



Contact heat evoked potentials as a measure of the analgesic component of anesthesia – a patient study

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Abstract

To assess the applicability of contact heat evoked potentials (CHEPs) as a direct measure of analgesia, we analyzed the following endpoints. (1) Correlation between remifentanyl-induced changes in VAS and CHEP amplitudes. (2) Correlation between CHEP amplitude reduction and remifentanyl infusion rate. Furthermore, we investigated the sedative effects of remifentanyl and the effect of propofol-induced loss of responsiveness (PI-LOR) on CHEPs. After determination of the individual pain threshold (visual analog scale (VAS) of 10), 120 adult ASA physical status I or II patients randomly received remifentanyl in one of four predefined infusion rates (0.05, 0.1, 0.2, or 0.4 $\mu\text{g/kg/min}$). After equilibration, a heat stimulus 20% above the individual pain threshold was applied to the volar forearm. Eventually, propofol was infused until LOR, and the heat stimulus was applied again. CHEPs, VAS, and the Observer's Assessment of Alertness/Sedation (OAA/S) scale, as well as middle latency auditory evoked potentials (MLAEPs), were assessed. A total of 119 patients were included in the analysis. CHEP amplitudes could not be detected for all patients at all times. Remifentanyl dosage and VAS showed a strong inverse correlation ($r=-0.46$; $p<0.001$). We also detected a correlation between remifentanyl dosage and CHEP amplitudes ($r=0.29$; $p=0.003$) but not between VAS and CHEPs ($r=-0.17$; $p=0.868$). Both the OAA/S score and MLAEPs indicated a correlation between remifentanyl dosage and degree of sedation. After PI-LOR, CHEPs were no longer detectable. The exact mechanism for the detected CHEP reduction remains to be determined. CHEPs monitoring appears unsuitable for direct assessment of the analgesic component of general anesthesia.

Trial registration: German Clinical Trials Register ID DRKS00003300, Oct 24, 2011.

Keywords Contact-heat evoked potentials · General anesthesia · Pain assessment · Analgesia

1 Introduction

General anesthesia consists of the main components hypnosis, analgesia, and neuromuscular blockade. These components can be individually targeted with specific drugs during anesthetic procedures. While the hypnotic component and

the degree of neuromuscular blockade can be objectively assessed using electroencephalogram (EEG) monitoring [30] and acceleromyography [33], no established method is currently available to directly measure the effects of analgesic drugs.

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The physiological neural processes triggered by noxious or potentially noxious stimuli are defined as nociception, whereas pain denotes the accompanying subjective experience [29]. Pain is a complex sensory perception of the conscious individual, influenced by physiological, cognitive, and emotional processes. Therefore, clinical scores like the visual analog scale (VAS) or the numeric rating scale (NRS) are used to quantify pain [8]. These measures are easy to use and valid [1].

General anesthesia (GA) prevents patients from waking up or moving upon surgical manipulation. It renders the patient unconscious, thereby abolishing pain perception. However, transmission of signals to the brain from noxious surgical stimuli can still be detected under GA, even when clinical responses are absent [28]. Excessive intraoperative nociceptive stimulation can trigger postoperative adverse effects, including increased catabolism, suppression of immune and inflammatory responses, cognitive impairment, and severe postoperative pain, underlining the importance of regulating nociceptive input [18].

In routine clinical practice, the body's reaction to nociceptive stimulation, i.e., changes in physiological variables indicating increased sympathetic tone, such as increases in heart rate and/or blood pressure, is used as a surrogate to estimate the balance between nociception and antinociception. However, these parameters are indirect, unspecific, and subject to the personal judgment of the particular anesthetist. Furthermore, the effects of drugs acting on the cardiovascular system [17], intravascular fluid status [15], choice of anesthetics [26], and age [27] represent significant limitations for these parameters. Direct monitoring of the effects of noxious stimuli and analgesic drugs on the central nervous system (CNS) may help the clinician establish an adequate nociception-antinociception balance during surgery, thereby reducing the incidence of the above-mentioned complications.

Nociception monitoring is fundamentally based on the neurophysiology of nociceptive processing. Therefore, understanding its general principle is of critical importance [22]. Noxious stimuli are physiologically processed via complex pathways involving both the autonomic nervous system (ANS) and the CNS. The pathways presented here are very simplified, and the interested reader is referred to recent reviews on this topic for more detail [9, 19].

Transmission of nociceptive stimuli to the brain is provided by the ascending pathway: Upon injury, cells release chemical substances, e.g., prostaglandins, that trigger action potentials in peripheral primary afferent nociceptor neurons (unmyelinated C or myelinated A δ fibers). These action potentials are propagated along the axon of the primary neuron to the dorsal horn of the spinal cord, where they are transmitted to the second-order neuron via substance P. This

second-order neuron eventually reaches the thalamus via the spinothalamic, spinoreticular, or spinomesencephalic tracts. From there, nociceptive signals project to widespread areas of the forebrain via third-order neurons, from the somatosensory cortex and limbic system, to the frontal cortex. To generate the experience of pain in the wake subject, nociceptive input is processed by several brain regions in parallel, connecting sensory, affective, and cognitive components [3, 16].

Regulation of nociceptive signal transmission is provided by the descending pathway: nerve fibers, descending through the midbrain and the medulla oblongata to the dorsal horn, eventually inhibit substance P release between first- and second-order neurons of the ascending pathway and stimulate endogenous opioid release, further decreasing the pre- and postsynaptic exchange of substance P [31].

All three relays of the ascending pathways can be monitored. Therefore, nociception monitoring can principally be categorized as motor reflex-based, ANS-based, or CNS-based [22]. All three approaches have their limitations: reflex monitoring may be problematic during neuromuscular blockade, and the required setup might not be suitable for routine use. Monitoring changes in the ANS during surgical stress is complicated by many confounding variables (see above). Being less dependent on these confounders, CNS-based monitoring may overcome the limitations of ANS-based monitoring. However, currently available monitoring systems reflect cortical arousal dynamics rather than measuring nociception *per se* [40].

Over the last two decades, several nociception monitoring devices have been developed and made commercially available (for recent reviews see [22, 25]). Most of these indices are based on one or more variables reflecting nociception-induced changes in autonomic tone. Due to the lack of validated parameters for measuring nociception, the efficacy of these devices was assessed using several outcome measures, including postoperative pain scores, discharge from the post-anesthesia care unit (PACU), plasma levels of stress hormones, and opioid requirements [18]. Using these outcome parameters, the monitors showed some benefit over the sole use of traditional variables [22, 25].

Evoked potentials (EP) are electrophysiological signals recorded from the EEG in response to sensory stimuli. They provide information about the functional integrity and physiological responses of neuronal pathways throughout the peripheral and central nervous systems. Depending on the stimulus, these evoked potentials are characterized by their amplitudes and latencies [35]. EP due to a defined painful heat stimulus are termed contact heat evoked potentials (CHEPs). CHEPs may be a good candidate for direct nociception monitoring in routine clinical practice, because:

1. they resemble cortical responsiveness upon peripheral noxious stimulation and consecutive signal transduction via nociceptive pathways
2. they directly correlate with subjective perception of pain as assessed by the VAS [4, 11, 24, 36]
3. they are independent of the confounding variables of ANS-based nociception monitoring,
4. in a pilot study, we found a dose-dependent reduction of CHEP amplitudes during analgesia with remifentanyl in the absence of global cortical suppression [38].
5. they can easily and reproducibly be triggered by a special thermode without causing any damage to the skin or structures underneath.

This hypothesis was tested in the present study.

2 Methods

2.1 Study endpoints

The primary aim of this study was to investigate whether subjective changes in contact heat-evoked pain perception upon remifentanyl infusion, represented by a reduction in the VAS score, correlate with changes in CHEP P1-N2 peak-to-peak (P1N2) amplitudes, allowing for an objective assessment of the analgesic drug's effect. Secondary endpoints included (i) the correlation of CHEP amplitudes and remifentanyl dosage, (ii) possible sedative effects of the used remifentanyl infusions, (iii) the usability of CHEP monitoring during propofol anesthesia, and (iv) gender differences on CHEPs.

2.2 Patients and study design

The study protocol was in accordance with the Declaration of Helsinki and approved by the local ethics committee of Witten/Herdecke University, Germany. After approval, 120 American Society of Anesthesiologists (ASA) physical status class 1 and 2 patients aged 18 to 50 years scheduled for elective surgery were randomly assigned to one of four groups. According to the group, patients received infusions of 0.05, 0.1, 0.2, or 0.4 $\mu\text{g/kg/min}$ remifentanyl. After determining each patient's individual pain threshold for contact heat stimulation, the following variables were assessed: VAS, P1N2, as well as the Observer's Assessment of Alertness/Sedation (OAA/S) score and auditory evoked potential (AEP) amplitudes, which served as clinical and electrophysiological measures of possible sedative effects, respectively. The experiment consisted of three phases (Fig. 1):

- T0-reference: Recording of EEG (for AEP and CHEP amplitude determination), OAA/S, and VAS without remifentanyl infusion
- T1-remi: Recording of EEG, OAA/S, and VAS with group-specific remifentanyl infusion
- T2-propofol: Recording of EEG with group-specific remifentanyl infusion plus propofol infusion

After recordings under remifentanyl infusion were completed, propofol was administered in 20 mg boluses every 15 s until the patient stopped squeezing the investigator's hand to verbal command (PI-LOR). From there on, continuous propofol infusion was started to maintain State Entropy/Response Entropy values (Entropy module, GE Healthcare, Solingen, Germany) between 40 and 60, according to the manufacturer's recommendation. EEG recordings were started after 10 min of equilibration.

2.3 Contact heat stimulation and generation of CHEPs

Contact heat stimuli were applied to the volar forearm using the Pathway CHEPS Pain and Sensory Evaluation System (Medoc Ltd, Ramat Yishai, Israel). Due to the focus on subjective pain perception, heat stimuli were applied at individual pain thresholds instead of a fixed temperature. Therefore, each patient's individual pain threshold for contact heat stimulation was determined before the experiment began by increasing stimulation intensity in 1°C increments to avoid reaction time artifacts [42]. This pain threshold was rated as 10 on the VAS. Stimulation during the experiment was performed 20% above this threshold. To avoid habituation effects, the interval between stimuli was set to $8 \pm 10\%$ [4–6, 10, 11, 13], the number of stimuli per sequence was limited to 30 [4, 5], and a 5-minute pause was applied between stimulation sequences [13]. The thermode position was slightly varied after 5 stimuli to prevent erythema formation [6, 13, 41]. A total of four stimulation sequences were applied.

2.4 Generation of AEP

Acoustic stimuli for AEP generation were presented as click sounds via anatomically formed in-ear speakers. 1000 clicks were presented four times at 70 dB above the auditory threshold. The stimulus interval was set to $8.3 \text{ Hz} \pm 10\%$ to minimize habituation effects.

2.5 Visualization of EP

For the visualization of EP, an 8-channel EEG was recorded using actiCAP active electrodes at frontal, temporal, parietal,

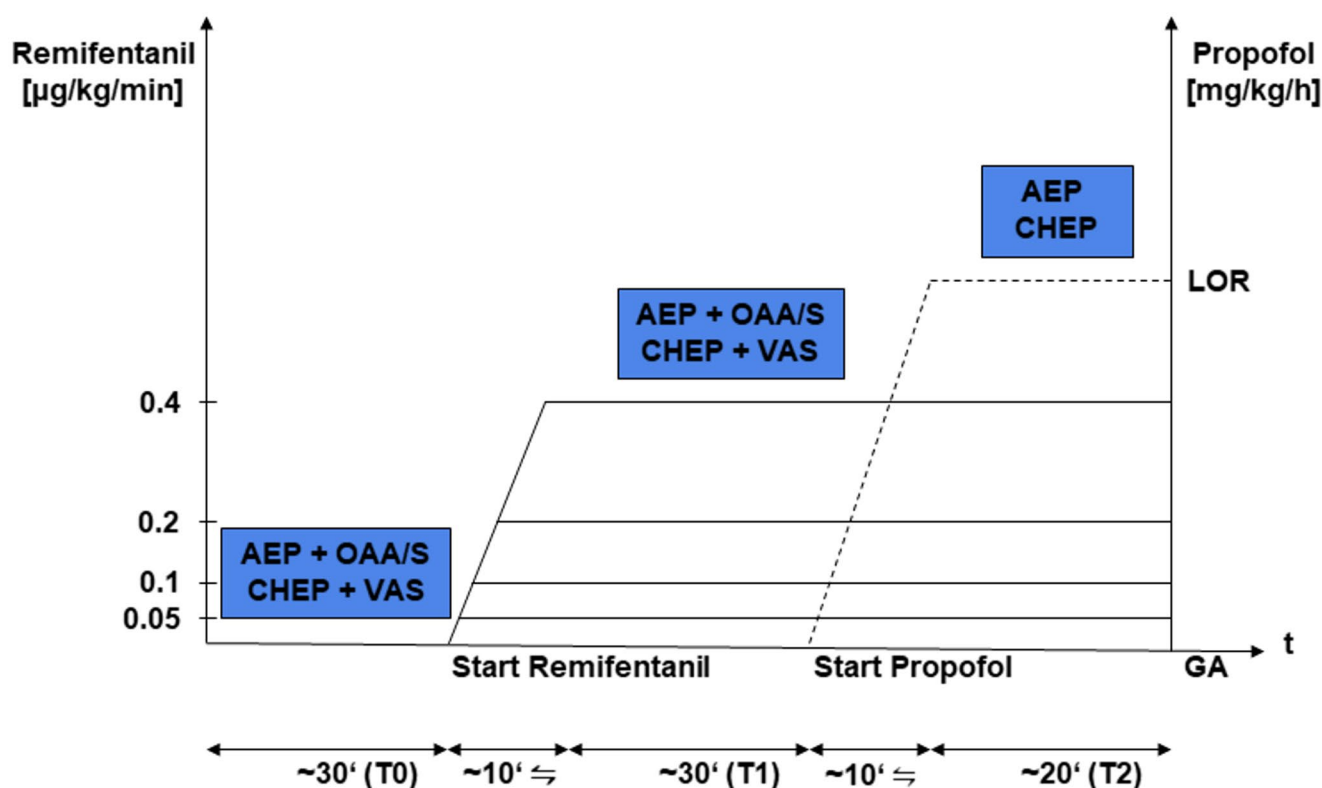


Fig. 1 Study protocol. First, recordings were performed without any medication (T0). Next, remifentanyl infusion was started in four different concentrations (T1). EEG recordings were initiated after a 10-minute equilibration period ($\rightleftharpoons$). Ultimately, propofol was administered

to induce loss of responsiveness (LOR; T2). Again, recordings began after 10 min of equilibration. After the recordings were completed, general anesthesia (GA) was maintained for surgery

and occipital positions, and the BrainVision Recorder software (Brain Products, Gilching, Germany). The sampling rate was set at 5 kHz. CHEPs were generated after 0.3–30 Hz bandpass filtering over a 2048 ms analysis time, with stimulus-synchronous averaging across 120 sweeps, i.e., the entire 4×30 stimulation sequences [39]. P1N2 amplitudes were analyzed using BrainVision Analyzer 2 software (Brain Products, Gilching, Germany). For analysis, the absolute P1N2 amplitudes at T0 were used. Due to high inter-individual amplitude variation at T0, we assessed the relative changes of P1N2 between T0 and T1. MLAEPs were produced after 26–400 Hz bandpass filtering and stimulus-synchronous averaging over 1000 sweeps. Pa and Nb potential peaks were analyzed using BrainVision Analyzer 2 software (Brain Products, Gilching, Germany).

2.6 Level of sedation

The level of sedation during remifentanyl infusion was clinically determined using the OAA/S scale, which ranges from 5 (patient responding to a name call in a normal tone, i.e., fully awake) to 1 (patient not responding to mild stimulation, i.e., deep sedation) [7].

2.7 Statistical analysis

For analysis of the primary endpoint, we applied Spearman's rank correlation. The total sample size calculation for the primary endpoint resulted in 112 patients (28 per group), assuming a 2-sided error of 0.0125 (Bonferroni's correction for four different dosage groups), a power of 80%, and a correlation coefficient of 0.6 [36]. We used non-parametric tests in our statistics as normality could not always be assumed. Each patient was randomly assigned to a single concentration group. To compare the analysis results between groups, we used the Kruskal-Wallis Test with Dunn-Sidak post-hoc correction to test for significant differences. In cases of a significant difference, we applied the Jonckheere-Terpstra test for trend to assess monotonicity. Therefore, we downloaded the *jtttest* function from MATLABCentral. We used the Spearman rank correlation to evaluate the relationship between VAS and CHEP amplitudes. To evaluate the relative change, we calculated the sign test.

Table 1 Basic characteristics and recorded variables stratified by the remifentanyl groups

	Group1	Group2	Group3	Group4	p-value
remifentanyl ($\mu\text{g/kg/min}$)	0.05	0.1	0.2	0.4	
n	31	30	31	27	
Sex (f/m)	12/19	14/16	19/12	16/11	0.246
Age (yrs)	41 (21,49)	41 (18,50)	43 (20,49)	39 (18,48)	0.122
Weight (kg)	86 (55,157)	78 (49,125)	80 (58,114)	78 (52,111)	0.196
Height (m)	178 (162,194)	175 (156,197)	172 (152,197)	170 (163,187)	0.338
BMI (kg/m^2)	26.0 (19.3,43.5)	26.7 (17.7,35.9)	26.5 (19.4,33.3)	26.2 (19.5,35.8)	0.811
VAS(0–10)	6 (1,10)	5 (0,10)	3 (0,10)	1 (0,9)	< 0.001
CHEPS [μV]					
@ T0	3.68 (1.24,13.04)	2.58 (0.28,8.12)	3.94 (0.91,26.11)	3.48 (0.95,17.80)	0.151
% change T1 vs. T0	−48.1 (−90.1,63.0)	−43.6 (−100,5.5)	−40.4 (−100,3.7)	−33.8 (−100.0,404.2)	0.914
Pa latency @ T0 [ms]	51 (37.56)	53 (33,59)	53 (36.58)	50 (37,60)	0.369
% change T1 vs T0	1.96 (−6.67,69.76)	1.79 (−6.78,78.05)	3.57 (−11.63,56.76)	4.65 (−9.80,19.51)	0.545
Nb latency @ T0 [ms]	60 (50.82)	62 (54.73)	61 (49.70)	59 (42.81)	0.325
% change T1 vs T0	1.72 (−5.00,58.18)	0 (−8.62,52.73)	3.23 (−5.26,8.57)	1.61 (−10.45,26.19)	0.198

All data are presented as median and range. The p-values were derived by the Kruskal-Wallis test or the Chi-Squared test. Statistical significance is presented in bold font.

3 Results

3.1 Patient data

During the course of the study, 11 patients were excluded due to intolerance to heat pain ($n=1$), loss of responsiveness at T0 ($n=1$), missing CHEP triggers ($n=1$), thoracic rigidity ($n=2$), and protocol violations ($n=6$). To include the calculated number of patients in the study, 10 additional patients were recruited after consulting the ethics committee and the statistic advisory board, and randomized as follows: patients replacing dropouts due to technical issues (missing CHEP trigger, protocol violations) received the same group distribution as the original patients. For patients who replaced dropouts due to thoracic rigidity and loss of responsiveness at T0, a new randomization was conducted. Therefore, the data of 119 patients were analyzed. The majority of patients underwent thyroid surgery ($n=74$; 62%), followed by joint and ligament surgery ($n=22$; 19%), trauma surgery ($n=8$; 7%), and spine surgery ($n=7$; 6%). Eight patients (7%) underwent surgery that did not belong to either of the above groups. Table 1 presents the patient characteristics in the analyzed patient population, stratified by remifentanyl concentration.

3.2 Alteration of VAS and CHEP amplitudes upon remifentanyl infusion

3.2.1 VAS

At T0, the median individual pain threshold was 53°C , ranging from 49°C to 54°C . The initial VAS values at T0 were set to 10 for all patients. At T1, median VAS values ranged

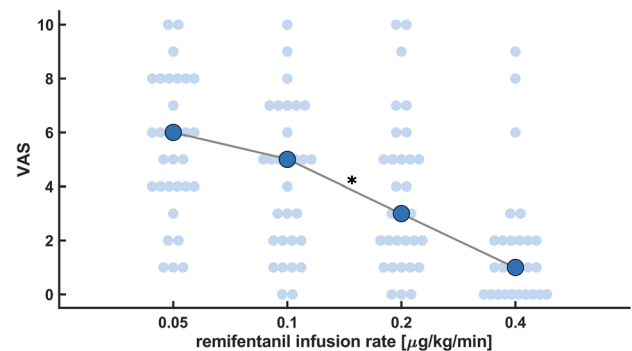


Fig. 2 Superplot presenting the VAS scores of the four remifentanyl groups at T1. The single dots represent individual patients. The large dots present the group-level median. The VAS showed a significantly decreasing trend with remifentanyl concentration ($p<0.001$; Jonckheere-Terpstra Test)

between 1 and 6 (Table 1 and Fig. 2). The VAS at the highest concentration was significantly lower than the VAS in the others. There were no significant differences in VAS in groups 1, 2, and 3. The Jonckheere-Terpstra Test indicated a significant monotonic trend ($p<0.001$)

3.2.2 CHEPs

CHEP amplitudes could not be detected in all patients. At T0, we did not detect PIN2 in 11 patients (group 1: $n=5$; group 2: $n=3$; group 3: $n=3$). Additionally, five patients (group 2: $n=3$; group 3: $n=1$; group 4: $n=1$) had no detectable amplitudes at T1.

At baseline (T0), we did not observe significant differences in PIN2 between groups (Fig. 3A and Table 1). Within the different remifentanyl groups, PIN2 significantly decreased from T0 to T1 (group 1: $p<0.001$; group

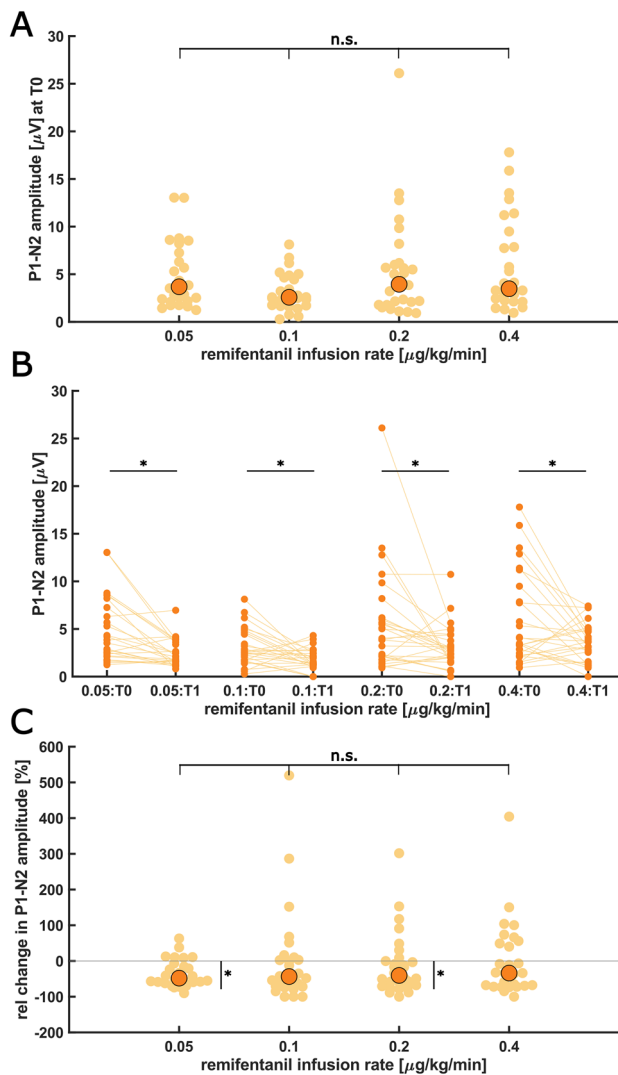


Fig. 3 Superplots presenting P1N2 of the four remifentanyl groups at T0 (A), T0 vs. T1 (B) and the relative change in P1N2 for each patient at T1 vs T0 (C) A) The amplitudes at T0 were not significantly different ($p=0.156$) B) P1N2 significantly decreased from T0 to T1 at each concentration C) The relative change in P1N2 was not significantly different among the groups ($p=0.914$), but group 1 and group 3 showed a significant relative change Note that patients with detectable P1N2 at T0 and none at T1 are displayed as -100% . The single dots represent individual patients. The large dots present the group-level median

2: $p=0.009$; group 3: $p=0.006$; group 4: $p=0.029$; Fig. 3B). This was also true for the relative P1N2 changes from T0 to T1 in groups 1 and 3 (Fig. 3C). However, we did not observe significant differences in the relative P1N2 changes between the different groups (Fig. 3C and Table 1). Furthermore, no correlation could be found between VAS and absolute P1N2 at T1 ($r=0.013$, $p=0.895$), as well as between VAS and relative changes in P1N2 between T0 and T1 ($r=0.067$, $p=0.491$). Supplemental Figure S1 shows the corresponding scatter plots.

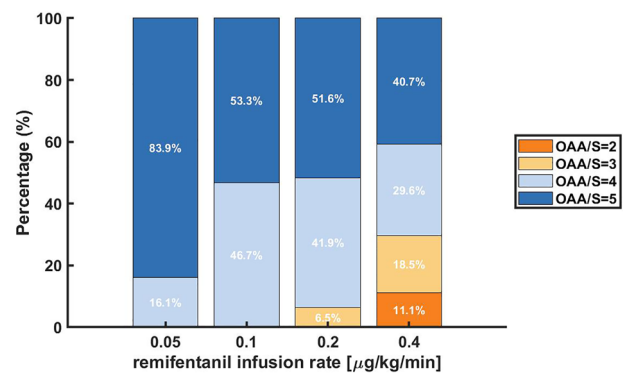


Fig. 4 OAA/S scores at T1

3.3 Sedative effects

As expected, the OAA/S score at T0 was 5 for all patients. At T1 (Fig. 4), a profound correlation with the infused remifentanyl dose could be found ($r=-0.35$; $p<0.001$; supplemental Figure S2).

3.4 AEPs

This clinical finding was corroborated by our AEP measurements (Table 1 and Fig. 5). Both, Pa and Nb latencies did not differ significantly among the groups at T0 (Fig. 5A and B). Pa significantly increased from T0 to T1 in groups 1 ($p=0.010$), 3 ($p=0.013$), and 4 ($p=0.029$), but not in group 2 ($p=0.134$) (Fig. 5C). For Nb, we found significant differences in groups 1 ($p=0.004$) and 3 ($p=0.003$), but not in groups 2 ($p=0.474$) and 4 ($p=0.435$) (Figure 5D). The relative changes were not significantly different among groups (Fig. 5E and F). But the within-group relative change was significant for Nb in group 1 and 3. We had missing AEP data in 11 patients (4 in group 1, 3 in group 2, and 2 in groups 3 and 4, respectively). Table 1 contains the statistical details.

3.5 Propofol-induced loss of responsiveness and CHEP

In the EEG data recorded during GA after propofol-induced loss of responsiveness, P1N2 could no longer be identified.

3.6 Gender differences

Gender differences were analyzed independently of the study groups (Table 2). Females showed significantly higher CHEP amplitudes at T0 compared with their male counterparts ($p=0.023$) as well as a greater absolute and relative reduction at T1. Furthermore, their VAS scores at T1 were significantly lower ($p=0.021$).

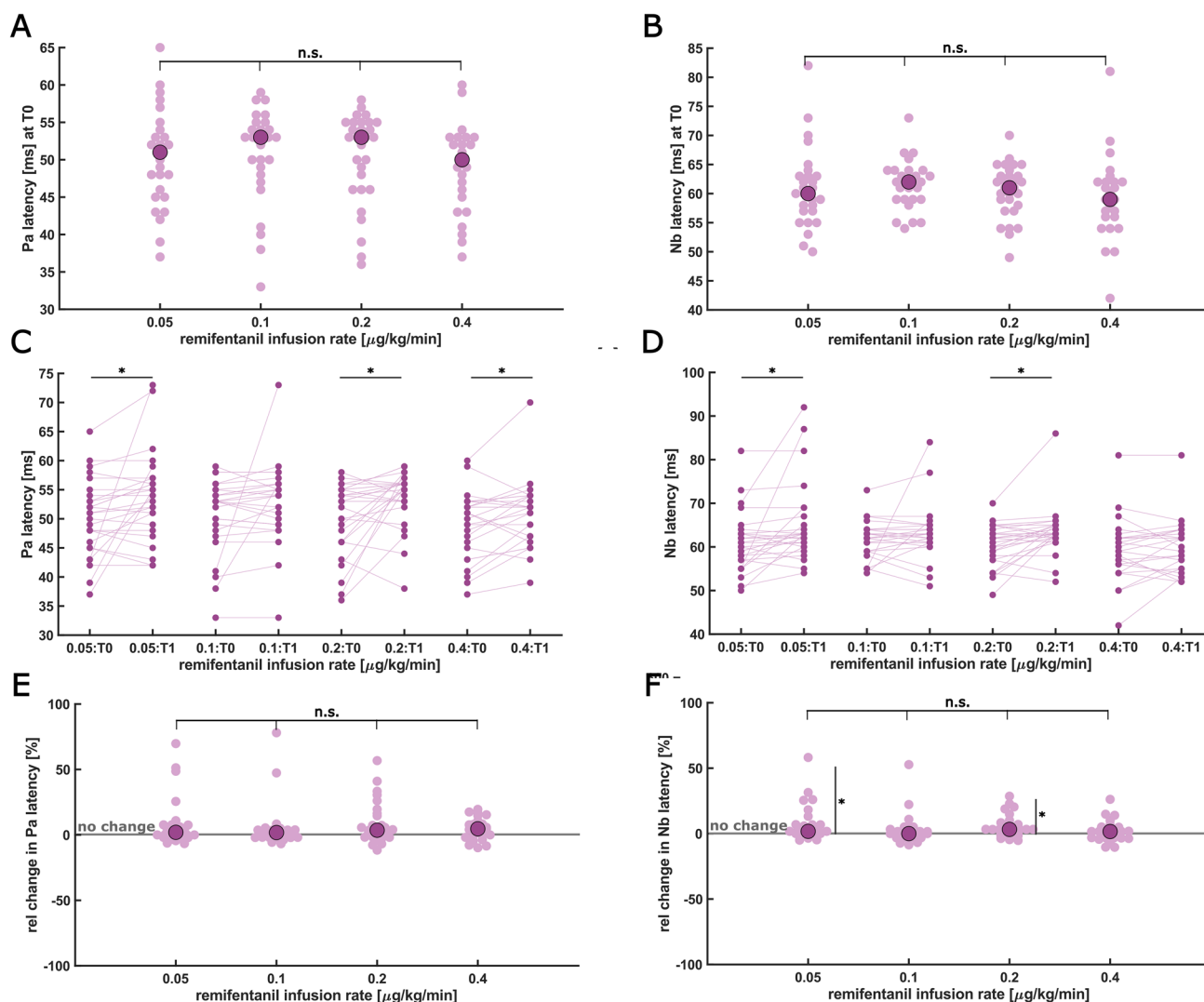


Fig. 5 AEP Pa (**A**, **C**, **E**) and Nb (**B**, **D**, **F**) latencies **A**) There was no significant difference in Pa latency at T0 among the 4 groups ($p=0.101$) **B**) There was no significant difference in Nb latency at T0 among the 4 groups ($p=0.098$) **C**) There was a significant increase in Pa latency from T0 to T1 in groups 1, 3 and 4 **D**) There was a significant increase

in Nb latency from T0 to T1 in groups 1 and 3 **E**) There was no significant difference in the relative change in Pa latency from T0 to T1 among the 4 groups ($p=0.545$) **F**) There was no significant difference in the relative change in Nb latency from T0 to T1 among the 4 groups ($p=0.198$), but groups 1 and 3 showed a significant relative change

Table 2 Gender specific differences. mean $\pm$ standard deviation

Group	female	male	p	total
n	61	58		119
T0				
VAS	10 (0)	10 (0)		10 (0)
CHEP- Amplitude [μ V]	5.76 (4.87)	3.91 (3.21)	0.023	4.85 (4.22)
T1				
VAS	3.3 (2.7)	4.5 (3.0)	0.021	3.9 (2.9)
P1-N2 Amplitude	3.13 (2.06)	2.57 (1.41)	0.11	2.86 (1.80)
D				
Amplitude T1/T0 (%)	81% (73)	108% (119)	0,16	94% (98)
Patients with amplitude reduction T1/T0 n (%)	38 (70%)	34 (69%)	0,91	72 (70%)

4 Discussion

The aim of our present study was to investigate the applicability of CHEPs as a direct and objective measure of the analgesic component of general anesthesia. We, therefore, primarily tested whether a reduction in subjective heat pain perception (represented by a reduction in the VAS score) upon remifentanyl infusion is accompanied by decreased CHEP amplitudes.

4.1 VAS and CHEPs

VAS scores and remifentanyl dosage showed a significant inverse correlation. This finding is in good agreement with

the known analgesic effects of remifentanyl that have been demonstrated in different pain models, such as the dose-dependent increase of the heat pain threshold [14, 20].

Analyzing the EEG recordings for P1N2, we yielded the following results. First, we could not detect CHEPs in all study patients. In general, there are many possibilities why CHEPs cannot be detected, ranging from structural damage of the nociceptive pathways at any stage (e.g., small fiber neuropathy, central transmission defects), skin alterations (e.g. scars, edema), inter-individual variability (e.g. age), drugs, vigilance, to technical aspects (e.g. artifacts, stimulation parameters) [2, 34, 37]. All patients experienced pain at T0, excluding structural damage to the nociceptive pathways as the possible cause. This is also true for the influence of (sedative) drugs, since no drugs were used at this stage of the study. Furthermore, we only included patients up to the age of 50; age should not be a relevant factor. We can also rule out visible alterations to the skin or underlying structures, as this was checked before the thermode was applied. All 11 patients in whom P1N2 were not detectable at T0 also had no detectable P1N2 at T1. Therefore, technical aspects, especially artifacts, seem most likely. In the 5 patients who showed no P1N2 at T1 only, additional factors, such as sedation or altered pain vigilance, may have played a role. Within each group investigated, we found a significant reduction of P1N2 upon remifentanyl infusion. In isolation, this result suggests that P1N2 reduction may resemble opioid effects on the nociceptive pathway, leading to reduced cortical responsiveness. However, P1N2 were not significantly altered between the groups, indicating a dose-independent effect. Furthermore, we could not establish the anticipated relationship between VAS scores and P1N2, suggesting the presence of further influences on CHEPs. These might be

1. sedative effects of remifentanyl: These effects were investigated clinically and electrophysiologically. Using the OAA/S score and MLAEP, we found dose-dependent sedative effects of the used remifentanyl concentrations (Figs. 5 and 4). With increasing concentrations, both the analgesic and the sedative components of remifentanyl increase, and sedation may have influenced conscious processing of pain. Unfortunately, the analgesic and sedative effects cannot be examined separately in our study design, limiting our ability to further examine their relative influences on CHEPs.
2. The high inter-individual variability of absolute P1N2 may have contributed to the low correlation between absolute P1N2 and VAS. However, relative changes in P1N2 also did not correlate strongly with VAS. This finding suggests that P1N2 seems sensitive to the presence of remifentanyl but may have limited ability to discriminate

between different remifentanyl concentrations (see Fig. 3B).

3. About 30% of the study population showed increased instead of decreased CHEP amplitudes during remifentanyl infusion compared with the initial measurement. This might be due to lower signal quality in the initial measurement, resulting from a higher rate of artifacts in awake patients (e.g. motion artifacts from agitation).
4. Furthermore, an investigator bias cannot be completely excluded since investigators who analyzed the EEG data were blinded against the used remifentanyl dose, but not against the time of measurement (T0 or T1). Having in mind that CHEPs must be detectable in the EEG in the absence of analgesics, investigators could have misinterpreted low-amplitude artifacts as CHEP amplitudes. At T1, with lower amounts of signal noise, correct potentials may have been detected with higher amplitudes.

In summary, we could not establish the expected correlation between subjective pain perception and P1N2 reduction following remifentanyl infusion. Besides the analgesic component of remifentanyl, P1N2 appear to be influenced by other factors, with sedation likely playing an important role.

4.2 CHEPs and propofol-induced LOR

We also investigated whether CHEP amplitudes could be used to measure antinociceptive drug effects under GA. For this purpose, LOR was induced by the hypnotic propofol. Unfortunately, we were unable to detect any CHEP amplitudes in the EEG data recorded during the simultaneous application of remifentanyl and propofol. In our previous study, we found that administration of propofol in subanesthetic doses induced a reduction in P1N2 amplitudes without generating hypnotic effects. The same was true for remifentanyl [38]. In the present study, propofol and remifentanyl were administered together in doses used for GA that are considerably higher. Propofol and remifentanyl act synergistically, amplifying their analgesic and hypnotic properties [21, 32]. Most likely, the combination and potentiation of the antinociceptive and hypnotic effects of both drugs led to the abolishment of CHEPs. Therefore, the use of CHEPs for monitoring analgesic drug effects during general anesthesia does not seem to be feasible.

4.3 The influence of sex on CHEPs

Depending on gender, pain manifests in different ways. There is a controversial discussion about sex-specific effects on CHEPs: Some authors have not found any gender-specific influence on CHEPs [6], while others have found higher amplitudes and shorter latencies in females compared to

males [12, 23]. In our study population, we also observed significantly higher amplitudes at T0 in women, in good agreement with data from a recently published international multicenter study [12].

4.4 Limitations

This study has, of course, several limitations. We observed a high inter-individual variability in CHEP amplitudes, especially at T0. Low values at T0 probably contributed to cases, where the amplitudes were higher at T1. Further, they were not detectable in all patients. This may limit their robustness as an objective marker of analgesic effects. Moreover, remifentanyl-induced analgesia cannot be separated from its sedative effects, which can influence cortical processing of nociceptive stimuli. Finally, CHEPs were abolished after propofol-induced loss of responsiveness, precluding their use for nociception monitoring during general anesthesia.

4.5 Conclusion

In summary, we could not demonstrate the anticipated correlation between subjective pain perception measured by the VAS and CHEP amplitude reduction. Nevertheless, we detected a significant reduction in P1N2 upon remifentanyl infusion. Further studies are needed to identify the precise mechanisms responsible for this finding. In conclusion, evaluating P1N2 does not appear to be an appropriate tool for directly assessing the analgesic component of general anesthesia.

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Author contributions G.S., G.U., and R.Z. conceived and designed the study. G.U. and R.Z. collected the data. D.J. and M.K. interpreted the data and performed the statistical analysis. R.Z., M.K., and G.S. wrote the manuscript and prepared the figures. All authors reviewed, edited, and approved the final version for submission.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of Interest None.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Witten/Herdecke University, Witten, Germany (15.08.2011, No. 62/2010).

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent to publication Not applicable.

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