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Auditory-evoked potentials during coma: Do they improve our prediction of awakening in comatose patients?

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ABSTRACT

Objective: The mismatch negativity (MMN), an auditory event-related potential, has been identified as a good indicator of recovery of consciousness during coma. We explored the predictive value of the MMN and other auditory-evoked potentials including brainstem and middle-latency potentials for predicting awakening in comatose patients after cardiac arrest or cardiogenic shock.

Materials and Methods: Auditory brainstem, middle-latency (Pa wave), and event-related potentials (N100 and MMN waves) were recorded in 17 comatose patients and 9 surgical patients matched by age and coronary artery disease. Comatose patients were followed up daily to determine recovery of consciousness and classified as awakened and nonawakened.

Results: Among the auditory-evoked potentials, the presence or absence of MMN best discriminated between patients who awakened or those who did not. Mismatch negativity was present during coma in all patients who awakened (7/7) and in 2 of those (2/10) who did not awaken. In patients who awakened and in whom MMN was detected, 3 of those awakened between 2 and 3 days and 4 between 9 and 21 days after evoked potential examination. All awakened patients had intact N100 waves and identifiable brainstem and middle-latency waves. In nonawakened patients, N100 and Pa waves were detected in 5 cases (50%) and brainstem waves in 9 (90%).

Conclusions: The MMN is a good predictor of awakening in comatose patients after cardiac arrest and cardiogenic shock and can be measured days before awakening encouraging ongoing life support.

1. Introduction

Clinicians must establish realistic goals for the management of comatose patients based on the potential for functional recovery. The initial concern is uncertainty about whether or not the patients will recover consciousness [1]. Predicting the recovery of consciousness is complicated by the use of hypothermia for neuroprotection, the presence of metabolic derangements, and the prolonged effect of anesthetic and sedative agents, which make the clinical examination unreliable, even after normalization of body temperature [2]. Several imaging diagnostic tests can be used, but their accuracy for estimating prognosis based on the magnitude and extent of the brain damage is also limited [3]. This uncertainty may lead to premature withdrawal of care in some patients or the futile continuation of life support in others.

Sensory-evoked potentials are voltage fluctuations within the electroencephalogram (EEG) associated with a series of sensory events elicited by the presentation of specific sensory stimuli within the somesthetic, visual, or auditory domains [4]. These potentials may provide a reliable assessment of the functional status of the brain during coma [5]. The absence of the early somatosensory-evoked potentials and particularly the negative wave called *N20* in comatose patients is a good indicator of the likelihood of nonawakening [3,6]. Their presence, however, does not guarantee the recovery of consciousness [3,6,7]. Currently, no practical tool that accurately predicts awakening is available.

Some studies have suggested that patients who show higher-order cortical processing of auditory stimuli during the course of coma may be more likely to make a good recovery [7,8]. Auditory event-related potentials (ERPs) in particular, which assess the subject's ability to discriminate different acoustic stimuli [4,5,9], can identify those comatose patients whose preattentive auditory memory remains active [8]. An example of this is the odd-ball paradigm where an occasional acoustic stimulus deviating in pitch, intensity, duration, or

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a combination of these is interspersed in a train of identical auditory stimuli [9,10]. The most distinctive response to this paradigm is a negative wave called *mismatch negativity* (MMN) [9], which has been identified as a good indicator for the recovery of consciousness in comatose patients [10-13]. A recent meta-analysis of 6 studies [14] has suggested that MMN has a specificity for predicting awakening of 91%. Despite its potential use, this technique has not been implemented in clinical practice. We assessed the value of MMN and other auditory-evoked potentials (AEPs) including middle-latency and brainstem potentials for predicting recovery of consciousness in a group of patients who developed coma after cardiac arrest or cardiogenic shock. We hypothesized that the presence of MMN during coma would be associated with recovery of consciousness.

2. Materials and methods

2.1. Study population

2.1.1. Coma group

The study was approved by our Institutional Research Ethics Committee. After verbal consent was obtained from the patient's legal guardian or family member (subsequently ratified with a written informed consent), patients in the coronary care or surgical intensive care units (ICUs) of our institution who remained unconscious and mechanically ventilated for at least 3 days after resuscitation following cardiac arrest or cardiogenic shock between January 2009 and October 2010 were enrolled. A diagnosis of coma was established if patients remained unconscious and unable to show a visible motor/verbal response to commands after sedatives and/or anesthetic agents were discontinued for at least 12 hours (Glasgow Coma Score [GCS] <8).

2.1.2. Control group

To match for age and presence of coronary artery disease, patients undergoing coronary artery bypass grafting (CABG) who had no history of neurologic disease or hearing deficits and with an uneventful postoperative course were used as a control group. The AEPs were recorded 3 days after the surgical procedure, when the patient was fully awake. Examinations were performed at the bedside while the patient was reading a book or asleep. Owing to time constraints, only brainstem AEPs (BAEPs) and ERPs were recorded in this group.

2.2. Clinical outcomes

Patients were followed up every day during their stay in the coronary or surgical ICU to determine recovery of consciousness. In addition, patients were followed up until their final discharge from hospital. Clinical information including patient characteristics, comorbidities and preexisting disease, circumstances surrounding cardiac arrest, resuscitation time, time of admission to ICU, GCSs [15], and any additional diagnostic procedures (ie, EEG) and laboratory tests were all recorded. In addition, results of the noncontrast head computed tomography (CT) scans and findings from the neurologic examination performed as part of standard care were recorded. Owing to the small sample size of our study, CT findings were reduced to a binary outcome as positive or negative. A positive head CT scan was defined by the presence of diffuse loss of gray and white matter differentiation, suggesting a diffuse severe hypoxic-ischemic encephalopathy and/or presence of a new brain infarct and/or intracranial haemorrhage. Recovery of consciousness was defined as the patient's ability to show a visible, oriented, and consistent motor and/or verbal response to commands. Based on this definition, we classified patients into those who recovered consciousness (awakened group) and those who died without regaining consciousness (nonawakened group). *Death* was defined as the cessation of life and all associated vital processes without the capability of resuscitation. This event was certified by a physician, and the circumstances leading to this event were documented. The results of our testing procedures did not influence clinical management, and the final functional status of all patients at the time of discharge from hospital was evaluated by using the Glasgow-Pittsburgh Cerebral-Performance Category scale [16].

2.3. Electroencephalogram

As part of standard care, a 17-channel EEG was recorded by a certified technician and interpreted by a board-certified neurophysiologist. To standardize the EEG changes, alterations were classified according to an EEG severity scale previously validated by Bassetti et al [17] in comatose patients (Supplementary Table E1).

2.4. Auditory-evoked potentials

Brainstem, middle-latency (MLAEP) AEPs and ERPs were recorded in all comatose patients in a single session that lasted, on average, 90 minutes [10,18-20]. Acoustic stimuli were delivered through insert earphones. Gold-plated clip and cup electrodes recorded the EEG from the scalp between A1 and A2 referred to Fz and Cz grounded to the forehead [21]. The EEG signal was amplified and averaged using a 17-channel EEG/4-channel EP Bravo Neurophysiologic system (Nicolet Biomedical Inc, Madison, Wis). Evoked potential testing occurred after at least 12 hours off sedation and at normothermia (bladder temperature, ≥35.8°C).

Brainstem AEPs were elicited in response to monaural clicks (100 microseconds) of alternate polarity at intensities of 80-dB normal hearing level (nHL) (relative to a normal hearing adult group) and stimulus rates of 11.3/s. Electroencephalogram activity from the initial 10 milliseconds after stimulus was band-pass filtered (100-3000 Hz), digitized (sampling rate: 66 KHz × channel), averaged (2000 samples), and replicated.

Middle-latency AEPs were triggered by monaural clicks (100 microseconds) of alternate polarity, intensities of 80-dB nHL, and stimulus rates of 11.3/s. Scalp recordings were similar to the BAEPs, except that the EEG was band-pass filtered between 10 and 3000 Hz, digitized (sampling rate, 50 KHz per channel), averaged (1500 samples), and replicated.

The auditory ERPs were obtained using the classical odd-ball paradigm technique (see “Introduction”) [4,10-14]; that is, auditory stimulation included 2 types of acoustic stimuli delivered binaurally using a randomly intertwined sequence of standard and deviant stimuli in proportions of 85% and 15%, respectively. Standard stimuli were 800-Hz tone bursts with intensities of 80-dB nHL and total duration of 75 milliseconds (rise/fall times, 5 milliseconds). Deviant stimuli were of identical frequency and intensity but with a total duration of 30 milliseconds (rise/fall times, 5 milliseconds). The interstimulus interval was 610 milliseconds, and the repetition rates were 1.6 stimuli per second. Analog EEG signals from A1 and A2 referred to Fz and Cz were band-pass filtered (1-150 Hz) using a time window of 500 milliseconds, including a stimulus delay of 50 milliseconds. Two samples of a minimum of 800 stimuli (ie, 120 deviants and 680 standards) were averaged (level of artifact rejection set at 90%).

2.5. Waveform identification

Wave identification and latency/amplitude measurements were performed offline by one of the investigators (R.R.), according to preestablished guidelines [19,22-24]. For the ERPs in particular, the technique of Fischer et al [10] for wave identification was followed (see Supplementary Figure E1).

2.6. Latency and amplitude measurements

Individual peak latencies of waves in the BAEPs (waves I, III, and V) and MLAEPs (Pa wave) were measured at its maximum peak referred to