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The effect of two low-dose propofol infusions on the relationship between six-pulse transcranial electrical stimulation and the evoked lower extremity muscle response

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Background: Transcranial stimulation of the motor cortex using high-voltage electrical stimuli given in train is a method of monitoring the integrity of the motor pathways during thoracoabdominal aortic aneurysm surgery. The purpose of this study was to assess the relationship between the stimulus intensity and the corresponding amplitude of the myogenic motor evoked potential (tcMEP) in response to six-pulse transcranial electrical stimulation during two levels of low-dose propofol infusion and stable fentanyl/nitrous oxide anaesthesia.
Methods: Nine patients (37–78 yr) scheduled to undergo surgery on the thoracoabdominal aorta were studied. After achieving a stable anaesthetic state the output voltage was decreased with 50 V intervals from 350 V to 200 V during a target propofol infusion aimed at a plasma steady-state concentration of 0.7 $\mu g \cdot ml^{-1}$ and increased with 50 V intervals from 200 V to 450 V during a target propofol infusion aimed at a plasma steady-state concentration of 1.4 $\mu g \cdot ml^{-1}$. TcMEPs were recorded from the right tibialis anterior muscle.
Results: Doubling the target propofol infusion to 1.4 $\mu g \cdot ml^{-1}$ resulted in a 30–50% decrease in tcMEP amplitude. The largest tcMEP amplitude using the six-pulse paradigm was found during a propofol infusion aimed at a plasma concentration of 0.7 $\mu g \cdot ml^{-1}$ and demanded a stimulus output of 350 V, corresponding to a charge density of 7.5 $\mu C \cdot cm^{-2}$ per phase.
Conclusion: Doubling the target propofol infusion to 1.4 $\mu g \cdot ml^{-1}$ provides less robust, but still recordable tcMEPs in response to six-pulse electrical stimulation. Safety guidelines are discussed.

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Key words: Motor evoked potentials; aortic surgery; propofol infusion; transcranial electrical stimulation; stimulus intensity; safety.

PARAPLEGIA is a devastating complication after operations on the descending thoracic and thoracoabdominal aorta (1). Monitoring of motor evoked responses to transcranial electrical stimulation (tcMEP) may be useful in reflecting the functional integrity of the vulnerable motor pathways during thoracoabdominal aneurysm surgery (2). The depressive effects of most anaesthetic regimens interfere considerably with the recording of tcMEPs evoked by single or double electrical stimulation (3). Neuromuscular blocking drugs also decrease the tcMEP response (4). Recently it was shown that multiple transcranial electrical stimulation of the motorcortex can overcome the depressive effects of the required anaesthetics (5). With trains of transcranial electrical stimuli, both facilitation of cortical motoneurons and temporal and spatial summation of excitatory inputs to the motoneuron pool may lead to muscle responses sufficiently robust for use in aortic surgery (6).

The aim of this study was to investigate the influence of two low-dose propofol infusions on the relationship between six-pulse transcranial electrical stimulation and the corresponding muscle response during stable fentanyl/nitrous oxide anaesthesia. Furthermore, for reasons of safety, we calculated the charge per phase, the charge density and current density per phase for each stimulus output voltage to compare the results with those found in the literature.

Methods

Nine patients (5 female, 4 male, aged 37–78 years) undergoing surgery on the thoracoabdominal aorta gave their written informed consent to participate in this

study, which was approved by the Institutional Ethics Committee. All patients were free from any neuromuscular disorder and epilepsy.

The patients were premedicated with morphine 10 mg and haloperidol 5 mg IM 1 h before surgery. After venous cannulation of the right arm and cannulation of the right radial artery, anaesthesia was induced with diazepam 0.2–0.3 $mg \cdot kg^{-1}$, fentanyl 20–30 $\mu g \cdot kg^{-1}$ and a low-dose propofol infusion ('Diprifusor' TCI system), aiming at a plasma steady-state concentration of 0.7 $\mu g \cdot ml^{-1}$ or 1.4 $\mu g \cdot ml^{-1}$. Tracheal intubation was performed using a left-sided double-lumen tube, after which the position of the tube was verified by fibreoptic bronchoscopy. If necessary, succinyl choline 20 mg was given intravenously to facilitate intubation. Controlled ventilation was adjusted to maintain normocapnia (end-tidal CO_2 4.0–4.5 kPa) and to administer nitrous oxide 50% in oxygen. A pulmonary artery catheter was inserted via the right internal jugular vein. A nasogastric tube, an indwelling bladder catheter, a rectal thermometer and a muscle thermometer (right tibialis anterior muscle) were placed. The right-sided thenar eminence was used to monitor neuromuscular block. Before a neuromuscular blocking drug was given, the compound muscle action potential (CMAP) was obtained from the thenar eminence (EMG response) following supramaximal stimulation of the median nerve at the wrist using a general evoked response stimulator (SMP 3100, Nihon Kohden) triggered from a personal computer. An atracurium infusion was used to maintain the first twitch, T1, of the train-of-four (TOF) response at 45–55% of the control CMAP. The T1 response was displayed on the computer screen. The patient was positioned on a beanbag (Olympic Medical, Seattle, Washington, U.S.A.) in the right lateral decubitus position and two intrathecal catheters (one for monitoring intrathecal pressure, one for drainage of cerebrospinal fluid) were placed via the second and third lumbar interspaces. Spinal fluid drainage was continued throughout the procedure to maintain the intrathecal pressure below 10 mm Hg. This strategy improves the perfusion of the spinal cord vascular network (7). Routine anaesthetic monitoring for major vascular surgery was performed and electronically recorded every 30 s (Datex, Helsinki, Finland).

Anodal six-pulse electrical stimulation was delivered paracentrally at the C3 position with the cathode at the C4 position (International 10–20 system for the placement of the electroencephalogram electrodes). Before surgery, custom-made disc electrodes of a silver-copper alloy with a diameter of 25 mm filled with conduction paste were attached to the skull. To improve electrode stability, gauze pads were fixed over the discs with collodion. Both disc electrodes were connected to a multipulse electrical stimulator D185 (Digitimer Ltd, Welwyn Garden City, U.K.). The pulse duration was 50 μs. The pulses in the train were spaced apart for 2 ms (500 Hz) and the train (duration 12 ms) was triggered from a computer every minute. The output voltage was set at 350 V, 300 V, 250 V, 200 V during a propofol infusion aiming at a plasma steady-state concentration of 0.7 $\mu g \cdot ml^{-1}$ and from 200 V up in 50 V increments to 450 V and thereafter a maximum of 490 V during a higher propofol infusion aiming at a plasma steady-state concentration of 1.4 $\mu g \cdot ml^{-1}$. At each output voltage two tcMEPs were recorded from the right tibialis anterior muscle in response to six-pulse transcranial electrical stimulation. So in each patient a total of 22 stimuli were delivered

Table 1

TcMEP amplitude from the right tibialis anterior muscle to six-pulse electrical stimulation during fentanyl/low-dose propofol (plasma steady-state concentration of 0.7 $\mu g \cdot ml^{-1}$ and 1.4 $\mu g \cdot ml^{-1}$, respectively)/N_2O 50% in oxygen anaesthesia and corresponding stimulus intensity parameters. n=9 patients, SD=standard deviation.

Stimulus output (V)	Charge per phase (μC)	Current density ($a \cdot cm^{-2}$)	Charge density per phase ($\mu C \cdot cm^{-2}$)	Propofol 0.7 $\mu g \cdot ml^{-1}$ amplitude (μV)	Propofol 1.4 $\mu g \cdot ml^{-1}$ amplitude (μV)
	mean (SD)	mean (SD)	mean (SD)	median 25th–75th percentile	median 25th–75th percentile
200	18.7 (3.9)	0.07 (0.01)	3.9 (0.8)	402 (210–788)	270 (169–925)
250	24.2 (4.5)	0.10 (0.01)	5.2 (0.9)	450 (301–678)	518 (311–701)
300	30.5 (5.2)	0.12 (0.02)	6.2 (1.0)	813 (598–986)	526 (298–782)*
350	36.0 (5.9)	0.15 (0.02)	7.5 (1.2)	900 (551–1230)	468 (391–712)*
400	44.2 (6.7)	0.18 (0.02)	9.0 (1.3)		494 (331–597)
450	51.8 (6.7)	0.21 (0.02)	10.6 (1.3)		425 (261–636)

* $P<0.001$ compared with the propofol infusion rate aimed at a plasma steady-state concentration of 0.7 $\mu g \cdot ml^{-1}$ (Wilcoxon signed rank test).

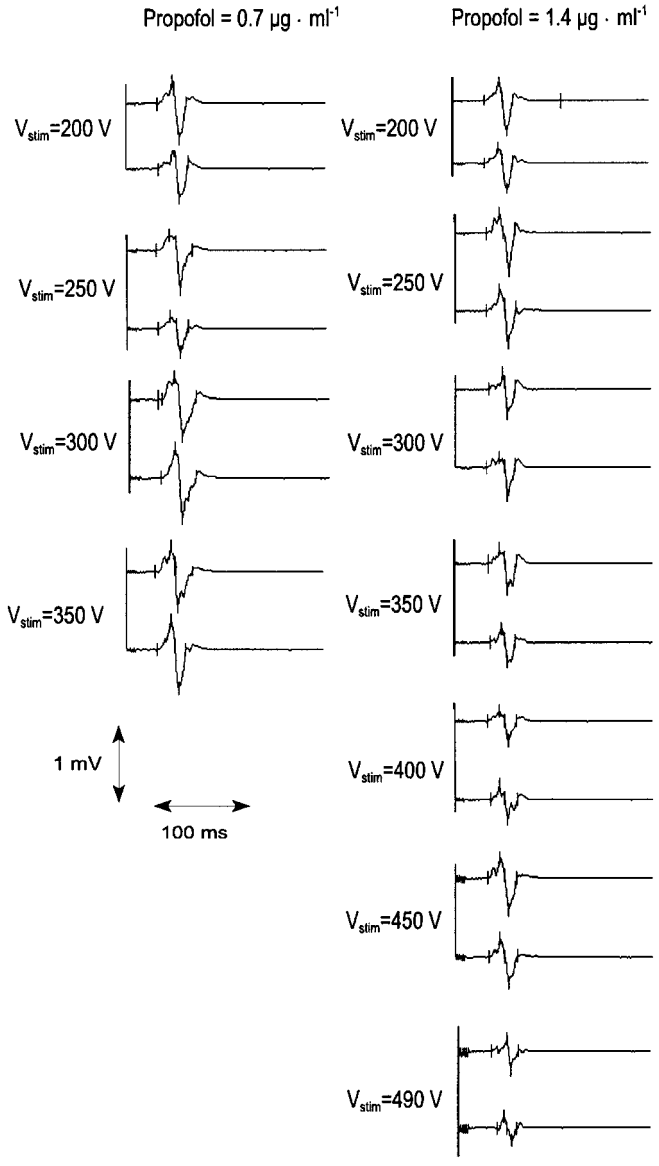

Fig. 1. Stimulation output (V) vs amplitude muscle response (mV). Left: plasma concentration propofol 0.7 µg · ml^{-1}. Right: plasma concentration propofol 1.4 µg · ml^{-1}.

during the study period. The study was performed 20–25 min after the induction dose of diazepam/fentanyl and before any surgical action was undertaken to avoid interference that might have resulted in impaired spinal cord functioning. After this initial period of measurement recording, which lasted approximately 40 min, surgery proceeded as usual for total thoracoabdominal aortic replacement.

The myogenic potentials were recorded on a timebase of 150 ms, traversing a bandpass filter of 50–500 Hz and amplified 10 000 times (Neurotop, Nihon Kohden). The signals were sampled at 1 kHz, digitized with a 12-bit analogue-to-digital converter and displayed on a standard computer screen. The amplitude was measured as the voltage from the most negative component to the most positive component of the evoked electromyographic activity (=tcMEP). TcMEPs were recorded from the lower extremity at the right side of the body, i.e., the tibialis anterior muscle, because the left lower limb is not perfused continuously using the left heart bypass in contrast to the right side. Standard silver-silver chloride disc electrodes filled with conducting paste were placed as above on the muscle belly and on the tendon of this muscle. For each six-pulse train the requested stimulus output voltage was set on the D185, and the actual amount of current delivered (as displayed on the D185) and the amplitude of the tcMEP were determined. At least one minute was allowed to elapse between each train of six pulses. The charge per phase (the amount of charge traversing the area under the electrode during each pulse of the stimulus train), the charge density (the charge per phase divided by the surface area of the electrode) and the current density (the amount of current divided by the surface area of the electrode) of the first pulse in the train were calculated from the current delivered by the D185.

Each patient was questioned, if possible, for recall of intraoperative events on the first postoperative day in the intensive care unit.

Statistical analysis

The amplitude data distribution is skewed and therefore we present the amplitudes as medians with 25th and 75th percentiles. Differences in tcMEP amplitude between the stimulus output voltages were compared using the Wilcoxon signed rank test. Statistical analysis was applied to the data in the range from 200 V to 350 V. A *P*-value less than 0.05 was considered significant.

Results

In all patients the systolic pressure was maintained between 80 and 100 mm Hg and the pulse rate was maintained between 50 and 100 bpm. There was no significant change in measured rectal temperature (36.1±0.4°C) and no significant change in end-tidal carbon dioxide (4.2±0.5 kPa) during the recording period. No burn marks were observed at the stimulation sites. No neurologic sequellae in the sense of epileptic seizures were observed perioperatively as a consequence of six-pulse transcranial electrical stimulation; likewise, there was no incidence of paraplegia as a consequence of spinal cord ischaemia. There was no suspicion of awareness during the recording

period and no patients experienced recall of intraoperative events, especially those related to the stimulation.

The stimulus output voltages, the amplitudes obtained from the right tibialis anterior muscle responses and the calculated charge delivery parameters are listed in Table 1. The Wilcoxon signed rank statistics are given in the table. The largest tcMEP amplitude using the six-pulse paradigm was found during the propofol infusion aimed at a target blood concentration of 0.7 $\mu g \cdot ml^{-1}$ and demanded a stimulus output of 300–350 V, corresponding to a charge density of 6.2–7.5 $\mu C \cdot cm^{-2}$. After doubling the propofol target blood concentration to 1.4 $\mu g \cdot ml^{-1}$, the maximum amplitude with a stimulus output voltage above 350 V was in a range from 420 μV to 470 μV. Even the maximum stimulus output of 490 V, corresponding to a charge density of 11.6 $\mu C \cdot cm^{-2}$, did not prove to be high enough to elicit tcMEPs with an amplitude of 900 μV, as shown from an individual case in Fig. 1.

Discussion

Our data indicate that an anaesthetic regimen consisting of fentanyl/N_2O 50% in oxygen anaesthesia and a low-dose propofol infusion during partial neuromuscular blockade results in recordable tcMEP waveforms following six-pulse electrical stimulation, but that doubling the propofol infusion to 1.4 $\mu g \cdot ml^{-1}$ resulted in a marked reduction in tcMEP amplitude. Even increasing the stimulus intensity to a maximum of 490 V did not overcome this reduction in amplitude.

The effect of the induction dose of diazepam and fentanyl is limited after 10–20 min and a stable MEP is observed (3). The use of a target controlled infusion (TCI) of propofol is more and more accepted as an intravenous technique for the maintenance of anaesthesia (8). During this computer-assisted infusion the infusion rates are continuously calculated to obtain and maintain a given propofol blood concentration, based on average pharmacokinetic parameters. An open-loop population-based pharmacokinetic infusion system may have its limits in achieving target values, but the system makes use of infusion anaesthesia analogous to that of inhalational anaesthesia, where the concentration of the inhalational agent can be changed. The anaesthesiologist using TCI of propofol has the opportunity to investigate the required target propofol infusion compatible with recording of tcMEPs after six-pulse electrical stimulation. To optimize the clinical efficacy of tcMEP monitoring, thoughtful infusion of propofol is necessary during anaesthesia for thoracoabdominal aortic aneurysm surgery. By standardizing the administration of anaesthetic drugs the sensitivity and clinical practicality of recording tcMEPs will further improve. In this study we used a low target propofol infusion regimen, which would result in inadequate anaesthesia when given as a single anaesthetic drug. In combination with the employed fentanyl/N_2O 50% in oxygen anaesthesia, a sufficient hypnotic effect for surgical anaesthesia was achieved (8–10). Doubling the propofol infusion not only causes a deeper level of anaesthesia but, very likely, sets up inhibitory events to electrical stimulation at the level of the motor cortex. In our setup, those inhibitory events cannot be ruled out to be active at the motor neuron pool in the anterior horn as well (3).

Ubags et al. (11) described the effect of propofol infusion (starting dose 1 $mg \cdot kg^{-1}$; 10 $mg \cdot kg^{-1} \cdot h^{-1}$ for the first 10 min, 8 $mg \cdot kg^{-1} \cdot h^{-1}$ for the next 10 min and then a maintenance dose of 6 $mg \cdot kg^{-1} \cdot h^{-1}$) administered concurrently with sufentanil on the MEP response to transcranial electrical stimulation with a stimulus output voltage varying between 500 V and 700 V during partial neuromuscular blockade (T1%=20). The median amplitude was 36 μV after single-pulse and 655 μV after two-pulse transcranial electrical stimulation. In contrast, our data show with less stimulus output, that is 350 V, a median amplitude of 900 μV during a low-dose propofol infusion aimed at a plasma steady-state concentration of 0.7 $\mu g \cdot ml^{-1}$ and 470 μV during a propofol infusion aimed at a plasma steady-state concentration of 1.4 $\mu g \cdot ml^{-1}$. This is probably the result of the six-pulse stimulation technique we have used. Multipulse stimulation of the motorcortex may partly overcome the propofol induced depression of the motorcortex, most likely the result of increased stimulation spread within the cortex and increased temporal and spatial summation of excitatory inputs to the motoneuron pool (6). Furthermore, compared with the two-pulse paradigm, six-pulse transcranial electrical stimulation results in a reduced within-patient variability (12). It is also clear that, apart from a larger pulse train, a higher stimulus ouput may also contribute to a higher current density through the motor area of the tibialis anterior muscle, hence a higher probability of pyramidal cell depolarization and consequently a proportionally greater descending volley, bringing the alpha motoneurons, after synaptic transmission, to the firing threshold. The effect of the two low-dose propofol infusions on the relationship between the stimulus intensity and corresponding tcMEP amplitude became

more apparent when the intensity was increased from 5.2 $\mu C \cdot cm^{-2}$ to 6.2 $\mu C \cdot cm^{-2}$.

All these observations have clinical significance regarding the safety of the method. Utilizing higher charge densities per phase may carry the risk of neural damage following six-pulse electrical stimulation. To prevent direct neuronal injury, Agnew and McCreery (13) suggested that the charge density must not exceed 40 $\mu C \cdot phase^{-1} \cdot cm^{-2}$, based on disc-shaped electrodes of 0.01 cm^2 lying at the surface of the brain. We used much larger disc-shaped electrodes of 4.9 cm^2 lying over the skin, and it is unknown to what extent the activation of a larger population of neurons will lead to neural damage. We measured only the actual amount of current delivered by the first pulse in the train, so our stimulus paradigm could not exceed a total charge density of 70 $\mu C \cdot cm^{-2}$ (charge density per phase$\times$total number of pulses) when employing the maximum stimulus output of 490 V. Besides, Levy et al. (14), measuring the current density at the human brain surface during extracranial stimulation, estimated that the current density was attenuated 30 times between skin and brain surface. Our stimulus paradigm is within the safety ranges mentioned in the literature. However, any adverse effects can neither be excluded nor demonstrated by this study.

In conclusion, this study indicates that an anaesthetic regimen consisting of a low-dose propofol infusion (aiming at a plasma steady-state concentration of 0.7 $\mu g \cdot ml^{-1}$ rather than 1.4 $\mu g \cdot ml^{-1}$), fentanyl/N_2O 50% in oxygen anaesthesia during partial neuromuscular blockade allows, within the routine ranges of output voltages, recordable tcMEP responses to six-pulse electrical stimulation.

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