sheath behind the globe and correlates with intracranial hypertension at ONSD values ≥0.48 cm [52].

TCU has long been employed to detect vasospasm, particularly after SAH. Compared to angiography, TCD showed good accuracy in detecting vasospasm in the MCA and anterior cerebral artery (ACA) [28, 53, 54]. However, TCD showed limited sensitivity in identifying DCI [54]. In another study, vasospasm observed by increased TCD velocities were partially related to DCI, especially in the region ipsilateral to the ruptured site if the aneurysm developed from ACA, MCA, or ICA [55]. In order to reach a higher correlation between vasospasm and DCI, Nakae et al. [56] proposed applying a mean blood FV ratio of the ipsilateral to contralateral MCA and reported a higher positive predictive value. After ICH, TCU revealed a vasospasm incidence of between 5.7 and 37% in patients with ventricular involvement [57, 58].

TCU has been applied to demonstrate low flow, hyperemia, brain autoregulation, and vasoreactivity to CO_2. Cerebrovascular reactivity (CVR) to CO_2 was standardized, monitoring changes in SAH and TBI patients by using TCD [59, 60]; here, CVR values were significantly lower in patients than in controls but did not correlate with DCI [59]. We only found one study on the role of cerebral emboli after SAH and surgery for intracranial aneurysm, with embolisms in 4 out of 105 patients only [61].

Some investigators assumed that enhanced blood FV in SAH increases regional brain vascular resistance, resulting in cortical activity changes. Therefore, they investigated whether FV reduction in the MCA section according to TCCS correlated with N20 cortical somatosensory-evoked potential (SSEP) changes and suggested that before structural ischemic damage developed, simultaneously evaluating SSEP and TCCS abnormalities would predict ischemic penumbra due to vasospasm [61].

Finally, TCU has been suggested to have prognostic value since several studies—both prospective and retrospective—demonstrated a correlation between PI ($p < 0.03$) [41, 62], Mx, Mxa, Sx, Sxa, Dx [30, 32, 33], MLS [30, 44], and outcome, either defined as survival/death, Glasgow Outcome Scale (GOS), or modified Rankin Scale (mRS) at different points in time (2 weeks, 90 days, or 6 months).

Evoked Potentials (EP)

Evaluating EP, mainly SSEP and brainstem-evoked potentials (BAEP), provides information about neuronal pathway integrity, input conduction, and the capacity to process and integrate stimuli [14, 64–67]. EP can be easily interpreted, are comparable, and not susceptible to the influence of sedatives and other medications [68].

However, MEP are contraindicated in epileptic patients, in patients with cardiac pacemakers and intracranial metal clips, and can interfere with electronic devices on the ICU [69].

The MMM consensus conference underlined the utility of EP for outcome prediction in selected patients [4]. Our search on NICU applications revealed 4 retrospective studies (*n* range 30–123) and 12 prospective studies (20–215) since the year 2000 (Table 1).

Among the EP, SSEP are applied most widely, mainly to predict outcome, a bilateral absence of SSEP usually being associated with poor prognosis. The utility of SSEP appears to be controversial, although the majority of recent studies confirmed, for example, that SSEP predicted death [70–81] even in long-term, unconscious TBI patients [82] as well as cognitive outcome [74]. Some authors suggested that SSEP improvement in the first days after TBI is associated with better functional outcome [74]. These results, however, could not be completely confirmed by Wachter et al. [83] in a sample of SAH patients who were electrophysiologically monitored by using SSEP, BAEP, and visually evoked potentials (VEP); these authors concluded that none of the EP was a good predictor of outcome, except for SSEP at admission and VEP two weeks after admission. Likewise, other authors did not find significant differences in SSEP between AIS patients with a malignant course (MLS or uncal herniation due to space-occupying brain edema) and those without [84].

Other EP, such as BAEP and VEP, showed encouraging results in some studies on AIS, ICH, and SAH, reporting correlations with outcome (mRS, malignant course, or GOS at 4 weeks) [71, 75, 76, 81, 84, 85]. However, no correlation with outcome was found in other studies on patients after TBI, SAH, AIS, and ICH [70, 81, 83].

Motor-evoked potentials (MEP) by transcranial magnetic stimulation have hardly been systematically studied in the NICU. Only one study employing MEP was carried out in critical AIS and ICH patients and proved to be a better predictor for motor outcome than radiological findings [69]. In an acute care setting, other investigators employed MEP and SSEP for monitoring AIS stroke patients during endovascular recanalization treatment, obtaining good prediction of outcome (mRS) with a PPV of 92% [86].

Some authors applied combined continuous monitoring with SSEP and EEG to evaluate patients with brain injury. This system requires a particular set-up, with specific competence, electrodes, installation, and software, and aims to combine the advantages of the two neurophysiological techniques, yielding insights on prognosis or cerebral complications sooner than NM methods such as ICP or TCD [68, 73, 87].

Electroencephalography (EEG)

EEG has been applied in severe neurological diseases to evaluate acute brain dysfunction, detect epileptic activity, start treatment early, and obtain prognostic information in NICU patients [13, 14, 16, 64, 88–91]. Continuous EEG (cEEG) is a digitally recorded method by which cortical cerebral activity can be monitored over days with high temporal resolution. The numerical EEG data processing by fast Fourier transforms and wavelet analysis furnish quantitative displays, such as color spectrograms and total power in specific EEG frequency bands or power ratios in distinct bands. This system defines a quantitative EEG (qEEG) [92]. However, experienced operators are required to interpret the EEG patterns, cerebral activity needs to be distinguished from artifacts, the data volume is high, damage localization is not always optimally captured, and it is sensitive to sedation, which represent major disadvantages of the methods [16, 68, 73, 87].

EEG monitoring is strongly recommended by the NCS MMM consensus group in all TBI patients with unexplained and persistently altered consciousness. It is only weakly recommended for detecting DCI in comatose subjects after SAH and is not considered useful for revealing DCI after AIS. Moreover, its combination with invasive brain monitoring is also recommended [5]. Our current search yielded 4 retrospective (*n* range 28–140) and 7 prospective studies (*n* range 12–68) on EEG (Table 1).

QEEG was shown to predict vasospasm and DCI after SAH, even 2.3 days earlier on average than DCI documented by neuroimaging, vasospasm detected by TCD, or clinical changes [93, 94].

Pathologies such as SAH, ICH, AIS, and TBI may involve cortical spreading depolarization (CSD). CSD is characterized by a slow wave of sustained depolarization of neurons, but also by neuron swelling, dendritic spine distortion, and cortical silence with the risk of developing severe hypoperfusion (spreading ischemia)—possibly due to distal vasoconstriction in the cortical microcirculation—and progressive damage [95–99]. Monitoring CSD might be valuable in order to start treatment early and avoid secondary injury, but this was restricted to invasive electrocorticography (EcoG) for a long time. Recently, however, cEEG detected 81% of CSD recorded by EcoG [100, 101].

Monitoring by cEEG detected seizures in 23% of TBI patients [102], nonconvulsive seizures in up to 8.6% of SAH cases [103], and EEG anomalies such as periodic discharges, rhythmic activity, and focal slowing in 75% of SAH cases with no clinical suspicion of seizures [104]. These phenomena were not necessarily associated with outcome, though, as some recent studies showed [104–107]. Interestingly, seizures were not significantly

correlated with changes in brain tissue oxygen evaluated by intracerebral probes [108]. However, some authors found that nonconvulsive seizures were partially associated with increases in inflammatory serum biomarkers which, in turn, correlated with poor outcome after SAH [109]. Severe generalized slowing of waves was predictive of worse outcome in TBI and SAH patients [107].

cEEG was also applied to compare the effect of antiepileptic drugs, for instance, revealing that levetiracetam was better than phenytoin in terms of seizure prophylaxis and neurological status deterioration after SAH and TBI [107, 110, 111].

Near-Infrared Spectroscopy (NIRS)

NIRS uses the near-infrared spectrum of light to penetrate brain tissue, to estimate oxy/deoxy-hemoglobin concentration changes and oxidation status of cytochrome c oxidase, and, finally, to measure the cortical regional oxygen saturation (rSO_2) [112, 113]. Through bi-frontal optodes placed on the scalp, real-time brain oxygenation of mainly cortical venous vessels can be estimated using NIRS with high temporal and fairly good spatial resolution [114, 115]. By processing time-varying NIRS data via a quantitative hemodynamic model, physiological perturbations of cerebral blood volume, blood flow, and metabolic rate of oxygen [116] can be measured, providing continuous data on rSO_2. Desaturation is usually considered as rSO_2 below 50% or a decrease by 20% from the baseline value [117]. NIRS monitoring is simple and does not require much training. The output represents more an intraindividual trend than absolute values, and interpretation is limited by the uncertainty of whether signal changes are due to changes in CBF or cerebral oxygen extraction fraction (OEF). Signal contamination by extracranial tissue, which varies between the commercially available devices, represents a further problem [115]. Some algorithms and system settings based on the spatial resolution principle can subtract this nonessential information, and some authors even suggested that noninvasive NIRS results were comparable to those obtained by brain tissue probes [115–118].

The NCS MMM consensus conference recommended solely using NIRS for research purposes only and not to guide patient management since data were considered controversial and insufficient [5]. Our current search identified 3 retrospective (n 21–42) and 8 prospective (n range 14–163) studies on NIRS (Table 1).

NIRS was recently employed to explore cerebral hemodynamics and oxygenation in AIS, ICH, SAH, and TBI and to monitor ischemia related to cardiac or carotid surgery under general anesthesia [13, 112, 116, 117, 120]. rSO_2 was also evaluated during endovascular treatment for AIS, showing that good reperfusion was reflected by a lower median area under the curve, 10% below baseline, while lower interhemispheric difference and higher variability in rSO_2 were predictors of poor outcome [121].

NIRS-derived parameter indices, such as THx [a moving correlation coefficient of the tissue oxygenation index and arterial blood pressure (ABP)], were correlated with the autoregulation index Mx, assessing the validity of this method for continuous evaluation of the cerebral vascular autoregulation and reactivity in patients with TBI and SAH [34, 122, 123]. THx appeared analogous to the reactivity index derived from ICP (PRx) [123]. By elaborating another index (Fix), a moving correlation coefficient derived from the association between ICP and FV was able to identify impaired cerebral autoregulation after TBI [124].

Moreover, changes in cerebral oxygenation were detected by NIRS earlier than by invasively measuring $PbtO_2$ after TBI [125], and it was used to estimate the cerebrovascular pressure reactivity instead of monitoring ICP directly, showing a highly significant correlation between NIRS and ICP-derived indices [126]. Furthermore, NIRS showed lower bias than some intraparenchymal brain probes (CBF thermal flow sensor, $PbtO_2$, and brain temperature sensors) [127].

Some investigators applied time-resolved NIRS (TR-NIRS)—which employs picosecond light pulses—to evaluate the MCA territory of the temporal lobe, resulting in a potential tool reported to detect vasospasm and brain damage after SAH with a 100% sensitivity and 85.7% specificity as based on angiography and TCD [128].

Finally, NIRS was reported to be a good predictor of hospital mortality and outcome in TBI patients (e.g., $p \leq 0.029$) in two studies [127, 129].

Emerging Noninvasive Monitoring Methods and Their First NICU Applications

Bispectral Index

The bispectral index (BIS) is a value obtained by processing EEG parameter signals recorded from an electrode strip placed on the forehead. A device computes EEG information through algorithms, bispectral analysis, or fast Fourier transformation, taking electromyographic activity of the temporal muscle as well, and ultimately providing a dimensionless number ranging from 0 to 100. BIS is related to the consciousness level of the patient, whereby 100 reflects wakefulness (higher frequency of beta waves) and 0 cortical silence (EEG suppression). Scores of 65–85 are considered adequate for sedation, while values between 40 and 60 are considered adequate for general anesthesia [130–132]. BIS can be easily applied and interpreted,

continuous monitoring is possible, and temporal resolution is high, but adjustments may be required frequently because of artifacts, electrical device interference, and frontal and temporal electromyographic contamination [131, 133].

The NCS MMM consensus group concluded that there are not enough data currently to support the use of BIS for patients in critical neurological condition on the ICU [4]. Our search revealed 5 prospective studies (*n* range 11–53) on BIS (Table 1).

BIS was used as a tool to monitor depth of anesthesia after SAH, working better than clinically observed depth of anesthesia (i.e., to detect eyelash reflex) [132]. In TBI patients, BIS hemispheric differences were evaluated by comparing patients with unilateral frontal and those with diffuse asymmetrical injuries on the damaged side [133]. BIS also provided information during barbiturate treatment after TBI and ICH, displaying burst-suppression induced by drugs [133, 134] and demonstrating correlation with EEG results [135]. Scores between 5 and 15 were obtained during barbiturate coma for elevated ICP in patients with severe TBI [133–135]. Finally, BIS predicted clinical improvement in patients with AIS receiving endovascular treatment and showed good correlation with infarct volume and outcome [136].

Bioimpedance

The bioimpedance technique applies electrical current to the biological tissues to assess their electrical impedance spectrum. Since each tissue has its particular value of conductivity due to the constitutive elements and structure, the measurements via integrated electrodes of electrical impedance may differentiate and evaluate the state of the tissues, resulting in an enticing method for cerebral monitoring. Different impedance modalities for brain injury are available, such as basic electrical bioimpedance (EBI), electrical impedance spectroscopy (EIS), and electrical impedance tomography (EIT), applying single/alternating current or reconstructing an image of a volume conductor [137–140]. The method is safe—it employs small-amplitude, alternating currents—is portable, and continuously gives temporal information.

We found 4 prospective studies (*n* range 69–129) on bioimpedance (Table 1).

In consideration of resistivity changes in hemorrhagic or ischemic brain lesions, the bioimpedance techniques were used in AIS including large hemispheric infarction, ICH, and surrounding edema [141–143]. EBI was reported to predict a malignant course of AIS and found valuable to reveal brain edema, especially with infarct volume >20 ml [143, 144].

Furthermore, imaging results of the 2D head model by EIT and a 3D numerical model of the head through EBI were used for simulations able to reveal unilateral stroke lesions, based on the principle that the damaged volume modifies the left–right asymmetry between the two cerebral hemispheres [145, 146]. Simulations in a 3D numerical model focusing on the MCA were also conducted to monitor cerebral artery stenosis, but the specificity of measurements related to the stenosis degree requires further research [147].

Pupillometry

Pupillometry is an emerging tool that emits infrared light to the eyes to objectively measure the pupil's response by using a digital camera to acquire images. It evaluates the pupillary light reflex, pupil diameter and shape, onset latency, constriction and dilatation velocities, and percentage/ratio reduction in amplitude. By an algorithm, the pupillary light reflex parameters are turned into the neurological pupil index (Npi) set on a scale from 0 to 5. The pupillometer is a hand-held, portable, user-friendly, automated, accessible, inexpensive device, with the capability to perform reproducible, precise, and quantitative measurements [148].

The NCS MMM consensus conference stressed that pupillometry needs more validation and development and did not recommend its routine use [4]. Our search on recent publications revealed two prospective studies (*n* range 31–134) on pupillometry (Table).

Pupillary function has recently been studied in several pathological conditions, such as acute, severe TBI, brain edema, MLS, herniation, ICH, and SAH, to investigate elevation of ICP [149–154], and appeared to be a valuable prognostic indicator in NICU. Pupil constriction velocity of less than 0.8 mm/s was related to ICP increase in 31 patients after TBI or SAH, and NPi scores under 3 were considered pathological [155]. ICP $>$ 30 mmHg or ICP $>$ 20 mmHg and MLS $>$ 3 mm led to reduction of constriction velocity <0.6 mm/s [155]. Some authors studied a sample of 134 patients after TBI, SAH, and ICH, concluding that Npi $<$ 3 was associated with ICP increase, and pupillary abnormalities were found 15.9 h prior to the ICP peak [149].

Cranial Accelerometry

Cranial accelerometry evaluates the subtle tissue oscillations caused by blood pulsations. Accelerometers are placed on the scalp (bi-frontally, bi-temporally, occipital region, and vertex). They obtain signals that are averaged to the cardiac cycle by ECG or pulse oximeter and

processed during systolic and diastolic phases. The subtle skull vibrations originate from the turbulent or higher velocity of blood flow in case of arterial narrowing, which is later quantified by taking into account the transferred energy during systole and diastole. Advantages of this technique are that minimal training is required, no precise positioning is needed for the recordings, and recording time can be kept short (a few minutes).

We found only one prospective study in which investigators applied skull accelerometry with simultaneous TCD recordings to detect vasospasm in 14 patients after SAH, reporting promising predicting values [156].

Discussion

Bedside neuromonitoring in patients suffering from SAH, TBI, AIS, or ICH aims at directing neurocritical care to minimize morbidity and mortality of the primary condition and, in particular, to prevent or reduce secondary brain damage. Noninvasive monitoring tools have been received with considerable skepticism and controversy among some neurointensivists as regards their accuracy, validity, parameter dimensions, plausibility, and interpreter reliability. The devices described here are applied to assess perfusion, blood flow, oxygenation, brain parenchymal status, circuit integrity, neuronal activity, and cerebral function to various degrees.

Many of the current studies presented and discussed here are small and quite heterogeneous observational studies, 25% of them retrospective, and have considerable methodological shortcomings. Most are directed at physiological correlation, and only few are related to outcome or NICU management. We found just one randomized comparative interventional study. Due to our structured—yet not strictly systematic and meta-analyzing—approach and our broad inclusion criteria, there remains a considerable risk of selection bias. These limitations and the overall weak base of evidence must be taken into account and should evoke caution in interpreting the findings.

Transcranial ultrasound represents a widespread and versatile utility, yielding information potentially beneficial in the care of patients suffering from both cerebrovascular and trauma brain injury, concerning evaluation, planning, treatment monitoring, and prognosis [40, 51, 157, 158]. A mainstay in its application remains the detection of vasospasm in SAH and—to a lesser extent—in ICH and TBI, where results seem to grow in validity and reliability, while capacity to predict DCI appears limited, however [22, 40, 48]. Furthermore, by assessing ONSD [52] and PI, TCU has been used to estimate and monitor ICP and CPP with quite convincing results. Hence, more confirmatory correlation data provided, TCU may be particularly useful in deciding whether patients require ICP probe insertion or brain imaging [14, 33, 40]. It may also take up a role in the diagnosis and monitoring of ICH and ICH growth, especially utilizing ultrasound contrast agents [159–163], and inasmuch support or at times even substitute serial control imaging. The greatest and most intriguing part of current NICU research in TCU comes from monitoring cerebral autoregulation, with very encouraging results and with some studies even linking this to outcome. Finally, there exist few but interesting studies on TCU-detected effects of NICU procedures such as osmotherapy and CSF drainage and studies on combining TCU with other NM technologies. Both of these study directions may be very relevant but need more confirmation.

TCU represents a highly valuable tool for neurointensivists, particularly because of the broad variety of questions that can be addressed. To be able to gather bedside information on brain parenchyma, hematoma volume, ventricle enlargement, MLS, elevated ICP, cerebral circulation and autoregulation, etc. with just one single monitoring device demonstrates its value. More advanced TCU techniques employing signal-enhancing agents to assess perfusion have been found useful in non-NICU settings already. Continuous TCU is being improved. If adequately adapted to the NICU setting, these developments have the potential to save the patients and care team unnecessary transports for imaging and to improve patient management.

EP research appears to focus almost exclusively on predicting outcome. Unfortunately, some clinically interesting questions (such as trigger for decompressive surgery, peri-interventional/-surgical complications) that were addressed in the past by using EP have not been followed up further. Serial EP shows potential for quantifying damage severity and neuronal pathway integrity in various pathological conditions, possibly differentiating reversible from irreversible damage, and predicting outcomes, although controversies remain in the more recent study results [65, 70, 79, 81, 83, 86]. Early EP—especially SSEP and BAEP—predicts worsening AIS, TBI, and SAH in most studies and hence may help triggering decisions on invasive treatment—such as decompressive surgery in large hemispheric or cerebellar stroke [73, 80, 85]. Since each EP study investigates different neural pathways, combining complementary neurophysiological methods may provide better information about the systems affected and the prognostic value [81].

EP belongs to the routine armamentarium in the NICU, but more recently, research on its potential has been neglected and deserves to be reactivated. Potential current fields of application are neuromonitoring during endovascular treatment of AIS and SAH (SSEP), trigger criteria for decompression in space-occupying cerebellar processes

(AEP) and integration into multimodality monitoring set-ups.

EEG is probably the most traditional, accepted, and widespread type of noninvasive NM in the NICU. The methods have also been used to detect and follow CSD and monitor the evolution of cerebral damage, offering the possibility to promptly start and guide treatment [16, 64, 100]. Current research has focused on cEEG demonstrating good concordance with invasive electrocorticography for detecting CSD [100]. The nonconvulsive seizures and, in particular, the anomalous wave patterns detected by cEEG have yet to be clarified in terms of relevance to outcome. The EEG therapy study (levetiracetam vs phenytoin) in TBI patients [107, 110] is a singular encouraging example for linking NINM to a NICU treatment measure and outcome and calls for followers.

EEG clearly belongs to any NICU and its gold-standard application level in (nonconvulsive) status epilepticus is beyond dispute. Continuous/compressed EEG techniques certainly have great potential, particularly if integrated into multimodality monitoring. However, the challenge of handling and interpreting a flood of data and implementation into clinical routine still has to be met, both as far as industry solutions and skilled personnel are concerned. An exciting field to be further developed for EEG in the future will be the noninvasive detection of CSD.

NIRS has been applied to detect SAH-related vasospasm, hematoma growth, evaluate CPP, monitor cerebral autoregulation, and make indirect assumptions on CBF [124, 126, 128]. Among the current applications, its potential in reflecting autoregulation has been particularly noteworthy. Some of the studies presented here report quite sensationally appearing results, such as very high sensitivity values for vasospasm detection or very high correlation values for autoregulation parameters. A few studies have even linked NIRS parameters to patients' outcomes [119, 129]. It has to be stressed, however, that some of these studies have a really small simple size (few extending $n = 50$) and that the NIRS set-up used in many studies has been a sophisticated, at time custom-made, one that may not be practicable everywhere.

Summary and outlook: Despite all its shortcomings, NIRS is certainly one of the NINM methods with the greatest potential. Putative future fields of application may be NM during endovascular procedures and individualized optimal CPP strategies based on multimodality monitoring for cerebral autoregulation. A particularly desirable development would be the further development of a robust combination of NIRS with TCD, to then be able to distinguish changes in cerebral oxygen consumption from changes in perfusion.

BIS has been used to monitor sedation depth, to adjust ICP treatment by barbiturate infusion, to adapt sedative-hypnotic therapy, to monitor burst-suppression patterns, and to predict outcome [133–136, 164]. These current studies largely focused on correlating BIS with EEG, not always yielding convincing results.

More research on BIS is clearly necessary in the NICU setting. The method does have potential in areas such as steering sedation, steering anesthesia during endovascular and other invasive interventions, and as a substitute EGG in the ER or the NICU during status epilepticus if no more advanced EEG solutions are available.

Bioimpedance is a very young technology almost exclusively applied to monitor the brain edema related to ischemic or hemorrhagic stroke [141–144]. It may evolve as a real-time bedside complement to neuroimaging, with EIT appearing to be the most promising diagnostic parameter. The reported potential to predict malignant course of AIS early is particularly intriguing. Even if good reconstruction algorithms and hardware were developed, however, it is hard to imagine that bioimpedance may achieve the accuracy of imaging [137] and indications and timing for its application need to be further developed.

Pupillometry is obviously useful to obtain objective, reliable, and reproducible measurements of pupillary reactivity. Current investigations mainly focus on early detection of ICP increases in mixed NICU patients, directed at the potential to guide neuroprotective and neurosurgical procedures, such as early decompressive craniectomy after TBI or AIS. Although principally interesting there are far to few studies to sufficiently judge this potential. Also, the device cannot explore consensual response because it is monocular, and ocular disease and some medications may interfere with the response [149–152, 155]. Much more confirmatory research is necessary, but is also warranted.

Since we only found one study [156] on accelerometry to predict vasospasm in SAH (only 14 patients and TCD as a comparator), although theoretically quite interesting, we cannot judge this method for lack of data.

Summary

Various noninvasive neuromonitoring methods can be applied in the NICU. Their most important advantages are—naturally—noninvasiveness, but also repeatability and adjustability, rather low costs, and often easy execution and interpretation. In particular, TCU, EEG, and SSEP are the best studied methods and are certainly able to guide neurointensivists in managing patients. Other methods, such as BIS and NIRS, are promising but have not been studied sufficiently. In the future, NINM should be analyzed in combination with several parameters derived from invasive or other NINM methods, thus collecting

multimodal information in a real-time process, and then integrating data to confirm and/or improve existing correlation studies and to improve our knowledge on pathophysiologic relationships. Such insights should inform about which types of neuromonitoring can optimally be combined (e.g., global + regional, oxygenation + hemodynamics, invasive + non-invasive) and in what clinical situations they may be most helpful. With more data on the plausibility of NINM, its potential as adjunct and alternative to INM should then be tested, aiming to spare patients invasive procedures and transports. Eventually, treatment algorithms involving NINM should be studied in a prospective fashion.

Ultimately, the goal should be to replace or complement invasive with noninvasive neuromonitoring to achieve safe, feasible, affordable, and valid bed-side monitoring of neurocritically ill patients who cannot (sufficiently) be evaluated clinically because of sedation, ventilation, and critical conditions to improve their management and outcome.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest with regard to this work.

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