The suppression of spinal F-waves by propofol does not predict immobility to painful stimuli in humans


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Background. The immobilizing effects of volatile anaesthetics are primarily mediated at the spinal level. A suppression of recurrent spinal responses (F-waves), which reflect spinal excitability, has been shown for propofol. We have assessed the concentration-dependent F-wave suppression by propofol and related it to the logistic regression curve for suppression of movement to noxious stimuli and the effect on the bispectral index™ (BIS™). The predictive power of drug effects on F-waves and BIS for movement responses to noxious stimuli was tested.

Methods. In 24 patients anaesthesia was induced and maintained with propofol infused by a target controlled infusion pump at stepwise increasing and decreasing plasma concentrations between 0.5 and 4.5 mg litre$^{-1}$. The F-waves of the abductor hallucis muscle were recorded at a frequency of 0.2 Hz. BIS values were recorded continuously. Calculated propofol concentrations and F-wave amplitude and persistence were analyzed in terms of a pharmacokinetic–pharmacodynamic (PK/PD) model with a simple sigmoid concentration–response function. Motor responses to tetanic electrical stimulation (50 Hz, 60 mA, 5 s, volar forearm) were tested and the EC$_{50\text{tetanus}}$ was calculated using logistic regression.

Results. For slowly increasing propofol concentrations, computer fits of the PK/PD model for the suppression by propofol yielded a median EC$_{50}$ of 1.26 (0.4–2.3) and 1.9 (1.0–2.8) mg litre$^{-1}$ for the F-wave amplitude and persistence, respectively. These values are far lower than the calculated EC$_{50}$ for noxious electrical stimulation of 3.75 mg litre$^{-1}$. This difference results in a poor prediction probability of movement to noxious stimuli of 0.59 for the F-wave amplitude.

Conclusions. F-waves are almost completely suppressed at subclinical propofol concentrations and they are therefore not suitable for prediction of motor responses to noxious stimuli under propofol mono-anaesthesia.

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Mechanisms by which volatile anaesthetic suppress motor responses to painful stimuli are predominantly of spinal origin. It has been shown in rats that neither decerebration$^1$ nor hypothermic transection between the brain and the spinal cord$^2$ alter the anaesthetic requirements to produce immobility.

The spinally-mediated H-reflex and F-waves have been recommended for monitoring surgical immobility in humans.$^{3,4}$ F-waves are low amplitude motor responses to nerve stimulation. After electrical stimulation of peripheral motor fibres, the impulse propagates orthodromically to the corresponding muscle and antidromically to the spinal motoneurons. The orthodromic potential elicits a direct muscle response (M-wave), whereas the antidromic potential results in a recurrent discharge (‘backfiring’) of some motoneurones which finally lead to a late muscle response, the F-wave (for reviews on F-wave application see refs 5 and 6). F-waves represent a sensitive measure of changes in motoneurone excitability.$^7,8$

Previous studies have shown that propofol depresses F-waves in humans.$^9–11$ However, there are no reports comparing the concentration- and time-dependent suppression of spinal cord excitability and suppression of the EEG for propofol. In this study we simultaneously examined the effect of propofol on spinal F-waves (amplitude and

$^1$Presented in part at the annual meeting of the American Society of Anesthesiologists 2004 in Las Vegas.
pharmacokinetic dataset of Marsh and colleagues. Every infusion pump, programmed using the weight-corrected (Fig. 1) and encephalographic variables were obtained for establishment. Thereafter baseline recordings of F-waves and pulse oximetry) and i.v. access via a forearm vein were monitored (non-invasive blood pressure monitoring, ECG premedication. After arrival in the operation room, standard Patients fasted at least 6 h before the study and received no premedication. After the study period, the propofol concentration was increased to 4.5 mg litre\(^{-1}\) and patients received fentanyl 0.1 mg and cis-atracurium 0.1 mg kg\(^{-1}\) before their tracheas were intubated and surgery commenced.

### Material and methods

The protocol for this study was approved by the local ethics committee (Charité, Berlin, Germany), and written informed consent was obtained from all patients. The study was performed before elective gynaecological or urological surgery on 20 female and 4 male patients who were classified as American Society of Anesthesiologists physical Status I or II. Patient exclusion criteria were pregnancy, any neuromuscular disease, use of CNS-acting medication, abuse of alcohol or illicit drugs, and contraindications to the use of propofol. The data evaluation and propofol administration used in this study resembles a previous study we performed on different patients studying the effect of propofol on the H-reflex.\(^{12}\)

#### Study design

Patients fasted at least 6 h before the study and received no premedication. After arrival in the operation room, standard monitoring (non-invasive blood pressure monitoring, ECG and pulse oximetry) and i.v. access via a forearm vein were established. Thereafter baseline recordings of F-waves (Fig. 1) and encephalographic variables were obtained for 10 min before induction of anaesthesia.

Propofol was infused i.v. via a computer-controlled infusion pump, programmed using the weight-corrected pharmacokinetic dataset of Marsh and colleagues.\(^{13}\) Every 3–5 min, the target plasma concentration was increased by 0.5 mg litre\(^{-1}\) until F-waves were abolished (Fig. 2). The point at which patients lost consciousness (defined as loss of verbal response to repeated loud verbal command) was recorded. The propofol infusion was then stopped until the F-wave amplitude increased again to at least 20% of the baseline value and patients became conscious again. During the period of decreasing propofol concentrations loud verbal commands were repeated every minute to avoid the propofol anaesthesia merging into a ‘natural’ sleep, which might influence the F-wave.\(^{14}\) The time of return of consciousness, defined as when there was a verbal response to the loud verbal command, was also recorded. During the entire recording period, patients breathed pure oxygen from the circle system of an anaesthesia machine (Modulus, Ohmeda, Madison, WI, USA) via a tight fitting face mask. End-tidal carbon dioxide was monitored continuously when patients were unconscious and kept constant by assisting ventilation manually, if necessary. The tight fit of the mask was checked by monitoring the capnograph.

In 12 patients, the response to a noxious electrical stimulus was investigated. An electrical stimulus (50 Hz, 60 mA, 5 s, 0.2 ms square wave tetanic stimulus) was applied with a peripheral nerve stimulator (Fischer and Paykel, Auckland, New Zealand) to surface electrodes placed on the volar surface of the forearm at the various target propofol concentrations. A positive response was defined as a gross purposeful movement of the head or extremities, excluding the stimulated arm.

After the study period, the propofol concentration was increased to 4.5 mg litre\(^{-1}\) and patients received fentanyl 0.1 mg and cis-atracurium 0.1 mg kg\(^{-1}\) before their tracheas were intubated and surgery commenced.

### Neurophysiologic data acquisition

A detailed description of the method has been given previously.\(^{15}\) In brief, F-waves were recorded over the abductor pollicis muscle after stimulation of the tibial nerve at the ankle. Stimuli were applied continuously throughout the study with a frequency of 0.2 Hz and duration of 0.1 ms. Stimulus intensity was kept constant for the entire study period. F-wave persistence, that is, the number of measurable F-waves divided by the number of stimuli, was determined offline from a series of nine successive stimuli. To distinguish F-waves from background noise the recorded EMG-signal was reviewed visually; only appropriately timed deflections, which clearly contrasted with the baseline noise, were accepted as F-waves. Depending on the individual background noise level the smallest accepted F-wave amplitude varied between 30 and 50 μV.

The EEG was recorded in a bifrontal montage (Fpz-A1 and Fpz-A2) using an A-1000 EEG monitor (Aspect Medical Systems, Natick, USA). The BIS (version B31v02) was used for further analysis. Data from time periods where burst suppression occurred (burst suppression index>0) were discarded.

### Pharmacodynamic analysis

Individual concentration–response functions were fitted to the data and the calculated plasma concentrations using a spreadsheet program (EXCEL, Microsoft) and a simple sigmoidal model:

\[
E = E_0 \times \left(1 - \frac{c_{\text{eff}}}{EC_{50} + c_{\text{eff}}} \right)
\]

In this model, \(E_0\) is the baseline effect, \(c_{\text{eff}}\) is the apparent effect site concentration, \(EC_{50}\) is the concentration that causes 50% of the maximum effect and \(\lambda\) (Hill coefficient) describes the slope of the concentration–response relation. The time lag between changes in calculated plasma
concentration and observed effect was modelled by an effect compartment and a first-order rate-constant determining the efflux from the effect compartment $k_{eo}$:

$$\frac{dC_{eff}}{dt} = (C_p - C_{eff}) \times k_{eo}$$

where $C_p$ is the predicted plasma propofol concentration, $C_{eff}$ is the effect compartment concentration of propofol and $k_{eo}$ is the first-order rate-constant determining the efflux from the effect compartment.

The effect site equilibration half-life $t_{1/2}$ $k_{eo}$ was calculated as $\ln 2/k_{eo}$.

The fitted parameters of the different electrophysiological measures were compared using one way ANOVA with Tukey’s multiple comparison post hoc test (Prism 3.0; Graph pad Software, San Diego, USA).

The logistic regression model developed by Waud$^{16}$ was used to determine the EC$_{50}$-value for both the loss of movement response to noxious electrical stimulus and the loss of consciousness. For the latter, the propofol effect site as predicted by the pump concentration was averaged more than 2 min before and after loss of and return of consciousness; for the former, the predicted plasma concentration was averaged more than 1 min before the tetanic stimulation.

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**Fig 1** Original tracings of M-wave and F-wave. Original tracings of M-wave and F-wave (A) before anaesthesia and (B) under 2 mg litre$^{-1}$ propofol plasma concentration in a male patient (characteristics: age, 49; body height, 200 cm; weight, 110 kg). (Note: as F-wave latency is related to the body height it is far above the average in this patient.)
To estimate and compare the predictive value of the different variables, we calculated the prediction probability ($P_k$) introduced by Smith and colleagues.\(^\text{17}\) $P_k$ is a non-parametric correlation measure that indicates the probability that a variable correctly predicts anaesthetic depth, that is, in this case, a movement response. A $P_k$ value of 1.0 indicates perfect prediction, whereas a value of 0.5 indicates that the predictive value of the variable is no better than chance.

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**Fig 2** Individual hysteresis loops (effect vs propofol plasma concentration) and collapsed loops (effect vs effect compartment concentrations) of the different drug effect measures. Original data were collected from all patients. The collapsed curves were generated from the individual equilibration time constants. To estimate the goodness of fit the grey line in the collapsed loops shows the mean concentration–response curve of all patients (see Fig. 6). Loops for F-wave amplitude are shown in (A) for plasma concentration and (B) for effect site concentration, for F-wave persistence in (C) for plasma concentration and (D) for effect site concentration and for the BIS in (E) for plasma concentration and (F) for effect site concentration. For the F-wave amplitude the data were averaged within a time-window of 20 s.
alone. The calculation of the $P_k$ was based on values of each variable that were averaged more than 1 min before the noxious electrical stimulation.

**Results**

In all 24 patients included in the study, F-waves were reliably elicited. The F-wave data of three patients could not be further evaluated as the F-wave amplitude did not recover after reducing the propofol concentration which was probably caused by electrode displacement after uncontrolled movement during propofol wash-out. In four other patients the EEG data could not be evaluated because of a data transmission error that led to a complete loss of the EEG data. The characteristics (mean±SD) of the 24 patients (20 female) were an age of 40±12 yr (range 21–50), a body weight of 65±14 kg and a height of 170±10 cm. The increasing propofol concentration caused a clear reduction of the F-wave amplitude and persistence (Fig. 1). When propofol concentration was decreased there was recovery of the F-waves. The sigmoidal model adequately described the concentration-dependent suppression of the F-wave amplitude and persistence. To evaluate the goodness of fit all individual hysteresis loops and the corresponding collapsed loops are presented in Figure 2. The individual EC$_{50}$ values and equilibration half-time values are displayed in Figure 3. The other fitted parameters are presented in Table 1.

The average F-wave minimal latency (shortest latency on a series of 10 stimuli) in our study was 49.5±6.3 ms (mean±SD) and is in the range of results reported previously (for references see ref. 6).

The noxious electrical stimulation at the wrist led to an increase in F-wave amplitude in the abductor pollicis muscle only in those patients that moved after the noxious electrical stimulation (Fig. 4A). After 15 s, the F-wave amplitude reached pretetanic levels again. The time-course of the F-wave amplitude and the BIS around the tetanic stimulation are presented in Figure 4B and C.

Figure 5 displays the different sigmoidal concentration–response curves constructed with the mean values for the EC$_{50}$ and slope parameters together with the logistic regression curves for the movement response to noxious electrical stimulation and for the loss of consciousness.

The logistic regression curve of the tetanic electrical stimulation, based on a total of 19 tetanic electrical stimuli (9 positive and 10 negative responses), yielded an EC$_{50}$ of 3.75 mg litre$^{-1}$ (SE 1.1) and a steepness coefficient of 1.86 (SE 1.9).

The prediction probabilities of the different parameters for the movement response to painful electrical stimulation are given in Table 2. The logistic regression curve of loss and return of consciousness is based on 40 changes of consciousness (20 loss of consciousness and 20 return of consciousness). Loss and return of consciousness (note: return of consciousness was determined during the study period, i.e. before surgery) mostly occurred during periods of quickly changing plasma concentration, which resulted in a high interindividual variability of the plasma concentration values. Therefore, the calculated effect site concentration derived from the individual BIS fits, rather than the plasma concentration, was used for this regression calculation. It should be noted that neither loss of consciousness nor return of consciousness occurred at steady state concentrations.

The shape of the observed concentration–response curve for the F-wave amplitude resembles the logistic regression curve for the change of consciousness. To eliminate the possibility that change of consciousness leads to an abrupt change of the F-wave amplitude, the time-course of the F-wave amplitude around the time point of changing
Fig 4 Response of F-wave amplitude to noxious electrical stimulation. (a) Consecutive F-wave tracings around noxious stimulation in one patient. The noxious stimulation was performed during a calculated propofol plasma concentrations of 4.5 mg litre$^{-1}$, which equals a calculated brain concentration or 3.5 mg litre$^{-1}$ ($k_{e0} 0.25$ min$^{-1}$). The patient did move after stimulation. Note: background noise remained stable during the tetanic stimulation at the wrist which did not cause any recordable artefacts. Response of F-wave amplitude (b) and BIS (c) to noxious electrical stimulation (at $t=0$ s; stimulus intensity: 50 Hz, 60 mA, 5 s, 0.2 ms square wave) for all patients who did not move after stimulation (non-movers) and those patients who did move (movers). Data are means and standard error of the mean.
consciousness was examined. In order to pool the data from loss of consciousness and return of consciousness the time-course for the return of consciousness was inversed. The 4 min time-course around the change of consciousness averaged for all 20 patients shows a gradual attenuation of the F-wave amplitude (Fig. 6) but no sudden decrease at loss of consciousness.

**Discussion**

This study investigated the relationship between propofol concentration and suppression of the spinal F-wave in comparison to an EEG effect, the BIS. Furthermore, the different concentration–response curves were related to the suppression of movement to noxious stimulation. The results demonstrate that the same sigmoidal model used for EEG variables can describe the suppression of the F-wave by propofol. The propofol concentration at which the F-wave amplitude and persistence is suppressed by 50% in this study is in accordance with the results published by other groups.9–11

However these *in vivo* results are at variance with the results obtained by *in vitro* studies. Matute and colleagues18 have shown in isolated rat spinal cord preparations that propofol did not suppress a monosynaptic reflex, which reflects motoneurone excitability, even at supraanaesthetic propofol concentrations. This difference may be because of the absence of supraspinal input in the isolated spinal cord preparation. Suppression of F-waves might be partly caused by the reduction of facilitating or enhancement of inhibitory supraspinal input. Our method, however, does not differentiate between spinal or supraspinal contributions to the reduced motoneurone excitability. To distinguish between spinal and supraspinal effects, recordings from spinal motoneurones deprived of any supraspinal input would be necessary, but this is impossible in man.

We found that the F-wave amplitude is almost completely suppressed at propofol concentrations below the EC50-value for the motor response to tetanic electrical stimulation. Taking into account that the EC50-value for the motor response to tetanic electrical stimulation in this study is below the EC50-value of 10 mg litre\(^{-1}\) reported for skin incision19 leads us to conclude that F-wave amplitude or persistence is unsuitable for monitoring immobility under propofol anaesthesia. During sevoflurane anaesthesia the spinal H-reflex, another measure of spinal excitability, but not the F-wave predicted motor responses to painful stimuli better than the BIS.20 During sevoflurane anaesthesia F-waves were also completely suppressed around the MAC value of sevoflurane.15 It is therefore likely that F-waves are generally too sensitive to anaesthetic drug effects in humans.

A possible explanation for a high sensitivity to anaesthetics...
might be the fact that full F-wave production requires only \(\sim 1-2\%\) of the entire motoneurone pool of the tested muscle.\(^{21}\) The likelihood that motoneurones will produce F-waves depends upon the summation of multiple excitatory and inhibitory inputs from various sources of the central and peripheral nervous system and so even a small increase in inhibitory input by propofol could lead to a complete suppression of F-wave production. The marked increase of the F-wave amplitude after the noxious stimulation only in those patients that moved indicates that the movement response is associated with an increase in spinal excitability, which can be detected by the F-wave. It is therefore possible that under surgical stimulation the F-wave might be less suppressed by propofol than under our experimental conditions. Nevertheless our data imply that F-waves will not be suitable for monitoring immobility during propofol anaesthesia.

In contrast to sevoflurane anaesthesia, in this study the BIS predicted movement to tetanic stimulation during propofol anaesthesia quite well. There is controversy in the literature concerning the prediction of movement in response to noxious stimuli by the BIS during propofol anaesthesia. While earlier studies\(^{22-24}\) reported a good predictive power a recent study has called these findings into question.\(^{25}\) In contrast, during sevoflurane anaesthesia the BIS probably does not predict movement responses.\(^{20,26}\) This difference may either reflect the better correlation of propofol concentration with BIS values or may be because of a greater supraspinal component in the immobilizing effect of propofol compared with sevoflurane.

This study is the first to analyse the equilibration half-time for F-wave suppression during propofol anaesthesia. This allows generation of complete concentration–response curves and effect site models, and a separation of different pharmacokinetic or pharmodynamic effects. The equilibration half-time found for suppression of the F-wave amplitude was 1.6 times longer than that of the BIS. The phenomenon that effects on spinal cord indices occur ‘slower’ than effects on EEG variables is in line with the findings in previous studies. Comparing the equilibration half-times of the spinal effects expressed as a multiple of the BIS equilibration half-time yields 1.53, 2.38 and 1.74 for the H-reflex suppression under sevoflurane,\(^{27}\) for the H-reflex suppression under propofol\(^{12}\) and F-wave suppression under sevoflurane,\(^{15}\) respectively.

The different equilibration half-time of spinal cord and forebrain effects may originate either from differences in the anaesthetic wash-in and wash-out of two different effect compartments or from different neuronal effects at possibly identical anatomical sites. Evidence for the former is given by studies in rats that indicate substantially less blood flow to the spinal cord than to the brain.\(^{28}\) In the latter case, the suppression of F-waves by propofol would be only secondary to forebrain effects. Such a possible mechanism seems rather unlikely, as F-waves persist independently of cortical influence. F-wave amplitudes in spastic patients with upper spinal cord injury affecting corticospinal pathways are not different from healthy volunteers.\(^{29}\) The delay in the spinal action of propofol could explain why reflex movements can be still observed after induction of anaesthesia even though low BIS values indicate deep sedation.

In summary we have shown that F-wave persistence and amplitude are abolished at propofol concentrations much lower than those at which immobility to noxious stimulation...
occurs. This suppression at subclinical propofol concentrations indicates that the F-wave is not a useful tool to measure anaesthetic induced immobility. The PK/PD analysis of our data indicate that there may be different effect sites for suppression of spinal excitability as measured by F-waves and the hypnotic effect of propofol measured by EEG variables such as the BIS. However it remains unclear whether the immobilizing effect of propofol is indeed caused by a direct spinal effect.

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