

## Effect of Hypothermia on Visual Evoked Potentials (VEP) in Humans

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Moderate and deep hypothermia often are utilized in cardiovascular surgery. Studies of the resulting physiologic changes have led to the development of monitoring techniques for patients undergoing these hypothermic procedures. Cerebral perfusion may be reduced deliberately or accidentally during such surgery. The only means of detecting a decrease in cerebral function is by some form of direct and continuous monitoring of the functional state of the brain.<sup>1</sup> Most efforts to monitor brain function in the operating room have employed electroencephalography, often with a computerized form like the cerebral function monitor (CFM),<sup>2</sup> augmented delta quotient monitor (ADQ-monitor),<sup>3</sup> or the compressed spectral array (CSA).<sup>4</sup> There are a number of conflicting reports of the effects of hypothermia on the EEG.<sup>5-7</sup> Recently evoked cortical potentials as a noninvasive monitor of the brain were used.<sup>8</sup> Evoked potentials are an objective measure of cerebral function and integrity. They depend on the integrity of cerebral blood flow.<sup>9</sup> Reilly and co-workers<sup>10</sup> reported on visual evoked potentials (VEPs) during hypothermia in 1978: Evoked potentials tend to become smaller with decreasing temperature. Brain-stem auditory evoked responses (BAERs) were investigated by Stockard *et al.*<sup>11</sup> at definite steady state temperatures. Until now systematic evaluation of the effects of hypothermia on VEPs have been limited to animal studies. In humans only sporadic cases have been described.

## PATIENTS AND METHODS

Forty-three patients with a mean age of  $52.9 \pm 5.6$  yr gave informed consent to be studied. Patients with preexisting psychiatric, neurologic, or visual deficits were excluded. The planned surgical procedure was coronary artery bypass grafting. First the patients were premedi-

cated with 0.02 mg/kg flunitrazepam im 60 min before induction of anesthesia. Systemic and pulmonary arterial and peripheral venous lines were established, and electrocardiographic monitoring was initiated prior to induction of anesthesia. Induction of anesthesia was accomplished with 10  $\mu\text{g}/\text{kg}$  fentanyl and 200  $\mu\text{g}/\text{kg}$  etomidate iv. The patients breathed 100% oxygen through a semi-closed system. Intubation was facilitated with 100  $\mu\text{g}/\text{kg}$  pancuronium bromide. Ventilation was controlled with 50% nitrous oxide in oxygen to maintain a  $\text{PaCO}_2$  between 35 and 40 mmHg. When additional doses of fentanyl (20  $\mu\text{g}/\text{kg}$ ) and flunitrazepam 30  $\mu\text{g}/\text{kg}$  failed to ablate hemodynamic responses to skin incision, a nitroglycerin infusion was begun. Additional doses of 20  $\mu\text{g}/\text{kg}$  fentanyl were given prior to sternotomy. Neuromuscular blockade was maintained by repeated doses of pancuronium bromide. The management of extracorporeal circulation (ECC) was standardized with a pump-flow of  $2.4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . Arterial pressure during ECC was kept between 50–100 mmHg, with a perfusion pressure ( $p_{\text{art}}-p_{\text{ven}}$ ) always above 40 mmHg. Arterial pressure and nasopharyngeal temperature were recorded and monitored continuously. The nasopharyngeal thermistor was placed above the soft palate in the nasopharynx. VEPs were elicited with biocular flashes (rate 1.1/s,  $\lambda = 630$  nm) by means of the NIC 107 LED eyepiece through the closed eyelids. Evoked potentials were recorded bipolar from scalp electrodes  $\text{O}_z$  and  $\text{C}_z$ ,<sup>12</sup> with one of the mastoids as a ground. Interelectrode impedance was less than 1 K $\Omega$ . Electrical activity was preamplified and the evoked responses were recorded after 100 computer averages (filter settings 1–100 Hz, sensitivity 50  $\mu\text{V}$ ). Latencies of the major negative ( $n_2$ ) and positive ( $p_2$ ) peak were measured with a special cursor. Nomenclature and further information with respect to the method may be taken from the literature.<sup>13,14</sup>

Patients with difficult peak identification were excluded from the study. Recordings were made during steady state opiate analgesia: first at 35° C, then at different temperature levels during cooling (31° C, 29° C, 27° C, 25° C), then during rewarming (27° C, 29° C, 31° C, 33° C, 38° C), and finally 1 h after ECC. The rapidity of cooling (° C/min) was measured for each patient. In order to ascertain that evoked responses were related to the visual stimulus and not to artifacts, a control was done. The eyepieces were removed from the patients, while computer averaging, synchronized with the flash,

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TABLE 1. Latencies of the Major Negative ( $n_2$ ) and Positive ( $p_2$ ) Peak

Temperature (°C)	Mean latency (ms) of $n_2$			Mean latency (ms) of $p_2$		
	Mean	SD	%	Mean	SD	%
Before ECC						
35	97.1	8.0	100	121.0	10.0	100
Cooling						
31	119.6*	9.2	123	146.4*	13.4	121
29	134.7*	12.8	139	166.7*	17.9	138
27	148.5*	15.8	153	192.4*	26.5	159
25	184.1*	27.0	189	235.5*	49.8	195
Rewarming						
27	128.7*	12.8	133	163.1*	11.9	135
29	120.0*	14.0	124	149.8*	15.0	124
31	108.9*	11.5	112	134.7*	14.2	111
33	99.2	10.8	102	120.5	14.2	100
38	87.5*	9.4	90	106.4*	9.7	88
1 h after ECC						
36	91.2†	8.4	94	111.8*	10.4	92.4

\*  $P < 0.001$ .†  $P < 0.01$ .

continued. The components  $n_2$  and  $p_2$  immediately disappeared after removal.

Statistical evaluation was done with an analysis of variance and covariance including repeated measures for temperature as the independent variable.<sup>15</sup> In order to compare the values at 35° C with 29° C, 27° C, and 25° C, a Student's  $t$  test for paired samples was performed;  $P < 0.01$  was regarded significant.

### RESULTS

Four patients (10.2%) had to be excluded because of difficulties in identifying peaks. From the remaining 39 patients mean latencies of  $n_2$  and  $p_2$  at different temperatures are listed in table 1. Typical changes in VEPs associated with cooling and rewarming are shown in figure 1. With decreasing temperature the latencies of the major negative and the positive component of the VEP increased continuously. Changes in latencies were significant for  $n_2$ :  $F = 106.9$  ( $P = 0.001$ ) and for  $p_2$ :  $F = 47.6$  ( $P = 0.001$ ). Each of the hypothermic values was significantly different from the control values. At 31° C during cooling, depression of afterdischarge occurred (figs. 1 and 2). During ECC, nasopharyngeal temperature decreased continuously at an average rate of  $0.36^\circ \text{C} \pm 0.13^\circ \text{C}/\text{min}$ . Depending on the rapidity of cooling, visual evoked potentials disappeared at different temperature levels. At a cooling rate of  $0.6^\circ \text{C}/\text{min}$ , VEPs disappeared at 27° C (fig. 1), while at a cooling rate of  $0.25^\circ \text{C}/\text{min}$ , VEPs disappeared at 25° C or less. During rewarming an im-

mediate recovery of latencies was demonstrated (fig. 1). At 33° C during rewarming the pre-ECC values were reached again. With decreasing temperature, standard deviations of  $n_2$  and  $p_2$  became larger. This indicated that identification of peaks was sometimes difficult at lower temperatures, especially when cooling was fast.

### DISCUSSION

The occipital VEP generally consists of five or more identifiable peaks and a group of waves appearing later than 250 ms after stimulus onset. The latter is known as the rhythmic afterdischarge (fig. 2). In awake healthy adult patients, the normal values for the latencies of these peaks are in the range of 70–120 ms for  $n_2$  and 95–155 ms for  $p_2$ .<sup>16</sup> The latencies for our patients at normothermia after induction of anesthesia ( $n_2 = 97.1 \text{ ms} \pm 8.0 \text{ ms}$ ,  $p_2 = 121 \text{ ms} \pm 10.0 \text{ ms}$ ) were in accordance with

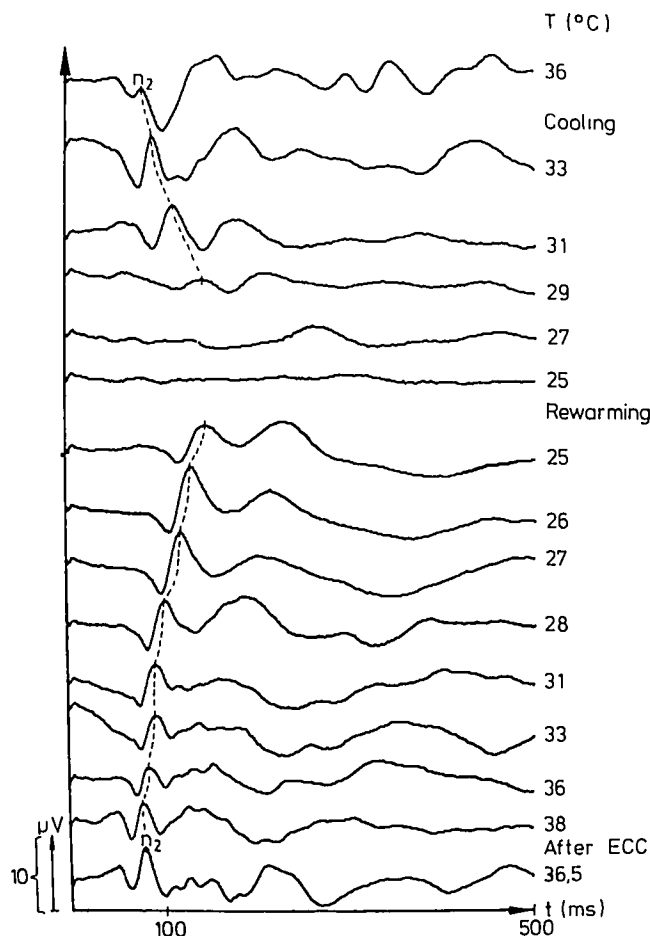


FIG. 1. The visual evoked potential disappears at 27° C in a patient, where cooling was rapid ( $0.6^\circ \text{C}/\text{min}$ );  $n_2$  is marked with a dotted line. During rewarming the recovery of latency is demonstrated.

these results. In patients not anesthetized, VEPs appear earlier.<sup>17</sup> Neuroleptanalgesia causes a latency increase of about 12%.<sup>18</sup> The appearance of  $n_2$  and  $p_2$  depends on the integrity of the afferent visual pathways and the occipital lobe. Results in experimental local cooling<sup>19</sup> of defined brain structures suggest that  $p_2$  might originate from the extrageniculocortical system.  $P_2$  then is transformed at the superior colliculus, while the lateral geniculate body is responsible for the onset  $p_1$ . In our study, VEPs were recorded at different temperature levels during systemic cooling and rewarming. The reported changes of visual evoked responses were due to temperature changes and correlate well with literature findings.<sup>20</sup> Perfusion pressure was kept constant,  $Pa_{O_2}$  and  $Pa_{CO_2}$  were in the normal range. Hemodilution did not alter the results of our studies.

After the onset of ECC, a decrease in hematocrit occurred due to isovolemic hemodilution caused by the bloodless priming volume of the heart-lung machine.

Nagoa and colleagues<sup>21</sup> described a gradual amplitude increase until the hematocrit decreased to 20%. At hematocrits in the range of 10–15%, they found a latency increase of the evoked responses. In our patients hematocrit was kept between 20 and 25%, so that the effect of hemodilution could be ignored. The amplitude of VEPs was not statistically analyzed because of its large inter-individual variability.<sup>18</sup> Peak to peak amplitude tends to become smaller during hypothermia.

During rewarming, latencies become shorter even before a measurable change in temperature was observed (fig. 1, two recordings at 25°C). Latency return during rewarming is almost instantaneous. This probably can be explained by the characteristics of nasopharyngeal temperature recording. This temperature is relatively insensitive as far as reflecting rapid temperature changes.<sup>22</sup> During the rewarming phase the actual brain temperatures probably were greater than those measured by the nasopharyngeal thermistor. Reilly<sup>10</sup> reported on VEPs during hypothermia in children. After rewarming, the latencies were shorter than before the initiation of cooling. We used nasopharyngeal temperature because of its widespread use in similar clinical investigations.<sup>7,10,23</sup> With steady state temperatures, the nasopharyngeal temperature correlates well with directly recorded brain temperatures. For example at a depth of 4 cm, the maximum variations of the local brain temperature and the nasopharyngeal temperature are in the range of 0.35° C–0.90° C.<sup>24</sup>

For each temperature the normal range for latencies of the VEP ( $\bar{x} \pm 2$  SD) must be determined. If the latency falls outside this range for a certain time, this must be considered pathologic. Diffuse or localized brain damage

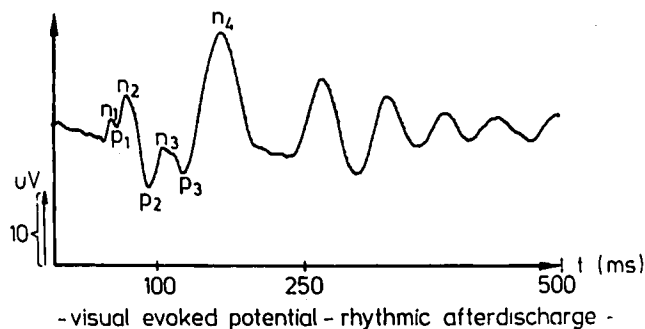


FIG. 2. VEP recording in an adult, awake patient. The visual evoked potential with its components and rhythmic afterdischarge can be seen.

may be the reason. At the present time it is not possible to describe patterns of evoked responses that correlate with impaired cerebral function and neurologic deficits postoperatively.

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## Epidural Morphine Analgesia in Children

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Epidural blockade in children has not received wide acceptance as a mode of anesthesia and analgesia. Successful postoperative analgesia with epidural blockade in the pediatric age group has been achieved by Russian clinicians.<sup>1-3</sup> In a series of 220 pediatric patients, Parnes *et al.*<sup>2</sup> found epidural injection easy to perform and observed an improvement in respiratory and cardiac function postoperatively.<sup>2</sup> Recently Katzenelson *et al.*<sup>§</sup> described similar experiences with caudal opiates in children. No reports have been published describing lumbar or thoracic epidural narcotic analgesia in children. We describe five children who received thoracic epidural morphine for analgesia after surgery and trauma.

### REPORT OF FIVE CASES

Five children, aged between 3 and 11 years, were admitted to the Intensive Care Unit (ICU) with thoracic epidural catheters in place for analgesia. Four of them had thoracic surgery, with the epidural catheters inserted at the end of surgery while still receiving general anesthesia (table 1). The fifth patient, a child with multiple trauma, which included flail chest, pneumothorax, and fractures of the humerus and femur, was admitted to the ICU after having undergone a laparotomy for a ruptured spleen. Ventilation was controlled for the first 6 h after surgery, after which his trachea was extubated and an epidural catheter was inserted under local analgesia. The four postthoracotomy patients breathed satisfactorily at the end of surgery, their tracheas extubated, and they received oxygen ( $F_{I_{O_2}} = 0.4$ ) via a mask for 3 h.

Morphine 1.0-2.0 mg diluted in 5 ml normal saline was injected into the thoracic epidural space (table 2). Every hour the children were instructed to cough, take several deep breaths, and lift their legs off the bed where possible. They were asked if they had pain, and when pain was confirmed, whether they wanted to be relieved of the pain. Additional doses of morphine thus were administered at the request of the patient. We found this method simple to use, all five children including the youngest being cooperative. Because of being in the ICU, we were able to inject the morphine epidurally as soon as pain returned and document the duration of analgesia. The three children under seven years of age received 1.0 mg in 5 ml of saline, while the 8-year-old was given 1.5 mg and the 11-year-old 2 mg in 5 ml saline. The analgesia following the initial dose of morphine lasted between 8 and 25 h (table 2). Additional doses of morphine in the three older children were the same as the initial dose. However, in the first patient, a 3-year-old child, we decreased the subsequent dose

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