Metabolic encephalopathy in critically ill patients suffering from septic or nonseptic multiple organ failure

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Objective: Evaluation of changes in the peak latencies of sensory evoked potentials in different patient groups, to evaluate differences in metabolic encephalopathy of critically ill patients with multiple organ failure as a result of septic or nonseptic conditions.

Design: Prospective cohort study.

Setting: Intensive care units of the university hospital, Vienna.

Patients: Patients (n = 103) treated on an intensive care unit because of multiple organ failure with additional metabolic encephalopathy. Multiple organ failure was induced by sepsis (group A; n = 56), surgery (group B; n = 29), or both (group C; n = 18).

Interventions: None.

Measurements and Main Results: Metabolic encephalopathy was determined by measuring median nerve-stimulated short-latency and long-latency sensory evoked potentials. No differences in the peak latencies of the sensory evoked potentials were detected among the groups. Septic patients had a N70 peak latency of 131 ± 21 msecs, nonseptic postsurgical patients of 132 ± 17 msecs, and septic postsurgical patients of 134 ± 17 msecs. The cervicomedullary N13 to cortical N20 conduction times were 6.4 ± 1 msec, 6.4 ± 1.4 msecs, and 6.8 ± 1.2 msecs, respectively. All measured peak latencies were significantly prolonged compared with peak latencies of healthy controls. The severity of illness assessed by the Acute Physiology and Chronic Health Evaluation III score was not different between the three groups. An increase of the delay of N70 peak latencies was significantly correlated with the severity of illness (r² = .15; p < .00005).

Conclusion: There was no difference in sensory evoked potential measurements detectable among septic patients with multiple organ failure, nonseptic postsurgical patients with multiple organ failure, and septic postsurgical patients with multiple organ failure. The N70 peak latency was significantly correlated with the severity of illness but not with the presence or absence of sepsis. In postsurgical patients with multiple organ failure and superimposed sepsis, the N70 peak latencies were not further prolonged compared with postsurgical patients without sepsis.

Key Words: metabolic encephalopathy; multiple organ failure; sepsis; septic encephalopathy; sensory evoked potentials; peak latencies; critical illness; severity of illness; Acute Physiology and Chronic Health Evaluation III; Glasgow Coma Scale; intensive care.
Metabolic encephalopathy is a common finding in 12% to 33% of patients suffering from multiple organ failure (MOF), ranging from irritability to stupor and unresponsive coma (1, 2). The underlying mechanisms for the development of metabolic encephalopathy in these patients remain unknown in most of the cases. One of the most common reasons seems to be sepsis. However, the incidence of metabolic encephalopathy in sepsis (i.e., septic encephalopathy) depends on its definition and ranges from 9% to 71% of all admissions to an intensive care unit (ICU) (3-5). Nonetheless, metabolic encephalopathy is also occurring in nonseptic patients suffering from MOF (2, 6).

Recording of sensory evoked potentials (SEP) turned out to be very sensitive for the detection and the quantification of metabolic encephalopathy in various neurologic and metabolic disorders (7-10). Short-latency SEP represent the functional status of the central sensory pathway between the cervicomedullary junction (N13 peak) and the sensory cortex (N20 peak) (9). Long-latency SEP are generated by complex thalamocortical and cortical interactions representing widespread cortical function (10).

We, therefore, studied metabolic encephalopathy using an objective and non-invasive evoked potential method, to find out whether metabolic encephalopathy is more severe in septic patients with MOF compared with nonseptic postsurgical patients with MOF and whether metabolic encephalopathy is aggravated in postsurgical patients suffering from MOF, complicated by additional severe sepsis. In this prospective cohort analysis, we compared metabolic encephalopathy of three groups of patients with MOF: septic patients, nonseptic postsurgical patients, and septic postsurgical patients.

MATERIALS AND METHODS

The Institutional Review Board approved the recording of SEP in critically ill patients with multiple organ failure and waived the need for written informed consent.

We included 103 consecutive patients (40 females, 63 males; age, 58.2 ± 13 yrs) suffering from MOF as a result of sepsis, surgical procedures, or surgical procedures with subsequent sepsis. The definitions of organ system failure are based on previously published objective physiologic criteria (Table 1) (11). Additionally, hepatic failure was defined by an elevation of serum bilirubin ≥6 mg/dL and/or an elevation of the serum aspartate aminotransferase ≥50 U/L; gastrointestinal tract failure was defined by bleeding from stress ulcer necessitating transfusion of >2 units of blood per 24 hrs, necrotizing enterocolitis and/or pancreatitis, and/or spontaneous perforation of the gallbladder (12). MOF was defined as the presence of two or more organ system failures during the same day. Patients were further characterized by the length of ICU stay, mortality, the MOF score, and the Acute Physiology and Chronic Health Evaluation III (APACHE III) score (12, 13). Three different groups of critically ill patients were studied. Group A comprised patients who suffered from septic MOF, fulfilling the criteria for severe sepsis according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (14). Group B consisted of nonseptic patients, without any evidence of infection, who suffered from MOF caused by major abdominal, cardiac, or thoracic surgical procedures. In group C, patients were included fulfilling the post-surgical criteria stated for group B and developing MOF as a consequence of an occurred subsequent severe sepsis (14). SEP measurements of these patients were compared with 45 healthy controls, recruited out of the inhabitants of Vienna (age, 18-72 yrs).
All patients studied showed metabolic encephalopathy from the onset of trauma (i.e., sepsis or surgery) to the time of SEP measurement, presenting a Glasgow Coma Scale (GCS) score of $\leq 10$ (15). All patients included in the study revealed no neurologic disturbances (GCS = 15) before trauma and ICU admission. The neurologic conditions of all patients were screened at hospital admission. All patients with preexisting metabolic encephalopathy at hospital admission were excluded from the study to avoid the influence of preexisting metabolic encephalopathy on SEP peak latencies.

Metabolic encephalopathy was defined as a diffuse cerebral state characterized by disturbances of consciousness (ranging from stupor to coma; GCS $\leq 10$) in the absence of focal cerebral signs on clinical neurologic examination. Patients presenting with clinical signs of increased intracranial pressure like asymmetries of the pupillary size or pupils with no reactivity to light, comatose patients after blunt or penetrating head trauma, and patients with intracerebral lesions observed by a computed tomography scan were excluded, as well as patients with known epilepsy, episodes of resuscitation, severe hypotension (mean arterial pressure of $\leq 40$ mm Hg), bradycardia ($\leq 50$/min), and/or a severe respiratory disorder causing possible cerebral hypoxia ($n = 12$) before the recording of SEP.

Patients in the three different groups were evaluated on a daily basis concerning the inclusion criteria of severe sepsis and MOF. Patients belonging to groups B and C were evaluated not earlier than 24 hrs after admission to the ICU to avoid the influence of anesthesia. Metabolic encephalopathy was assessed by the measurement of SEP peak latencies. SEP measurements were done within the following 48 hrs after the patients met the inclusion criteria, resulting in a maximal time period of 72 hrs after the onset of MOF. Patients who developed MOF later than 72 hrs after the onset of severe sepsis or septic shock were excluded from the analysis ($n = 9$). SEP were measured $9 \pm 9$ days after ICU admission. Short-latency and long-latency SEP were recorded on a Nicolet Spirit (Madison, WI) with cup-shaped Ag/AgCl-sintered electrodes (Picker International, Munich, Germany). SEP were obtained by delivering an electrical stimulus transcutaneously to the median nerve at the left and right wrist to produce a minimum thumb twitch. Two sets of 700 (short-latency SEP) or 200 (long-latency SEP) responses were recorded in all patients. Electrical stimulation was delivered by a bipolar surface electrode with either 3.3 electrical impulses/sec (short-latency SEP) or 1.2/sec (long-latency SEP), with a duration of 0.2 msecs. Filter bandpass was 5-3000 Hz for short-latency and 1-1000 Hz for long-latency SEP. Electrodes were placed according to the international 10-20 system over the brachial plexus at the Erb point (N9 peak) to test the correctness of the input signal, C2 (N13 peak), and the somatosensory areas (N20 peak) contralateral to the side of stimulation. Active electrodes were referenced to the mid-frontal Fz electrode. Electrodes were attached by EC2 electrode cream (Grass Instruments, Quincy, Mass) after skin preparation to ensure an electrode impedance of $\leq 1.5 \, \text{k}\Omega$.

All results are presented as mean $\pm$ SD. For the comparison of gender distribution and mortality, the
chi-square test was used. For overall group comparison, we used the Kruskal-Wallis test. To detect significant differences among the individual groups, we used the two-sample Student's \( t \)-test for normally distributed data (age, APACHE III score, MOF score, N70 peak latency, temperature, blood urea nitrogen, and sodium) and the Mann-Whitney U test for data that were not normally distributed (GCS, day of measurement, length of ICU stay, remaining peak latencies, heart rate, respiratory frequency, \( \text{PaCO}_2 \), white blood cell count, systolic blood pressure, serum lactate, serum pH, glucose, creatinine, and bilirubin). For testing the relationship between SEP peak latencies and the severity of illness as assessed by the APACHE III score, the Spearman's rank-order correlation coefficient was calculated. A \( p < .05 \) was considered significant. Means of left-sided and right-sided evoked potential stimulation were used for calculation.

**RESULTS**

The mean duration of ICU stay of all patients was 24 ± 21 days, ICU mortality was 50.5%, the APACHE III score of all patients at ICU admission was 101 ± 24, and the average MOF score classifying the degree of organ failure was 7 ± 2.3 at the day of SEP measurement. Sixty patients (58%) were continuously sedated at the time of the study either by midazolam (3.6-50 mg/hr; \( n = 40 \)) combined with fentanyl (0.04-0.35 mg/hr; \( n = 34 \)) or sufentanyl (0.04-0.175 mg/hr; \( n = 5 \)), or buprenorphin (0.036-0.12 mg/hr; \( n = 15 \)) combined with flunitrazepam (0.24-0.64 mg/hr; \( n = 13 \)). Additionally, one patient was given sodium \( \gamma \)-hydroxybutyrate (600 mg/hr) and two patients were given ketamine (150-250 mg/hr) for sedation. Ninety-two patients (89%) were mechanically ventilated.

Fifty-six septic patients with MOF (group A), 29 nonseptic postsurgical patients with MOF (group B), and 18 septic postsurgical patients with MOF (group C) were studied. Further characteristics of patients are presented in Table 2 and Table 3.

Table 2. Characteristics of patients

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>MOF score</td>
<td>10</td>
<td>15</td>
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Table 3. Clinical and laboratory variables on day of the measurement of the sensory evoked potentials

Among septic patients (group A), 20 (36%) showed positive blood cultures (Gram-positive bacteria in 13, Gram-negative bacteria in six, fungemia in seven, and one patient being positive for mycobacterium tuberculosis). Twenty-one (38%) patients showed evidence of pulmonary infection, six (11%) patients presented with urinary tract infection, four (7%) patients showed an infection of the central venous catheter, two (4%) patients suffered from endocarditis, one (2%) patient suffered from meningitis, one (2%) patient suffered from an orchitis, and one (2%) patient suffered from an inflammation of an
infrarenal aneurysm of the aorta. Among postsurgical patients suffering from a subsequent additional sepsis (group C), six (33%) showed positive blood cultures (Gram-positive in three, and Gram-negative in three). Four (22%) patients showed evidence of pulmonary infection, one (6%) patient showed a urinary tract infection, one (6%) patient showed an infection of the central venous catheter, and six (33%) patients showed wound infections. Among patients belonging to group B, no positive blood cultures were detected.

Among nonseptic postsurgical patients (group B), 22 (76%) suffered from MOF as a consequence of cardiac or thoracic surgery and seven patients (24%) developed MOF as a consequence of extensive abdominal surgery. Of postsurgical patients with a subsequent sepsis (group C), ten patients (56%) developed MOF after cardiac or thoracic surgery and eight patients (44%) developed MOF as a consequence of extensive abdominal surgery (Table 4).

Table 4. Surgical procedures

All common peaks of standard SEP recording were detected in the patients studied. Peak latencies are shown in Table 5 and Fig. 1. No differences in the peak latencies were detectable among the three groups. All peak latencies found in the patients were significantly different compared with healthy controls (Table 5). Peak latencies were not statistically different in continuously sedated patients compared with nonsedated patients (Table 6). The increase of the delay of N70 peak latencies correlated significantly with the severity of illness, as assessed by the APACHE III score ($r^2 = .15$, $p < .00005$). A similar correlation could also be shown comparing the SEP peak latencies and the APACHE III scores of patients after their recovery before ICU discharge ($r^2 = .56$; $p < .005$).

Table 5. Sensory evoked potentials-Frontal (Fz) reference
Figure 1. Long-latency sensory evoked potentials (SEP) in septic patients (A), nonseptic postsurgical patients (B), and septic postsurgical patients (C). For patients, SEP recordings are superimposed.

Table 6. Sensory evoked potentials of continuously sedated patients vs. nonsedated patients: Frontal (Fz) reference

A comparison of the amplitudes of the N20 peaks and the N70 peaks revealed no significant differences among the different groups. Amplitudes of the N20 peaks for the patients of group A were 5.5 ± 7.4 V, for the patients of group B 4 ± 2.9 V, and for the patients of group C 4.6 ± 4.5 V. The amplitudes of the N70 peaks were 3.2 ± 5 V, 1.9 ± 1.9 V, and 1.9 ± 2 V, respectively.

DISCUSSION

This study shows no differences among evoked potential measurements of septic patients with MOF, nonseptic post-surgical patients with MOF, and septic postsurgical patients with MOF. The prolongation of the N70 SEP peak latencies was significantly correlated with the degree of severity of illness (as assessed by the APACHE III score) but not with the presence or absence of severe sepsis. The latter finding has not been shown before.

The development of metabolic encephalopathy may be the first manifestation of a critical systemic illness and may be caused by various reasons (1-6). One of the most important causes of metabolic encephalopathy seems to be sepsis (i.e., septic encephalopathy) (3-6, 16). Many origins have been suggested to be a cause of septic encephalopathy (16). However, clinical signs of septic encephalopathy are not different from encephalopathy caused by other metabolic disorders (1, 6, 17).

In the present study, metabolic encephalopathy was detected and quantified by a bedside available and noninvasive somatosensory evoked potential technique. SEP-elicited by median nerve stimulation-are very sensitive indicators for the evaluation of various metabolic brain disorders. Correct median nerve stimulation is proven by unequivocal detection of peaks generated in the brachial plexus (N9 peak) and cervical spine (N13 peak) after bilateral stimulation. Short-latency SEP reflect the function of the central sensory pathway between the cervicomedullary junction and sensory cortex (18). Long-latency SEP reflect widespread structural abnormalities and functional impairment of the cortex and are useful to indicate cerebral outcome (7-10). Correspondingly, abnormal SEP were found in septic patients (19).

All patients in our study showed a significant impairment of their brain function, confirmed by an increase of the peak latencies in the long-latency SEP compared with healthy controls. Short-latency SEP
peak latencies were also increased, indicating an additional impairment of the central sensory pathway. Statistical evaluation revealed a highly significant correlation between an increased N70 peak latency and an increasing APACHE III score, indicating a tight relation between a progressive impairment of the cortical function and an increase of the severity of critical illness of our patients. This finding indicates that the severity of illness and, therefore, the degree of organ failure rather than the presence or absence of sepsis and rather than the underlying disease may be the most important cause of the prolongation of the N70 peak latency in critically ill patients. This is in accordance with other authors, who found the grade of a septic encephalopathy depending on the severity of illness (16). Eidelmann et al. (16) found an increased APACHE II score associated with an increase of the grade of encephalopathy in septic patients. The severity of encephalopathy in septic patients also correlated well with the mortality rate (16). However, it is not only in septic patients that an increasing severity of illness is accompanied by an increase in the mortality rate (11, 12, 20). In our study, the severity of illness and the mortality rates were not different among the three groups of patients, although patients after surgery (group B) tended to have a lower mortality rate compared with patients in the other groups (groups A and C). This finding is in accordance with other authors (11).

Infection, sepsis, trauma, and surgery have been identified as common causes for the development of MOF (21, 22). Head trauma patients may suffer from direct brain damage as a result of injury (23). In these particular patients, it may not be possible to estimate the degree of a metabolic encephalopathy. Therefore, head trauma patients were excluded from our study. Another well-established cause of MOF may be the artificial trauma of major surgical procedures. All postsurgical patients included in our study required treatment at the ICU. To exclude further causes of metabolic encephalopathy, only patients without resuscitation and/or episodes of hypotension before the SEP measurement were involved. Furthermore, no significant differences in serum glucose, serum bilirubin, serum creatinine, blood urea nitrogen, and serum sodium were detectable among the groups. Increasing serum levels of these laboratory variables were not significantly correlated with an increase of the peak latencies (data not shown). Thus, the degree of the prolongation of the N70 peak latency detected in our study was obviously caused by MOF, whereas MOF was caused by sepsis, surgery, or both. Based on our SEP findings, one may consider that septic encephalopathy is not a discrete entity. However, further studies concerning septic encephalopathy are mandatory to prove this presumption.

A possible limitation of this analysis may be the use of continuous sedation in our patients. Obviously, all regimens of standard sedation may cause a mild prolongation of the N70 peak latencies. Therefore, a continuous sedation therapy may mask differences of peak latencies among the different groups. However, previous studies demonstrated that the predictive ability of short-latency as well as long-latency SEP peak latencies was not affected by the use of intravenously administrated sedatives (7-10). Moreover, it was shown that peak latencies and amplitudes of short-latency SEP remain unaffected by sedation (24). Short-latency SEP can be recorded unchanged from patients whose electroencephalogram has been rendered flat during high-dose barbiturate therapy (25). These previous findings are confirmed by our results, demonstrating no significant differences for SEP peak latencies between patients sedated by our standard sedation regimen (i.e., midazolam combined with fentanyl or sufentanyl, or buprenorphin combined with flunitrazepam; patients with a continuous sedation with propofol have been excluded from further evaluation) and nonsedated patients.
CONCLUSIONS

We demonstrated in a representative series of critically ill patients with MOF caused by septic and nonseptic disorders that there was no difference in sensory evoked potential measurements detectable among septic patients with MOF, nonseptic postsurgical patients with MOF, and septic postsurgical patients with MOF. The prolongation of the N70 peak latency was significantly correlated with the severity of illness but not with the presence or absence of sepsis. Moreover, in postsurgical patients with superimposed sepsis, the N70 peak latencies were not further prolonged compared with postsurgical patients without sepsis.

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REFERENCES [Click here for reference links. (19 references linked.)]


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