Multimodal neuromonitoring of a brain death with electrophysiological markers of cortical and subcortical loss of functions

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Short Report

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Abstract

Brain death, characterized by the permanent cessation of all brain functions including the brainstem, is subject to varying diagnostic criteria internationally. In France, the confirmation of the clinical criteria requires ancillary tests such as CT angiogram or EEG. The timing of these tests presents challenges, especially in the intensive care setting.

This study outlines a novel approach for the assessment of brainstem and cortical functions, improving the precision of brain death diagnosis in high-workload intensive care environments. We detail the implementation of a continuous multimodal neuromonitoring system, utilizing electrocorticography to monitor cortical spreading depolarizations (SD) and employing advanced analytics to track variability in heart and respiratory rates as indicators of brainstem functions.

The SD-ICU single-center trial assessed the feasibility and safety of SD monitoring in patients with acute brain injuries, using cortical electrodes. In conjunction with the Moberg CNS monitor, this setup allowed for the collection and analysis of multimodal neuromonitoring data. We highlight the case of a patient who, exhibited an SD-initiated negative ultraslow potential, indicating cortical death. Subsequent fluctuations in heart and respiratory rates’ variability provided a real-time evaluation of the functionality of the brainstem's cardiovascular and respiratory centers. The integration of SD monitoring and variability analyses offers a continuous bedside evaluation, presenting clinicians with real-time biomarkers of brainstem and cortical death. This method could be incorporated into neuromonitoring software, enabling more timely and precise brain death determinations, a paramount improvement given the complexities and demands of ICU care.

Matin text

Dear editor,

Brain death, defined as the permanent cessation of all brain functions, including the brainstem, is diagnosed through various criteria that differ significantly between countries. In the United States, the 2023 guidelines emphasize a comprehensive and rigorous approach, requiring permanent cessation of all brain functions for diagnosis [1]. This necessitates a stringent, standardized diagnostic process and careful observation to confirm the permanency of brain injury and exclude confounders. In contrast, in France, brain death is defined by clinical criteria and must be confirmed by an ancillary test. The two common ancillary tests that can confirm the clinical diagnosis of brain death are the CT angiogram and repeated electroencephalogram. Determining the optimal timing for these ancillary examinations poses significant challenges and is influenced by both medical and logistical considerations. In practice, this can result in multiple trips to the scanner, leading to a waste of time, financial resources, and, at times, causing misunderstandings or distress among the patient's relatives. The need to balance prompt and accurate diagnosis with the constraints and dynamics of critical care environments makes the timing of brain death determination a contentious and impactful aspect of patient care. While transcranial Doppler
can be useful for determining the moment when there is no remaining cerebral perfusion [1], there is still a need for precise and continuous markers of brainstem and cortical death at the bedside. Herein we aim to illustrate how continuous multimodal neuromonitoring can provide novel biomarkers, thereby aiding in achieving a more accurate and timely diagnosis.

The development of secondary brain damage in brain-injured patients is a significant concern in ICUs. This damage can be caused by various events such as delayed cerebral ischemia, intracranial hypertension, recurrence of intracranial bleeding, and the occurrence of cortical spreading depolarizations (SD), which has recently raised considerable interest [2]. SD occurs in about 50% of patients with traumatic brain injury and 70–80% of patients with aneurysmal subarachnoid hemorrhage and is associated with poor prognosis. SDs can be monitored by electrocorticographic monitoring, providing valuable information on the state of the underlying cortex and the severity of new aggression [3–5]. Furthermore, the appearance of an SD initiated negative ultraslow potential (NUP) is always observed at the onset of cortical infarction or global cerebral ischemia, such as during brain death [2, 6, 7]. The NUP could therefore serve as a potent marker of permanent cortical damage under the electrode and a surrogate of cortical death.

In our institution, we conducted a monocentric feasibility and safety trial of SD monitoring with electrocorticography in acutely brain-injured patients (SD-ICU, NCT04585503). Cortical electrodes were positioned in one of two ways: either subdurally during a neurosurgical procedure, or intracortically through a bolt with intracranial pressure (ICP) or oxygenation sensors. Multimodal neuromonitoring data were collected with the Moberg CNS monitor (NATUS®). Between January 2021 and March 2023, we enrolled 20 patients who had either a severe traumatic brain injury or a poor grade subarachnoid haemorrhage (SAH). This report focuses on the case of one patient from this group who progressed to brain death. The patient was admitted to the intensive care unit after experiencing a sudden alteration of consciousness (GCS = 12) with a motor deficit in the left upper limb and facial paralysis. The state of consciousness deteriorated, leading to the patient's intubation. The CT scan revealed a Fisher grade 4 SAH due to the rupture of a right middle cerebral artery aneurysm, with a hematoma in the Sylvian fissure. The appearance of signs of right temporal hemiation (transient right mydriasis) led to surgical treatment with evacuation of the hematoma, clipping of the aneurysm without replacement of the bone flap. Upon her return from the operating room, the intracranial pressure was in normal ranges, then the patient again presented with right then bilateral mydriasis, refractory to medical treatment. A collegial discussion then led to a limitation of therapeutic interventions given the expected lesions of the midbrain and the severity of the cerebral lesions. After cessation of sedation on the 3rd day, the expected evolution was towards brain death, with a progressive elevation of ICP on the 4th day. The occurrence of clusters of SD highlights the progression of cortical injuries [3–5]. On the 6th day, the photomotor, oculogyric, and corneal reflexes were abolished, and there persisted a cough reflex, a nausea reflex, and spontaneous ventilation (first apnea test negative). The absence of all brainstem reflexes and the apnea test confirmed clinical brain death on the 7th day. Brain death was then confirmed by a cerebral CT angiography, according to the French regulation (Fig. 1).
Although clinical criteria for brain death had not been satisfied by day 6, the presence of an SD initiated NUP, coupled with a sustained suppression of background neural activity, suggests that cortical death occurred at 18:45 on that day. Conducting repeated bedside examinations of all brainstem reflexes to identify damaged structures may not always be practical in a clinical setting. Instead, we offer a technique for the ongoing evaluation of brainstem activity. Utilizing the pycns Python library (https://github.com/samuelgarcia/pycns), we processed data from the CNS monitor and used the physio library for our analyses [8]. We tracked changes in heart rate and respiratory rate variability as indicators of the functional integrity of the brainstem cardiovascular and respiratory centers. We observed that the SD-initiated NUP (i.e., permanent damage on the right temporal cortex) was followed by a marked decrease in respiratory rate variability within an hour (i.e., the disappearance of triggered respiratory cycles in controlled assisted ventilation mode at 19:45). This permanent cessation of spontaneous breathing was rapidly ensued by diminished heart rate variability and tachycardia, indicative of vagal withdrawal also reported during the Cushing response [9, 10] (Fig. 2). Herein, the right temporal infarction (Fig. 1) led to a progressive engagement, with a rostrocaudal degradation of cortical and brainstem functions.

Despite the focus on a single case, this report details an analytical approach that could be integrated into multimodal neuromonitoring software to evaluate brainstem and cortical functions. Such a system has the potential to aid clinicians in the early detection of cortical aggression during clusters of SD, and in identifying dysfunctions in brainstem functions. This also provides a mean to accurately pinpoint the timing of permanent cortical damage and transition to brain death within the demanding setting of an intensive care unit.

The top panel displays sequential computed tomography (CT) scans showing the evolution of brain injury. The underneath table describes the evolution over time of clinical and neuromonitoring data over seven days post-injury. Every 6 hours, the Glasgow Coma Scale (GCS) scores and the maximum intracranial pressure (ICP, in mmHg) are documented, alongside the number of spreading depolarizations (SD) detected and pupillary response (right and left pupil size and reactivity to light, denoted by R for reactive and NR for non-reactive). The orange color indicates the onset of brain injuries becoming permanent (red). The appearance of SD initiated negative ultraslow potential (NUP) preceded the identification of brain death. The bottom panel presents electrographic tracing from the 6 contacts electrocorticography (ECoG) strip with a bipolar montage. The signal is split with the background activity on the AC band (1-30Hz) in black, and the near-DC (0.005Hz-30Hz) changes in red. Repeated SDs on day 2 can be observed with a near-DC shift (red) leading to a transient depression of the background activity (black). On day 6 the SD is followed by an SD-initiated NUP (The DC traces are described in the Fig. 2) with a permanent depression of the background activity.

Panels A and B present electrographic tracing from the 6-contact electrocardiography (ECoG) strip with a bipolar montage, providing 5 derivations. A) DC potential (0–30 Hz) overlapping traces. Two spreading depolarizations (SD) can be seen just after 16:00 pm (light grey) and before 19:00 pm initiating a large Negative Ultraslow Potential (NUP, light red). B) AC amplitude (0.5-30Hz) overlapping amplitude
envelopes (using the Hilbert transform). Yellow and cyan dashed vertical lines outline the onset of cortical activity depressions triggered by SDs. The SD-initiated NUP lead to a permanent cortical depolarization and subsequent depression of the cortical activity. C) Respiratory activity. Cycle-by-cycle respiratory frequency (N cycles by minute) has been computed from the end tidal CO2 signal. Probability distribution of cycle frequencies has been computed in successive time windows of 4 minutes and displayed vertically for each time bin by a color map ranging from dark blue (zero) to yellow (maximal probability density). The red line presents the median cycle frequency value for each time bin (instantaneous respiratory rate). Respiratory variability abruptly diminishes at 19:45, as evident from the pronounced narrowing of probability distributions beyond this time point. D) Heart rate. Heart rate (in beats per minute) has been computed from each RR interval of the ECG signal. Probability distribution of instantaneous heart rates has been computed in successive time windows of 2 minutes and displayed similarly to respiratory activity. Like respiratory activity, heart rate suddenly loses its variability at 19:45 pm (narrowing of the probability distributions) while increasing from 80 to 140 bpm before decaying. The loss of variability in heart and respiratory dynamics may be attributed to the cessation of brainstem autonomic rhythm generator activity, indicating brainstem death.

Abbreviations

ICU: Intensive Care Unit.

GCS: Glasgow Coma Scale.

CT: Computed Tomography.

SAH: Subarachnoid Hemorrhage.

SD: Cortical Spread Depolarizations.

NUP: Negative Ultraslow Potentials.

ECoG: Electrocorticography.

ICP: Intracranial Pressure.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

Ethics approval and consent to participate:

Consent for publication: The SD-ICU trial was approved by the Comité de protection des personnes Est II (n°20.05.19.48947) on the 31th of August 2020. Patients’ relative approval and consent was obtained, as well as patients’ consent, if possible, during the period of investigation.
Availability of data and materials: The datasets reported herein are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: GV and BB wrote the manuscript and performed data analyses; GS analyzed the data; BaJ wrote the main manuscript; BB, BM, RS and BeJ designed the SD-ICU trial; BB, RT, GF, CR, BC, DF, BM, DC and HC were involved in conducting the trial; BB designed the figure 1; VG designed the figure 2; all authors critically revised the manuscript and approved the final version.

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References


Figures

Figure 1

Clinical and electrophysiological monitoring during the progression to brain death.
Figure 2

Advanced analysis of multimodal neuromonitoring for brainstem and cortical death identification.