Measurement of the nociceptive flexion reflex threshold in critically ill patients - a monocentric prospective observational study

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Abstract

Background Pain detection and treatment is a major challenge in the care of critically ill patients. However, in addition to the risk of analgesic undersupply, there is also the risk of overanalgesia. In the perioperative context, the measurement of the nociceptive flexion reflex threshold has become established for measuring the level of analgesia. To date, however, it is unclear whether measurement of NFRT can be usefully applied to noncommunicating, ventilated, and analgosedated ICU patients. Therefore, the aim of the present study was to investigate whether NFRT measurement correlates with the Behavioral Pain Scale (BPS) in critically ill, analgosedated, and mechanically ventilated patients and whether it can also detect possible overanalgesia.

Methods In this prospective, observational, single-center study, 114 patients were included. All patients were admitted to the surgical Intensive Care Unit of the University hospital Ulm, Germany. First measurements of the NFRT and the Behavioral Pain Scale (BPS) were conducted within 12 hours after admission. In the further observation period, a structured pain assessment was performed at least twice daily until extubation (Group A: BPS + NFRT, Group B: BPS). Univariate analysis was performed to evaluate possible associations between NFRT measurement and baseline characteristics. Furthermore, mixed linear regression modeling was used to evaluate possible effects of administered analgesics or sedatives on NFRT.

Results NFRT correlates negatively with the Behavioral Pain Scale. NFRT was almost twice as high in patients with a RASS of -5 compared with patients with a RASS ≥ -4 (RASS -5 - NFRT: 59.40 vs. RASS -4 - NFRT: 29.00, $p < 0.001$). By means of NFRT measurement, potential overanalgesia could not be detected.

Conclusion The NFRT measurement reliably correlates negatively with the Behavioral Pain Scale in critically ill patients. In patients with RASS scores ≤ -4, in whom analgesia level is often difficult to assess, NFRT measurement provides guidance in the assessment of nociceptive processes. However, in order to detect possible overanalgesia and to derive therapeutic consequences, a defined stimulus threshold must be determined for the critically ill patient, above which the absence of pain can be safely assumed.

Trial Registration Retrospectively registered at German Clinical Trials Register, registration number DRKS00021149, date of registration: March 26, 2020. https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00021149

Background

According to the International Association for the study of pain (IASP) Williams et al. describe pain as a "stressful experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components" (1). The conscious perception of pain and its emotional connotation are largely suppressed under general anesthesia (2,3). However, even under deep anesthesia, nociception, i.e. pain encoding and processing, occurs constantly (4). Pain is not only an important issue in the perioperative context, but also in intensive care patients. Despite the demand for a more moderate analgosedation, as mentioned in the eCASH concept and many guidelines, in critically ill patient an overuse in analgosedation is common (5–7). Therefore, potentially similar processes of nociception as under general anesthesia can be assumed for this specific patient group. In present, pain assessment in profoundly analgosedated, critically ill patients who are not able to self-address their pain, e.g .using Numeric Rating Scale (NRS), is predominantly limited to the interpretation of physiological parameters. Best validated score for this issue is the Behavioural Pain Scale (BPS) (8). The BPS uses adaption to ventilator, grimacing and upper limb movement for interpreting pain. However, interpretation of pain based on subjective criteria bears the risk of misinterpretation. Especially in patients with deep analgosedation the established pain assessment tools reach their limits (8–10). To address the limitations of pain assessment in critically ill non-communicable patients, measurement of the RIII-reflex threshold of the nociceptive flexor

reflex (NFR) is of particular interest. Under general anesthesia, measurement of the NFR-threshold (NFRT) has been shown to correlate negatively with the response rate to a painful stimulus (11–14). An equally important aspect in the context of pain assessment in critically ill patients is the quantification of adequate and appropriate analgesia. Especially in deeply sedated patients, analgesia is usually performed empirically. This carries the risk of opioid-induced overanalgesia with negative side effects such as respiratory depression, constipation, ileus and pruritus (15).

Therefore, the aim of the present study was to investigate whether the measurement of the NFRT in a heterogeneous patient population of critically ill and non-communicable patients correlates with the BPS and whether a possible overanalgesia can be detected with NFRT measurement.

Methods

The prospective, observational, single-center study was conducted in the observation period from 11/2018 until 03/2020 (positive vote of the local ethics committee, Trial-Code No. 284/18) in the interdisciplinary surgical intensive care unit (ICU), University Hospital of Ulm, Germany. The data evaluation took place in the period from 04/2020 to 11/2020. The study was retrospectively registered at the German Clinical Trials Register (DRKS-ID: DRKS00021149). The study protocol was in accordance to the Declaration of Helsinki ethical guidelines. All patients or their legal designees signed written informed consent to take part in this study.

Inclusion criteria:

- Age ≥ 18 years
- need for intensive care treatment due to an emergency or elective surgery
- expected stay on the ICU for at least 24 hours
- written informed consent of the patient's legal representative and post-hoc verbal and written patient consent

Exclusion criteria:

- Age < 18 years
- Pregnancy
- neurological diseases associated with a restriction of peripheral nerve conduction (paraplegia, muscular dystrophy, polyneuropathy, myopathy, multiple sclerosis, Guillain-Barré syndrome, other denervating neurological diseases)
- Pacemaker/implanted cardioverter defibrillator
- subsequently withdrawn consent to participate in the study
- missing informed consent

The following patient-related data were collected during the stay on the ICU:

- Age at enrollment
- gender
- ICU length of stay
- disease severity scores
- BPS and Richmond Agitation Sedation Scale (RASS)
- primary reason for ICU admission
- several laboratory parameters (subsumed under the Sequential organ failure assessment score - SOFA-Score, Therapeutic Intervention Scoring System TISS-28, Simplified Acute Physiology Score-SAPS II)

- vital signs (heart rate, blood pressure, respiratory rate)
- Analgesics and Hypnotics

Pain assessment

Behavioural Pain Scale

BPS is based on visual observation of facial expression, upper limb movements and compliance with mechanical ventilation in critically ill and analgosedated patients (Table 1).

Table 1 - Behavioural Pain Scale

Attribute	Description	Points
Facial Expression	relaxed	1 P
	partly strained	2 P
	strongly strained	3 P
	grimacing	4 P
Upper limb movement	no movement	1 P
	partially bent	2 P
	Tightening with flexion of the fingers	3 P
	Constantly bent	4 P
Adaptation to ventilator	Tolerates ventilation	1 P
	irritation of cough, but tolerates ventilation most of the time	2 P
	Breathing and pressing against the respirator	3 P
	controlled ventilation not possible	4 P

The 3 observation criteria are assigned point values from 0 points (no reaction) to 4 points (complete reaction). The interpretation of these values allows conclusions about the analgesia level of the patient. A score of 3 points indicates no pain. Scores between 4 and 5 points indicate slight pain. Scores between 6 and 11 points indicate an unacceptable level of pain and 12 points are classified as maximum pain. The BPS evaluates pain by assessing physiological patterns of behavior. If these physiological patterns are disturbed for various reasons, it is conceivable that a wrong interpretation of the actual pain level in critically ill patients is given (5). Under these circumstances, additional subjective parameters such as sweat secretion, heart rate and blood pressure response must also be used to interpret pain.

NFRT measurement

The nociceptive flexion reflex is a polysynaptic and multisegmental spinal retraction reflex of the lower limb. It is primarily caused by electrocutaneous stimulation of the ipsilateral anterior tibial nerve by activating afferent A-delta fibers. The quantitative measurement of the reflex responses is performed by means of surface electromyography (EMG) via the anterior tibial muscle. Of particular interest is the late reflex reaction, the so-called RIII component of NFR, with a latency of up to 150 ms (16,17). The automated measurement of the NFRT is performed by using the Paintracker® (Dolosys, Berlin). If the output parameters are correct, the device generates current pulses that start below the empirically determined stimulus threshold at 2 mA and gradually increase in steps of 0.1 - 3.0 mA. A complete measurement generates a data set based on a total of 50 emitted current pulses. A stimulus threshold of 15 mA or higher is assumed as adequate analgesia. For the measurement procedures at the patient, we kindly refer to the publication by Wildemeersch et al.(18).

Study plan

As displayed in Fig.1, potentially eligible patients were first evaluated according to inclusion and exclusion criteria. Then the simple, unrestricted randomization was performed using a random table generated by "Research Randomizer".

Patients assigned even numbers were randomized to the group in which both BPS and NFRT were measured, referred to as Group A. Patients who were assigned odd numbers were randomized to the group where only BPS was measured, termed Group B. Because no comparable study has yet been conducted to measure and interpret NFRT in critically ill patients, measurement of a comparison group in which pain was determined exclusively by BPS was intended to reveal possible structural inequalities in the NFRT group. A structured pain assessment was performed in all study patients within 12 hours of admission to the intensive care unit. The pain assessment was conducted by 2 trained doctoral students over the entire study period. Group A patients received both BPS- and NFRT measurements. In group B, pain levels were measured exclusively with BPS. In the further observation period, a structured pain assessment was performed at least twice daily until extubation (Group A: BPS + NFRT, Group B: BPS). BPS and NFRT were measured in all patients at rest with a minimum interval of 30 minutes from the previous nursing or medical intervention. Whenever possible, repetitive measurements were performed, which are included in the data analysis. This explains the difference between the number of patients measured and the number of NFRT- measurements as well as the different number of measured BPS and RASS values.

Analgesia and sedation

Analgesics

In both groups, patients received sufentanil (µg/h) or remifentanil (mg/h) as continuous intravenous infusions. Augmentatively, patients received Metamizole at a dose of 4 g/24 hours and, if deemed necessary, Piritramid as a bolus administration.

Hypnotics

As intravenous hypnotics, patients received either propofol (mg/h) or lormetazepam (mg/h) as a continuous intravenous infusion.

Data Analysis

Sample size calculation and power analysis

Initially, a case number per group of n = 100 patients each was calculated via GPower 3.1. Due to the SARS-CoV-2 pandemic that started in spring 2020, we decided to terminate the study with the current number of cases prematurely. Comparable studies include a patient population of between 40 and 100 patients (18,19). Nevertheless, to provide statistical evidence for the significance of the study results under the given number of cases, we performed a post-hoc power analysis. Based on the observed cross-sectional correlation of the NFRT with the BPS at baseline (N=52, r=0.35), the calculated power was 73%.

Statistical analysis

Data were collected in Microsoft EXCEL 2010® (Microsoft Corp., Redmond, WA) and analyzed using Sigma Plot Version 14® for Windows (Systat Software GmbH, Erkrath, Germany) and SAS Version 9.4 (SAS Institute GmbH, Heidelberg, Germany). Quantitative data were expressed as median, minimum and maximum and, for nonparametric distributions, were compared using the Wilcoxon matched-pairs test. For the analysis of the independent samples, the Student's t-test was used for normally distributed data (testing by Shapiro-Wilk). In the absence of normal distribution, the Mann-Whitney rank-sum test was performed. All results reported have to be interpreted in an exploratory manner, since we did not adjust the p-values for multiple testing. In order to evaluate possible associations between the measured NFRT and the most important baseline characteristics a linear model (LM) was applied. Further, we used mixed linear regression modelling (MLM) for assessing the effect of given analgesics and sedatives, respectively, which enabled us to account

for the repeated measures structure of the data. Specifically, the NFRT served as the depended variable in these models, while all single baseline characteristics (LM) and mediations (MLM) were defined as the independent predictors. For all MLMs the time point of measurement was added as a further independent predictor. The repeated measures structure was implemented by means of a random intercept. Resulting estimates along with their corresponding p-values may be used to evaluate each predictor's impact on NFRT. An explorative, two-sided type 1 error level of 5% was applied to all analyses.

Results

Patient characteristics

During the observation period, 144 potentially eligible patients were admitted to the interdisciplinary surgical ICU at the University Hospital Ulm, Germany. After simple randomization and enrollment into the study, 30 patients had to be excluded for the following reasons before a final data analysis could be performed: 2 patients died before obtaining written consent, 10 patients had not yet signed post-hoc informed consent at the time of data analysis, in 6 patients the data set was incomplete, 7 patients could not be measured in the specified 12-hour interval after admission to the ICU. 5 other patients were excluded after checking the NFRT due to an incorrect measurement (Fig 1). Finally, a total of 57 patients in each group was included in the further analysis (see Table 2). In Group B, patients were older and mortality was higher compared to Group A. Furthermore, compared to group A, group B patients had statistically significantly more frequent BPS point values of 4, which indicates slight pain. Men were over-represented in both groups. In group A, patients were sedated deeper on average compared to Group B and received more remifentanil.

The following comments on the results refer exclusively to Group A, as Group B served only as a control group:

In detail, the 57 patients in group A were 61 years old. 44 were male, 13 female. The mean length of stay at the ICU was 10 days. 6 patients died during their stay in the ICU. The NFRT was measured at least twice a day in all patients of Group A, preferably with repeated measurements (interval 30-60 minutes after the first measurement). In addition, BPS and RASS were recorded at each NFRT assessment. In 51 out of 57 patients, the pain assessment predominantly resulted in a BPS score of 3. 21 of these patients had a BPS score of 4 in at least one measurement. Higher BPS scores (> 4) could only be detected in 11 patients (Table 2). In terms of a reliable data analysis, the further evaluation of the data was performed in patients with a BPS of 3 or 4.

Table 2 Characteristics of patient population			
Variable	**Patients** n =114		
	Group A BPS-NFRT n = 57	**Group B BPS** n = 57	**P**
Age Median *	61.0 (54.0 - 72.0)	68.0 (63.0 - 81.0)	<0.001
Sex, n (%)			
male	44 (77.2)	37 (64.9)	0.221
female	13 (22.8)	20 (35.1)	0.070
ICU - LOS Median *	10.0 (5.0 - 19.0)	10.0 (5.0 - 20.5)	0.756
Mortality, n (%)	6.0 (10.5)	15.0 (26.3)	0.029
Disease severity scoring			
SAPS II *	36.0 (29.0 – 45.0)	38.0 (32.0 – 47.0)	0.374
TISS-28 *	19.0 (14.0 – 24.0)	18.0 (10.0 - 24.0)	0.285
Analgesics and Sedatives			
Sufentanil µg/h Median * n (%)	 12.5 (5.6 - 20.0) 8 (14.0)	 15.0 (5.0 - 20.0) 7 (12.3)	 0.388 0.68
Remifentanil mg/h Median * n (%)	 0.3 (0.2 - 0.4) 37 (64.9)	 0.2 (0.2 - 0.3) 37 (64.9)	 <0.001 1.000
Metamizol mg/h Median * n (%)	 168.0 (168.0 - 168.0) 36 (63.2)	 168.0 (168.0 - 168.0) 39 (69.4)	 0.167 0.570
Propofol mg/h Median * n (%)	 200.0 (140.0 - 200.0) 41 (71.9)	 200.0 (100.0 -280.0) 37 (64.9)	 1.000 0.462
Lormetazepam mg/h Median * n (%)	 0.6 (0.3 - 0.8) 12 (21.1)	 0.6 (0.5 - 0.8) 13 (22.8)	 0.801 0.74
Measurement of sedation depth and pain intensity			
Richmond Agitation Sedation Scale - Median *	-4.0 (-5.0 - -3.0)	-3.0 (-4.0 - -2.0)	0.001
Behavioral Pain Scale Median *	3.0 (3.0 - 3.0)	3.0 (3.0 - 4.0)	0.631
BPS 3 (n)	51	56	0.875
BPS 4 (n)	28	57	<0.001
BPS 5 (n)	6	4	0.38
BPS 6 (n)	2	1	n.e.
BPS 7 (n)	1	0	n.e.
BPS 8 (n)	1	0	n.e.
BPS 9 (n)	1	0	n.e.
Primary reason for ICU admission, n (%)			
neurosurgery & brain haemorrhage	13 (22.8)	16 (28.1)	0.37
abdominal surgery	15 (26.3)	15 (26.3)	1.00
trauma surgery	5 (8.8)	6 (10.5)	0.65
cardiac surgery	2 (3.5)	1 (1.8)	0.42
vascular surgery	4 (7.0)	8 (14.0)	0.16
thoracic surgery	5 (8.8)	3 (5.3)	0.37
respiratory failure	5 (8.8)	3 (5.3)	0.37
internistic medicine	----------	1 (1.8)	----------
Urology	7 (12.3)	4 (7.7)	0.24
Oral and maxillofacial surgery	1 (1.8)	----------	----------

Note: The number of cases are given in the second row for the group in which the NFR was determined, in the third row for patients in whom only the BPS was recorded. Data are shown as median* (interquartile range) or number (percentage). Rounding errors lead to a total percentage > 100%. Differences between groups are tested by Student's t-test (Shapiro-Wilk normality test passed) or Mann-Whitney U-test (normality test failed); *P* values are not adjusted for multiple testing. Abbreviation: ICU: Intensive Care Unit, SAPS II: Simplified Acute Physiology Score II, TISS-28: Therapeutic Intervention Scoring System 28, CAM-ICU: Confusion Assessment Method for the Intensive Care Unit.

Difference between NFRTs at BPS 3 and BPS 4

The NFRTs of all patients in group A show that with n = 57 patients and 297 measurements the median threshold is 32.00 mA (IQR = 16.85 - 52.30 mA). Patients whose NFRT was measured at a BPS point value of 3, correspondingly classified as free of pain, have a statistically significantly higher threshold (n = 51 patients, 210 measurements, median threshold 36.00 mA, IQR = 20.50 - 60.00 mA, Mann-Whitney rank-sum test - p-value: 0.048). With a BPS point value of 4, corresponding to slight pain, a median NFRT of 26.90 mA (IQR = 16.85 - 52.3 mA, measurements = 53) was determined in 28 patients. In comparison to the overall population, there is no statistically significant difference (Mann-Whitney rank-sum test - p-value: 0.079). However, a comparison of the measured stimulus thresholds between BPS 3 and BPS 4 indicates that patients with assumed absence of pain had a statistically significantly higher NFRT than patients with mild pain (Mann-Whitney rank-sum test - p-value: 0.005). The results are displayed in Figure 3.

Univariate Analysis

In a second step, univariate analysis was used to determine whether the NFRT is statistically affected by demographic factors. The univariate analysis did not show a statistically significant effect on NFRT for any of the investigated parameters (Table 3). Since the results of the univariate models exhibited no significance, we did not run a more complex multivariable regression model afterwards. In addition, a mixed linear model was used to investigate the effect of the applied analgesics and sedatives on the NFRT in group A (Table 4).

Table 3 Univariate analysis of NFR-threshold

independent variable	NFR-threshold		
	Estimate	SE	p-value
Age	-0.38	0.37	0.299
Sex (male vs female)	12.56	11.44	0.278
Size	0.87	0.58	0.143
Weight	0.42	0.31	0.184
Length of stay on ICU	2.55	1.81	0.166

Calculated Effects of the used analgesics and hypnotics on the NFRT in a mixed model

In patients with measured NFRTs at BPS 3 and 4 (Fig. 4), it could be shown in the mixed model that an increase of 1 mg/h in remifentanil would have led to a statistically significant increase in the NFRT by 56.29 mA (estimate = 56.29, SE = 21.90, p-value = 0.011). At BPS point values of 3, a 1mg/h increase in remifentanil dosage would have resulted in a statistically significant 60.03 mA increase in NFRT (estimate = 60.03, SE = 24.38, p-value = 0.015). At BPS point values of 4, a 1 mg/h increase in remifentanil would have resulted in a 75.30 mA increase in NFRT. Due to the number of available readings, the result is not statistically significant (estimate = 75.30, SE = 66.43, p-value = 0.267). If patients had a BPS score of 4, a dose increase of sufentanil by 1 µg/h would have resulted in a statistically significant decrease of the NFRT by -6.8 mA (estimate = -6.800, SE = 1.467, p-value = 0.017). At BPS point values of 3 and of 3 and 4 when considered together, there was no statistically significant effect of a dose increase of sufentanil on the NFRT (BPS 3 & 4: estimate = -0.014, SE = 0.904, p-value = 0.988, BPS 3: estimate = 0.166, SE = 0.972, p-value = 0.866). A dose increase of metamizole would not have led to statistically significant changes in the NFRT in the calculation model. A potential increase of metamizole by 1 mg/h did not lead to statistically significant changes in the NFRT in the calculation model. Likewise, no statistically significant change in the NFRT could be achieved by bolus administration of piritramide (1 mg). The decrease in the NFRT at a BPS point value of 3 can be explained as a statistical effect due to the small number of measured values.

Neither an increase in propofol nor lormetazepam dose by 1mg/h increased the NFRT in the mixed-model in a clinically relevant manner. The calculated statistical significance of an increase in propofol dose is interpreted as a purely statistical effect.

Table 4 Linear mixed model - NFR-threshold affecting parameters

independent variable	NFR-threshold (mA) - BPS 3 & 4			NFR-threshold (mA) BPS 3			NFR-threshold (mA) BPS 4		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
Remifentanil mg/h	56.29	21.90	**0.011**	60.03	24.38	**0.015**	75.30	66.43	0.267
Sufentanil µg/h	-0.014	0.904	0.988	0.166	0.972	0.866	-6.800	1.467	**0.017**
Metamizol mg/h	0.231	0.583	0.695	-0.009	0.680	0.989	0.403	0.747	0.598
Piritramid mg Bolus	6.185	14.01	0.668	-3.547	0.598	0.867	n.e.	n.e.	n.e.
Propofol mg/h	0.099	0.024	7.1e-05	0.102	0.025	6.6e-05	0.092	0.056	0.122
Lormetazepam mg/h	2.581	5.414	0.635	2.231	5.418	0.682	n.e.	n.e.	n.e.

n.e. = not estimated

NFRT at different RASS values

Comparing the measured median NFRTs at different RASS values, it is seen that the deeper the sedation, the higher the corresponding stimulus threshold. This is graphically depicted in Figure 4, with the corresponding statistical analysis. Since several measurements were performed per patient, analogous to the BPS-NFR measurements, a simple correlation analysis is not statistically valid. A multivariate analysis of the correlation between NFRT and RASS was not performed, since it was demonstrated in the mixed model calculation that a change in the dose of i.v.-hypnotics had no significant effect on NFRT.

Discussion

The present study demonstrates that NFRT correlates negatively with BPS in a heterogeneous analgosedated and ventilated population of critically ill patients. Nearly 49% of all patients examined in the NFRT group and 100% of the comparison group had at least once pain symptoms at rest classified as mild pain (BP ≥ 4). This is consistent with the findings of other studies on pain in the critically ill patient (18,19). The question that arises in this context is whether mild pain is to be tolerated in the context of an intensive care treatment? Considering the effects of pain on the organism, the aim of intensive care treatment must always be absence from pain (20,21). Untreated pain leads to psychological stress and to disturbances of the recovery process, which ultimately increases mortality (21). In particular, the paininduced endogenous stress response leads to increased catecholamine release, decreased tissue perfusion and impaired humoral immune response (20–22). Modern intensive care therapy is increasingly moving toward the best possible analgesia with only moderate sedation. This is called for both in guidelines and, for example, in Vincent's eCASH concept (5,7). Nevertheless, the vast majority of mechanically ventilated patients continue to be too deeply sedated (23–25). However, in deeply sedated patients, the established pain assessment tools reach their limits. In these patients, the interpretation of physiological parameters such as heart rate and blood pressure changes should allow conclusions to be drawn about the pain symptomatology (8,10). But what if, for example, the patient has developed tachyarrythmia absoluta due to sepsis or severe hemodynamic fluctuations occur in the setting of critical illness? Under such prerequisites, measurement of NFRT might be useful to objectify the analgesia level. However, to date, conclusive studies on NFRT measurement in a heterogeneous cohort of critically ill patients are still missing. The current evidence of NFRT measurement in a clinical setting is based on few studies. Jakuscheit et al. were able to demonstrate by measuring intraoperative NFRT that the mechanisms and processes of nociception and analgesia are adequately displayed. The median stimulus threshold determined in this study was 25 mA after skin suture but still under general anesthesia (19).

Wildemeersch et al were able to measure a median NFRT of 39 mA under remifentanil and 48 mA under sufentanil, but without correlating the results with a validated pain scale in their feasibility study of the use of the nociceptive flexion reflex in the critically ill patient (18). The obtained stimulus thresholds largely coincide with the NFRTs measured in the present study. This in turn demonstrates that the measurement of NFRT also works in a heterogeneous cohort of critically ill patients.

Part of the primary question was to find out whether NFRT measurement can be used to detect potential overanalgesia. During the data analysis, it became apparent that this question cannot be answered based on the current evidence and the data obtained within the study. To detect potential overanalgesia, a threshold would need to be known above which adequate analgesia could be assumed in all conceivable circumstances. Due to the individuality of pain, the inability of patients under analgesia to report their pain intensity, and the weaknesses of established pain recording instruments, determining this threshold seems difficult with current technical capabilities. Through the statistical mixed model approach, however, it could be calculated that a dose increase of remifentanil leads to a sufficient increase in NFRT. This corresponds with studies on the use of NFRT in the perioperative setting (19,22). Contrasting results were obtained by calculating a potential dose increase of sufentanil in the studied subjects. Under a dose increase of sufentanil, a decrease in the median NFRT would have occurred. The decrease in NFRT under sufentanil therapy can be interpreted as an indication of a hyperalgesia syndrome. So far, studies with this specific question in critically ill patients do not exist. However, it is well known that high-dose and prolonged opioid therapy can lead to opioid-induced hyperalgesia and possibly the development of tolerance (23–25). Furthermore, proinflammatory cytokines, such as those released in increased amounts in the context of surgical trauma or infection, may contribute to pain chronification (26). In conclusion, the observed phenomenon of NFRT decrease with a dose increase of sufentanil remains not adequately explained in the context of the current study.

However, the aim of modern intensive care therapy is to adapt both analgesia and sedation to each individual patient. The credo is less sedation, more analgesia. (5–7,27,28). Certain conditions, such as cerebral hemorrhages or ARDS, may still require deep analgesia (29,30). The risk of over- or under-analgesia is comparatively high. In the present study, patients with RASS scores of -5 had more than twice as high NFRTs compared with patients with RASS scores of -4 and higher. From a purely objective point of view, if the stimulus threshold > 20 mA assumed as adequate analgesia in the literature is taken into account, these deeply sedated patients can be considered to exhibit overanalgesia (11,14,18,19). In the interpretation of these results, however, it must be taken into account that ultimately only nociception is recorded. A valid assessment of pain sensation below RASS values of ≤ -4 is not yet possible. However, the effects of overanalgesia are not only of an apparent manner, such as hypotension, bradycardia, respiratory depression, and intestinal paralysis due to excessive use of opioids. Opioids can potentially cause negative immunomodulatory effects, which should be considered, especially in the critically ill patient (31–36).

The study is subject to some limitations that need to be discussed. The study was performed in an interdisciplinary surgical intensive care unit on a heterogeneous patient population. Thus, the results cannot be applied in general. Simple randomization was used to avoid structural inequalities. Adapted for the study design, matching of patients would also have been appropriate. Due to the SARS-CoV-2 pandemic, the study had to be terminated prematurely for various reasons (attention to infectiological features, reduction of scheduled surgical operations). Taking this into account, an extensive statistical analysis was performed as well as a posthoc power analysis for the primary research question. The statistical power of 73% calculated for the primary research did not reach the power of 80% specified in the study plan. It can be assumed that the power could have been achieved with a higher number of cases. The study design with multiple measurements per patient does not exclude the possibility that single patients with multiple measurements of NFRT are overrepresented in the present results. To statistically counter this effect, the possible factors influencing the NFRT, if known, were included in the calculations. The main criticism of NFRT-measurements remains the methodology per se. It is uncertain from which stimulus threshold one can speak of sufficient analgesia in critically ill patients. Furthermore,

only nociception can be recorded by the NFRT-measurement. Up to now, the extent to which the profoundly analgosedated critically ill patient perceives pain cannot be objectified by using NFRT measurement

Conclusion

In conclusion, based on the present study results, the clinical application of NFRT measurement may be indicated in profoundly analgosed critically ill patients when the measurement of the analgesia level with established pain assessment scales reaches its limits. The use of NFRT monitoring at least objectifies nociceptive processes. Its use is also conceivable in patients who are difficult to treat with established analgesic regimens. However, it must be emphasized that more studies on the use of NFRT monitoring in critically ill patients are urgently needed in order to be able to draw conclusions about the level of the stimulus threshold for adequate analgesia in the non-communicable patient.

Abbreviations

IASP	International Association for the study of pain
BPS	Behavioral Pain Scale
EMG	Electro Myography
ICU	Intensive Care Unit
LM	Linear Model
MLM	Mixed Linear Regression Modelling
NFR	Nociceptive Flexor Reflex
NFRT	Nociceptive Flexor Reflex Threshold
NRS	Numeric Rating Scale
RASS	Richmond Agitation Sedation Scale
SAPS II	Simplified Acute Physiology Score II
SOFA-Score	Sequential organ failure assessment score
TISS 28	Therapeutic Intervention Scoring System

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the University Ulm, Trial-Code No. 284/18. The study was retrospectively registered at the German Clinical Trials Register (DRKS-ID: DRKS00021149). Written informed consent was obtained from all patients, their next of skin, or another surrogate decision maker, as appropriate. If patients were unable to provide written informed consent and the next of skin or a designated person was not available, the inclusion procedure for emergency situations was applied. Post hoc written informed consent was obtained in these latter patients.

Consent for publication

not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors´ contributions

BZ and EB conducted the study, interpreted data and drafted the manuscript. BM revised the manuscript and did the statistical analysis. SW and SG revised the manuscript. PS und RS were responsible for the measurements and revised the manuscript.

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