EFFECTS OF HYPOTHERMIA ON SOMATOSENSORY EVOKED RESPONSES IN MAN

W. RUSS, J. STICHER, H. SCHELD AND G. HEMPELMANN

Inadequate cerebral perfusion is a recognized hazard of cardiopulmonary bypass (CPB). Brain dysfunction may vary from slight neuropsychological disability to complete infarction of a hemisphere and contribute to the overall morbidity following CPB (Kolkka and Hilbermann, 1980; Savageau et al., 1982).

Advances in the monitoring of haemodynamic and respiratory variables have led to improvements in the management of patients undergoing open-heart surgery and increased the margins of safety. Monitoring of cerebral function, on the other hand, is not used routinely, despite recent advances in computer technology.

Various methods of computerized electroencephalography have been proposed; most have been reviewed by Levy and co-workers (Levy et al., 1980; Levy, 1984a, b). Despite computerized data reduction, interpretation of the different EEG descriptors such as spectral edge frequency (Homer and Stanski, 1985), peak power frequency or median power, remains difficult, especially under the influence of anaesthetic agents and hypothermia (Levy, 1984a).

Recording of evoked potentials is used widely as a neurophysiological means of investigating peripheral and lemniscal pathways up to the sensory cortex (Chiappa and Ropper, 1982a, b). Considering the distribution of the cortical evoked potentials for visual, auditory (Kileny, Dobson and Gelfand, 1983; Thornton et al., 1986) and somatosensory stimulation, much of the cortical surface is available for monitoring. Evoked potentials, particularly those of short latency, like the brain stem auditory evoked potential (BAEP) and the short-latency somatosensory evoked potential after median nerve stimulation (SEP), provide information about cerebral function even when the EEG is completely suppressed by anaesthetic agents (Newlon et al., 1983; Drummond, Todd and U, 1985).

SUMMARY

Somatosensory evoked responses after median nerve stimulation were recorded in 21 patients during hypothermic cardiopulmonary bypass. During hypothermia a significant linear correlation (P < 0.001) was found between evoked potential latency and temperature. Correlation was best for tympanic membrane temperature during cooling and for perfusate temperature (arterial, venous) during rewarming. The increase in latency was more pronounced for middle latency components \( N_2, N_3 \) and for the early cortical \( N_1 \) than for the cervical \( N_0 \) and central conduction time. In all patients \( N_1 \) was detectable at 26°C, with slightly reduced amplitude. In the rewarming period the changes occurred in the reverse order and pre-bypass values were achieved at normothermia. The slopes of the regression lines were different during cooling and rewarming, when latencies were related to patient (tympanic, nasopharyngeal, rectal) temperature, but identical when arterial or venous blood temperature was used as the reference. No correlation was found between latency and perfusion pressure. We conclude that sophisticated temperature measurement is required to aid the interpretation of evoked responses used during hypothermia.
The original waveforms are present, with delayed latency, during hypothermia, depending on the type of potential used. However, the effect of hypothermia has to be established in a quantitative manner, and the temperatures to which the EP-variables should be related during hypothermia have yet to be defined under clinical conditions. The study presented contributes to these basic considerations for EP monitoring during hypothermic cardiac surgery and describes the correlation of different variables of the median nerve SEP with temperature.

PATIENTS AND METHODS

Twenty-one patients (19 male) aged 51—69 yr (mean 58 yr) undergoing coronary artery bypass grafting gave informed consent. Ethics committee approval was obtained.

Patients were premedicated with morphine 10 mg and flunitrazepam 0.02 mg kg⁻¹ given i.m. 60 min before the induction of anaesthesia. Central and peripheral venous and arterial cannulae were placed and electrocardiographic monitoring was initiated before the induction of anaesthesia. After induction with etomidate, anaesthesia was maintained with fentanyl 50 µg kg⁻¹ and flunitrazepam 30 µg kg⁻¹. Neuromuscular blockade was achieved with repeated doses of pancuronium. Management of extracorporeal circulation (ECC) was standardized with a pump flow of 2.4 litre min⁻¹ m⁻². Arterial pressure during ECC was kept between 50 and 100 mm Hg, with a perfusion pressure (P_an — P_ven) always greater than 40 mm Hg. Oxygenation was performed with a Travenol bubble oxygenator and controlled by repeated blood-gas analyses. For evaluation of temperature, temperatures in the venous (t_ven) and arterial line (t_an) of the oxygenator, and rectal (t_rec), nasopharyngeal (t_no) and tympanic membrane temperatures (t_ly) were recorded continuously with special thermistor probes (Yellow Springs Instrument Co., Yellow Springs, Ohio 45387). The technique of SEP monitoring has been described elsewhere for carotid endarterectomy (Russ and Fraedrich, 1984; Russ et al., 1985).

The median nerve was stimulated at the wrist by means of surface electrodes with a constant current of 19.9 mA, a duration of 0.2 ms and a frequency of 3.1 Hz. Recording electrodes were placed above the second spinous process C₂ and above the contralateral cortex C₃′, both referred to Fz. The ground electrode was placed near the elbow of the stimulated arm. Two hundred and fifty-six stimuli were averaged with the Nicolet CA 1000 system after amplification (10000) and filtering (30—1500 Hz). The cervical and cortical SEP were recorded simultaneously. Latencies of N14 (Nₒ), N20 (N₁) and of subsequent cortical peaks (N₂, N₃) were measured, as well as the peak-to-peak amplitudes. Central conduction time (CCT) (the interpeak latency between the primary cortical (N₁) and the cervical SEP (Nₒ)) was calculated.

In each patient, evoked responses were measured on at least 30 occasions—after the induction of anaesthesia, during the surgical procedure, and during cooling and rewarming on CPB until the patient was transferred to the intensive care unit. Other physiological variables such as arterial pressure and temperature were recorded at the time of SEP analysis.

For statistical evaluation the Kolmogoroff-Smirnow goodness of fit test, variance and covariance techniques for repeated measures were performed. To provide independency of the data, a computer randomly selected, from each patient, the variables from two measurements—one from the first record to the time when cooling was stopped by adjustment of the heat exchanger.
The electrical responses of the somatosensory system during hypothermia were very reproducible. As temperature decreased, the latencies of the cervical and cortical SEP increased. The increases were more pronounced for the later cortical peaks \( N_2 \) and \( N_3 \) than for the specific \( N_1 \) and the cervical \( N_0 \) (figs 1, 2).

### RESULTS

The data fitted best to a linear regression line. Table I summarizes the slopes, intercepts and coefficients of correlation for SEP variables and tympanic membrane temperature during cooling. The best correlation was observed, when tympanic membrane or nasopharyngeal temperatures were used as references (table II).

The amplitudes of the primary cortical SEP showed considerable inter-individual variability, but with the onset of CPB \( N_1P_1 \) increased from 2.7 \( \mu \)V to 4.0 \( \mu \)V, and showed a tendency to decrease with decreasing temperature: 15 min after initiation of CPB \( N_1P_1 \) was significantly different from the values obtained 3 min after onset of CPB (\( P = 0.05 \) (table III, fig. 2).

\( t_\text{ry} \) was reduced at a rate of about 0.5 \( ^\circ \)C min\(^{-1}\), and 15 or 20 min after start of CPB the temperature in the in-line heat exchanger was adjusted to a higher value to establish a steady state temperature. Body temperatures (\( t_\text{ry} \), \( t_\text{tp} \), \( t_\text{rec} \)) characteristically lagged behind the temperatures of the arterial and venous blood. SEP latencies as well as CCT decreased and \( N_1P_1 \) increased instantaneously with increasing blood temperatures, while patients’ temperatures were still decreasing (table III, fig. 2). All of the changes described above occurred in reverse order during the rewarming period, with some characteristic differences. From the time when active cooling was stopped (by adjustment of the heat exchanger) to the end of the operation, SEP latencies showed a linear correlation with all temperatures, but the coefficient of correlation was best for the extra-corporeal temperatures and worst for rectal

### TABLE I. Regression analysis of SEP variables and tympanic membrane temperature during cooling on cardiopulmonary bypass. Slope, intercept and correlation coefficient \( r \) are listed for latencies. Significance of \( r \) is \( P < 0.001 \)

<table>
<thead>
<tr>
<th>SEP latency (ms)</th>
<th>Slope</th>
<th>Intercept</th>
<th>( r )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N_0 )</td>
<td>-0.9</td>
<td>45.8</td>
<td>-0.92</td>
</tr>
<tr>
<td>( P_0 )</td>
<td>-1.1</td>
<td>58.1</td>
<td>-0.93</td>
</tr>
<tr>
<td>( N_1 )</td>
<td>-1.7</td>
<td>82.6</td>
<td>-0.96</td>
</tr>
<tr>
<td>( P_1 )</td>
<td>-2.2</td>
<td>103.3</td>
<td>-0.91</td>
</tr>
<tr>
<td>( N_2 )</td>
<td>-2.4</td>
<td>110.0</td>
<td>-0.87</td>
</tr>
<tr>
<td>( P_2 )</td>
<td>-2.6</td>
<td>120.5</td>
<td>-0.90</td>
</tr>
<tr>
<td>( N_3 )</td>
<td>-2.8</td>
<td>134.6</td>
<td>-0.88</td>
</tr>
<tr>
<td>( P_3 )</td>
<td>-2.8</td>
<td>154.7</td>
<td>-0.84</td>
</tr>
<tr>
<td>CCT</td>
<td>-0.9</td>
<td>36.4</td>
<td>-0.97</td>
</tr>
</tbody>
</table>

The amplitudes of the primary cortical SEP showed considerable inter-individual variability, but with the onset of CPB \( N_1P_1 \) increased from 2.7 \( \mu \)V to 4.0 \( \mu \)V, and showed a tendency to decrease with decreasing temperature: 15 min after initiation of CPB \( N_1P_1 \) was significantly different from the values obtained 3 min after onset of CPB (\( P = 0.05 \) (table III, fig. 2).

\( t_\text{ry} \) was reduced at a rate of about 0.5 \( ^\circ \)C min\(^{-1}\), and 15 or 20 min after start of CPB the temperature in the in-line heat exchanger was adjusted to a higher value to establish a steady state temperature. Body temperatures (\( t_\text{ry} \), \( t_\text{tp} \), \( t_\text{rec} \)) characteristically lagged behind the temperatures of the arterial and venous blood. SEP latencies as well as CCT decreased and \( N_1P_1 \) increased instantaneously with increasing blood temperatures, while patients’ temperatures were still decreasing (table III, fig. 2). All of the changes described above occurred in reverse order during the rewarming period, with some characteristic differences. From the time when active cooling was stopped (by adjustment of the heat exchanger) to the end of the operation, SEP latencies showed a linear correlation with all temperatures, but the coefficient of correlation was best for the extra-corporeal temperatures and worst for rectal

### TABLE II. Correlation coefficient (\( r \)) between different temperatures and SEP values during cooling and rewarming on CPB. Significance of values: *** \( P \leq 0.001 \); † \( 0.01 \leq P < 0.001 \); § \( 0.05 \leq P < 0.01 \); ‡ \( P > 0.05 \)

<table>
<thead>
<tr>
<th>SEP latency</th>
<th>Cooling</th>
<th>Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( t_\text{op} )</td>
<td>( t_\text{ry} )</td>
</tr>
<tr>
<td>( N_0 )</td>
<td>-0.947</td>
<td>-0.974</td>
</tr>
<tr>
<td>( P_0 )</td>
<td>-0.954</td>
<td>-0.957</td>
</tr>
<tr>
<td>( N_1 )</td>
<td>-0.926</td>
<td>-0.919</td>
</tr>
<tr>
<td>( P_1 )</td>
<td>0.275</td>
<td>0.172</td>
</tr>
<tr>
<td>( N_2 )</td>
<td>-0.865</td>
<td>-0.918</td>
</tr>
<tr>
<td>( P_2 )</td>
<td>-0.90</td>
<td>-0.938</td>
</tr>
<tr>
<td>( N_3 )</td>
<td>0.577</td>
<td>0.444</td>
</tr>
<tr>
<td>( P_3 )</td>
<td>†</td>
<td>‡</td>
</tr>
</tbody>
</table>
FIG. 2. Somatosensory evoked responses (SEP) after median nerve stimulation in a 53-yr-old man undergoing open heart surgery with cardiopulmonary bypass. Negativity of C₆ or C₇ is presented as an upward deflection. The cervical (N₀) SEP is placed in the left, the cortical (N₁, N₂, N₃) in the right part of the figure. In the upper tracings, after sternotomy, CCT is 6.6 ms and tympanic membrane temperature (Tₘ) 35.4 °C. With the onset of CPB, CCT and amplitude of N₁ increase. At the end of cooling later cortical peaks (N₃) tend to disappear and the amplitude of N₁ decreases slightly. At the beginning of rewarming, Tₘ is still decreasing, latencies decrease and amplitudes increase. With increasing temperatures, latencies decrease further and pre-CPB values are achieved at normothermia. Tₘ lags behind arterial blood temperature during the whole recording period. During hypothermia a splitting of the cervical SEP into its subcomponents becomes apparent; this phenomenon disappears with normothermia.
TABLE III. Central conduction time (CCT), amplitude of the primary cortical SEP (N1P1), tympanic membrane temperature (t0) and perfusion pressure immediately before and at intervals after onset of cardiopulmonary bypass. Means±SD. Significant differences (P < 0.05): *v. pre-CPB; †v. preceding value

<table>
<thead>
<tr>
<th>Before bypass</th>
<th>3 min of CPB</th>
<th>10 min of CPB</th>
<th>15 min of CPB</th>
<th>20 min of CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT (ms)</td>
<td>6.6±0.6</td>
<td>7.0±2.0</td>
<td>10.6±2.0*</td>
<td>13.5±2.1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13.5±2.1*</td>
<td>13.2±2.5*</td>
</tr>
<tr>
<td>N1P1 (µV)</td>
<td>2.7±1.2</td>
<td>4.0±2.3</td>
<td>3.0±1.8</td>
<td>2.1±1.3†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27.6±1.8*</td>
<td>25.8±1.0*</td>
</tr>
<tr>
<td>t0 (°C)</td>
<td>34.7±0.7</td>
<td>34.4±0.7</td>
<td>31.0±1.6*</td>
<td>27.6±1.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>58±11*</td>
<td>54±11*</td>
</tr>
<tr>
<td>Perfusion pressure (mm Hg)</td>
<td>82±17</td>
<td>47±15*†</td>
<td>47±15*†</td>
<td>62±19</td>
</tr>
</tbody>
</table>

DISCUSSION

The intraoperative monitoring of somatosensory evoked responses provides a quantitative measure of neural transmission in peripheral and central pathways. N0 represents the activity of the afferent volley as it ascends the spinal cord and is generated by the dorsal column nuclei. The thalamocortical response to median nerve stimulation is represented by N1, the specific cortical SEP, which is assumed to originate in Brodman’s area 1. N2 and N3 represent activities of somatosensory association fields with a widespread hemispheric distribution (Allison et al., 1980; Desmedt and Cheron, 1980).

SEP were selected as a monitor since they have been shown (Branston et al., 1974) to be sensitive indicators of critically reduced regional cerebral blood flow (rCBF). The early component N1 is topographically specific, and central conduction time (CCT), the interpeak latency between N1 and N0, reflects conduction through the lemniscal and thalamic system. Animal studies have shown that the degree of ischaemia necessary to cause disappearance of the EP is less than that necessary for permanent neurological damage (Astrup et al., 1977). This suggests that recognition of alterations in SEP may allow restoration of flow by adequate therapeutic measures before the onset of permanent damage—a concept that has been introduced successfully during carotid reconstructive surgery by means of intraoperative SEP monitoring (Russ and Fraedrich, 1984; Russ et al., 1985). Branston and others (1974) showed that, following middle cerebral artery occlusion (fig. 2). The postoperative course of the patients was uneventful and there was no clinical evidence of cerebral impairment.
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baboons, EP were not affected in areas with an rCBF > 16 ml min⁻¹/100 g; however, when it decreased to less than 12 ml min⁻¹/100 g, EP disappeared; between these two margins SEP amplitude was flow dependent. During hypothermic CPB the effects of temperature on EP have to be considered.

It has been shown in a variety of experimental conditions that, when body temperature is decreased, the electrical output of the system is altered (Brooks, Koizumi and Malcolm, 1955; Cohn and Rosomoff, 1958; Barker and Carpenter, 1970; Weight and Erulkar, 1976). In the present study a progressive diminution in the responsiveness of the somatosensory system was seen and the effects of reduced temperature on peripheral conduction (N₂), central conduction (CCT) and on oligo- and polysynaptic transmission (N₁, N₂, N₃) can be separated. Peripheral and central conduction are delayed to the same extent, expressed by nearly identical slopes for N₂ (-0.87) and CCT (-0.85). The more profound increase in the early cortical N₁ is caused by an additional suppression of synaptic transmission in the lemniscal–thalamic pathway. The later cortical SEP components (N₂, N₃) are slowed to a greater extent since an increasing number of synapses is involved in the generation of these peaks. The physiological principles of these effects were described by Suda, Koizumi and Brooks (1957) and Budnick, McKeown and Wiederholt (1981). Prolonged latencies of potentials from pre-synaptic structures were the result of slowed conduction velocity; potentials from structures with interposed synapses showed a more pronounced delay of latency.

N₂ and N₃ disappeared earlier during cooling, whereas N₀ and N₁ were present in all patients at tympanic membrane temperatures of 26 °C. Mean cortical amplitude was greater than 1.5 μV at this time.

Suda, Koizumi and Brooks (1957) described a diminution of the reflex response in the single afferent fibre of the dorsal column: action potentials from such single units showed an increase in duration and a delayed recovery of normal excitability. Stimulus frequency may, therefore, become an important factor during hypothermia: attenuation of amplitudes increased with stimulus frequency in animal experiments (Budnick, McKeown and Wiederholt, 1981) and during halothane anaesthesia (Gravenstein, Sasse and Hogan, 1984).

One hundred and twenty-eight averages are sufficient to produce a stable waveform, especially when background EEG activity is reduced. A frequency of 2-3 Hz may be the frequency of choice and SEP monitoring can be performed at 1-min intervals. This precludes detection of very short-lived changes. It was found that a phase of hyperresponsiveness did develop after the onset of CPB. This increase in magnitude of the N₁P₁ amplitude became apparent 2–3 min after the initiation of CPB at a temperature of 34.4 °C and persisted until temperature decreased below 31 °C. This increase, however, did not reach statistical significance because of great inter-individual variability in the amplitudes. At the onset of CPB many factors may have an influence on brain electrical activity: flow changes from pulsatile to non-pulsatile, arterial pressure decreases and there is acute haemodilution. The increase in N₁P₁ amplitude is related most probably to the reduction in haematocrit. Comparable results were found by Nagoa, Roccaforte and Moody (1978) during isovolaemic haemodilution. An increase in VEP- and SEP-amplitude was seen when haematocrit was decreased from 40 to 20 %.

The independence of perfusion pressure and SEP-variables indicates that the perfusion regimen was safe; a perfusion pressure of 40–50 mm Hg, together with an appropriate flow are tolerated well during hypothermia; Aren and colleagues (1985) reported on somatosensory evoked responses and cerebral metabolism during cardiopulmonary bypass. Although, in a subgroup of patients, perfusion pressure was decreased to 30 mm Hg, alterations in the metabolic demand of the brain and central conduction time were not more compromised than in a control group with a considerably higher perfusion pressure.

Although tympanic membrane temperature is thought to be the best approximation of cranial core temperature (Benzinger, 1969; Davis, Parmelazhagan and Harris, 1977; Ilsley, Rutten and Runciman, 1983; Cork, Vaughan and Humphrey, 1983) this temperature lags behind brain temperature, especially in a system in which temperature changes rapidly with resulting temperature gradients. This was demonstrated at the end of the cooling period: t₁y and t₁p were still decreasing, whereas arterial and venous blood temperatures were increasing. With increasing extracorporeal temperatures, latency decreased instantaneously. The slopes of regression lines for t₁y and t₁p were
found to be different during cooling and rewarming. This is probably explained by the assumption that real brain temperature, in the presence of blood–brain temperature gradients, is overestimated during cooling and underestimated during rewarming. Brain temperature is better reflected by $t_{art}$ or $t_{ven}$ in such a dynamic system; slopes for extracorporeal temperatures were found to be nearly identical during the two phases of operation. Comparable phenomena were demonstrated for the effect of hypothermia on visual evoked potentials by Russ and co-workers (1984). Rapid cooling, which implies a great blood–brain temperature gradient, caused more profound alteration in the waveform complexity than moderate temperature reduction. Unfortunately, other groups (Reilly et al., 1978; Coles et al., 1984; Markand et al., 1984; Doyle and Fria, 1985) using rapid cooling with a decrease in temperature of 1 °C min$^{-1}$, did not analyse these effects separately. It is known from the literature that rapid cooling elicits neural activity, as do gradients between cooled and non-cooled areas (Brooks, Koizumi and Malcolm, 1955; Suda, Koizumi and Brooks, 1957).

Among others, Budnick, McKeown and Wiederholt (1981) and Markand and colleagues (1984) demonstrated that latencies were related to temperature in a linear manner, whereas Coles and co-workers (1984), Doyle and Fria (1985) and Durkin and others (1985), using Arrhenius' transformation of latencies, found that the data fitted an exponential function. In the latter studies the temperature was less than 20 °C, and small infants were investigated. This may in part contribute to the differences.

Our study supports the concepts of a linear correlation in the temperature range 25–35 °C. The insufficient approximation of brain temperature, in the presence of temperature gradients, by $t_{sy}$ or $t_{sp}$ should be considered. Exact description of the effects of hypothermia on evoked potential variables require a steady-state temperature (Stockard, Sharbrough and Tinker, 1978)—a situation difficult to achieve under clinical conditions. Therefore, the establishment of different regression lines for cooling and rewarming is necessary or the various indices have to be related to blood temperature.

One limitation of the method presented is that cortical SEP cannot be recorded reliably below 25 °C. In the temperature range 25–35 °C the limitation of SEP monitoring is related to its specificity for the somatosensory afferent and cortical systems. Coles and colleagues (1984) reported on two patients who sustained visual impairment after profound hypothermic circulatory arrest with no alterations in SEP recordings during the operation. Symon, Pasztor and Branston (1974) demonstrated that, after unilateral middle cerebral artery occlusion, the median nerve SEP was not affected, whereas there were marked decreases in the trigeminal nerve cortical potentials. This difference corresponded to appropriate changes in rCBF at the two different sites. A localized reduction of rCBF in other than the stimulated areas, for instance caused by embolism or platelet aggregation, may not be recognized. Reduction of amplitude and increase in CCT were observed when perfusion was reduced to critical values; moderate alterations are probably better represented by computerized EEG techniques.

Malone, Prior and Scholtz (1981) demonstrated that the parieto–occipital region is a sensitive site for the development of minimal lesions, whereas more extensive lesions had a temporal and frontal distribution. Neuropathological findings correlated well with intraoperative cerebral function monitor recordings.

The SEP, along with the BAEP and EEG of the artery boundary zones (Malone, Prior and Scholtz, 1981) could provide the surgeon with sensitive, reliable and rapidly available data concerning brain stem and hemispheric function.

REFERENCES
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