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Clinical paper

The potential role of auditory evoked potentials to assess prognosis in comatose survivors from cardiac arrest

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ABSTRACT

Aim: Few data are available on the use of brainstem auditory evoked potentials (BAEPs) in combination with other electrophysiological tools to assess prognosis of comatose survivors from cardiac arrest (CA).
Methods: Retrospective analysis of data from all adult patients (>18 years of age) admitted to our Dept of Intensive Care after CA over a 6-year period who were comatose (Glasgow Coma Scale <9) on admission, had been treated with targeted temperature management and had BAEP testing. We collected variables related to CA, as well as electroencephalography (EEG) findings, N20 somatosensory evoked potentials, and the presence of I, III and/or V waves on BAEP testing. Outcome was assessed at 3 months using the Cerebral Performance Categories (3–5 = poor outcome).
Results: We studied 65 patients; 48 (74%) had a poor neurological outcome. BAEP assessment was performed day 3 [3,4] after the CA. At least one of the three waves was absent bilaterally in 34 patients (52%); of these patients, 29 (85%) had a poor neurological outcome (sensitivity 60%, specificity 71%, positive predictive value [PPV] 85% and negative predictive value [NPV] 39%). Three patients (5%) had bilateral absence of all three waves, all of whom had a poor neurological outcome.
Conclusions: In this series of patients after CA, at least one of the BAEP waves was absent bilaterally in half the survivors; however, their use for prediction of poor neurological outcome remains limited.

Introduction

Cardiac arrest (CA) is the most common cause of natural death in most Western countries and, despite initiation of resuscitation attempts, is associated with a mortality rate greater than 90% [1]. Improvement in the management of CA patients, including high-quality cardiopulmonary resuscitation (CPR) and early defibrillation, has enabled more patients to achieve return of spontaneous circulation (ROSC) and to be admitted alive to the hospital than in the past [1]; however, no more than one third will eventually be discharged with good neurological recovery [2].

Poor outcome after CA is associated with systemic and neurological complications of the so-called "post-cardiac arrest syndrome", i.e., the combination of systemic ischaemia/reperfusion response with myocardial dysfunction and severe hypoxic-ischaemic brain injury [3]. The use of targeted temperature management (TTM) is the only therapeutic intervention that may have beneficial effects on neurological recovery [4,5]. However, the need for sedative and analgesic drugs during TTM limits the accuracy of neurological examination for the assessment of prognosis in such patients [6], so that additional tools are needed to better evaluate the extent of neurological injury in this setting.

The best indicators of poor neurological outcome in this setting are lack of brain-stem reflexes and bilateral absence of the cortical response to stimulation of the median nerve using somatosensory evoked potentials (SSEPs), combined with an absent or posturing motor response at 48–72 h after CA [7]. Nevertheless, although the prognostic value of SSEPs is not significantly affected by TTM, the sensitivity of this test is relatively low and the presence of cortical responses does not necessarily indicate a favorable outcome [8]. A multimodal approach that includes several prognostic tools should, therefore, be used to improve the accuracy of outcome prediction in this setting [9].

Electrophysiological tests, such as the electroencephalogram (EEG) or middle latency auditory evoked potentials, have shown additional value in outcome prediction. Malignant EEG patterns (e.g., suppressed EEG, burst suppression, or generalised periodic discharges on a suppressed background) are extremely effective for predicting poor outcome in such patients [7,10]. Moreover,

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improvement in sound discrimination assessed using middle latency auditory evoked potentials during the early phase of coma is strongly associated with a high probability of awakening [11]. Electrophysiological tests of brainstem function, such as brainstem-evoked potentials (BAEPs), have been poorly characterised in CA patients treated with TTM. In one study, BAEPs were recorded immediately after ROSC; all patients without a detectable BAEP V wave had a poor outcome [12]. In another study, BAEPs recorded 24–48 h after CA were not correlated with outcome [13]. In view of these conflicting results, we analyzed our database of CA patients to evaluate the impact of BAEP findings when incorporated into a multimodal approach to predict outcome after CA.

Methods

Study population

In our 35-bed medico-surgical Department of Intensive Care, all patients surviving at least 12 h after in-hospital (IHCA) or out-of-hospital (OHCA) CA are included in an institutional database. We analyzed data from all the patients admitted from January 1st 2007 to January 1st 2013 who were comatose (Glasgow Coma Scale, GCS < 9) on admission, had been treated with TTM and had BAEP testing. The local Ethics Committee approved the study, but waived the need for informed consent because of the retrospective nature of the study.

Patient management

All comatose CA patients were treated with TTM (target body temperature: 32–34 °C) for 24 h, according to a standardised institutional protocol. Cooling was started immediately after hospital admission using a bolus of cold fluids (in general saline solutions, given as a dose of 20–30 ml/kg over 30 min) and a water-circulating blanket device (Medi-Therm II, Gaymar, NY, USA). Sedation and analgesia consisted of midazolam and morphine, which were adjusted to obtain a deep sedation status; cisatracurium was administered as a bolus to control shivering in the induction phase and then given, if needed, by continuous infusion. Rewarming (<0.5 °C/h) was achieved passively and sedation/analgesia discontinued at normothermia (>37 °C). Patients were kept in a 30° semi-recumbent position; ventilation was set to target $PaCO_2$ between 35 and 45 mmHg and SpO_2 >94%. Blood glucose was kept between 110 and 150 mg/dL using a local protocol for continuous insulin infusion; enteral nutrition was allowed from the early phase of TTM. Haemodynamic assessment included the continuous measurement of cardiac output (PiCCO, Pulsion, Munich, Germany), according to the decision of the attending physician, and the assessment of cardiac function by repeated transesophageal and/or transthoracic echocardiography. Mean arterial pressure was maintained >65–70 mmHg using volume resuscitation, dobutamine and/or noradrenaline (norepinephrine), as needed. Intra-aortic balloon counterpulsation (IABP) or extracorporeal membrane oxygenation (ECMO) was also used in cases of severe cardiogenic shock.

Definitions

Neurological function was assessed at 3 months using the Cerebral Performance Category score (CPC: 1 = no or mild neurological disability, 2 = moderate neurological disability, 3 = severe neurological impairment, 4 = vegetative state, 5 = death). Neurological recovery was subsequently dichotomised as good (CPC 1 and 2) or poor (CPC 3–5) at 3 months after CA, based on data in the medical files or by telephone call. Neurological examination (at minimum motor response and pupillary reflexes) was performed on admission and then daily thereafter. "Poor motor response" was defined as absent motor response or posturing. Life-support therapies were maintained for at least 72 h after CA; the decision process for withdrawal of life-support therapies was interdisciplinary and based on the combination of clinical evaluation (e.g., persisting coma with absent motor response or posturing, absence of pupillary and corneal reflexes and/or status myoclonus), SSEPs (e.g., bilateral absence of the cortical N20 response) and EEG findings (i.e., presence of non-convulsive status epilepticus refractory to three anti-epileptic drugs and continuous sedation OR persistent "malignant patterns" as defined above) [14].

SSEPs and BAEPs

SSEPs and BAEPs were recorded at the bedside in the ICU using a four channel evoked potential device (System Plus Evolution; Micromed SpA, Mogliane Veneto, Italy). The decision to record SSEPs were performed at 48–72 h after CA in all those patients not showing signs of neurological recovery (i.e. a motor response on the Glasgow Coma Scale of ≤4). Recording methods for SSEP have been described elsewhere [15]. BAEPs were recorded using silver cup electrodes applied to the earlobes referred to Cz with the ground electrode at Fz. A1-Cz and A2-Cz were recorded simultaneously. Clicks of 100 μs and 90–110-dB intensity were used through earphones at a rate of 10.7 Hz. A mask of 40-dB intensity was used in the contralateral ear. The bandpass was 160 Hz – 3 kHz and analysis time was 10 msec. At least two runs of 1000 stimuli were averaged and reproducibility was assessed by superimposing the traces on the screen. The procedure was performed with both right and left ear stimulation. The decision to perform BAEPs together with SSEPs was decided by the neurophysiologist, according to the presence of artifacts and also to the experience of the technician. Because BAEP latency did not correlate with outcome in a previous study [13], we chose to collect the presence of BAEP waves I, III and/or V (Fig. 1). We arbitrarily defined the bilateral absence of at least one of these waves as a "malignant" BAEP.

Data collection

We collected demographic characteristics for all patients. CA data were also recorded (location, initial rhythm, cause of CA, bystander CPR, time to ROSC, drugs administered) as well as the use of vasopressors or inotropes during the ICU stay and blood lactate levels on admission. Shock was defined as the use of vasopressors for more than 6 consecutive hours during the first 2 days after admission. EEG, using 21 electrodes placed on the scalp according to the classical 10–20 international convention, was initiated as soon as possible during cooling and recorded continuously for at least 48 h and until restoration of normothermia or death. We noted the presence of a malignant pattern (i.e., suppressed EEG, burst suppression, or generalised periodic discharges on a suppressed background) during the first 48 h, according to recent definitions, as reported in the medical charts [1].

Statistical analysis

Data were tested for normality and are presented as median (interquartile range) or mean ± standard deviation. Categorical variables are presented as n (%). Categorical variables were compared using the Fisher exact test or Chi-square test, as appropriate, and the Mann-Whitney *U* test was used to compare continuous variables. We analyzed the distribution of bilateral absence of BAEP waves in patients with good and poor neurological outcomes. The sensitivity, specificity, positive and negative predictive values (PPV and NPV) for good and poor outcome were calculated for all the BAEP findings. Different combinations of clinical (i.e., motor response, pupillary reflexes) and non-clinical tests (i.e., EEG, SSEPs