EJA-D-22-00110

EJA

Eur J Anaesthesiol 2022; **37**:1–10

ORIGINAL ARTICLE

Predicting personalised remifentanil effect site concentration for surgical incision using the nociception level index

A prospective calibration and validation study

Laurent Perrin, Max Bisdorff, Sarah Saxena, Ionut Tabolcea, Isabelle Huybrechts, Luc Van Obbergh, Edgard Engelman, Luc Barvais* and Sean Coeckelenbergh*

BACKGROUND Inadequate antinociception can cause haemodynamic instability. The nociception level (NOL) index measures response to noxious stimuli, but its capacity to predict optimal antinociception is unknown.

OBJECTIVE To determine if NOL index change to a tetanic stimulus in cardiac and noncardiac surgery patients could predict the required remifentanil concentration for haemodynamic stability at skin incision.

DESIGN A prospective two-phase cohort study.

SETTING University hospital.

PATIENTS Patients undergoing remifentanil-propofol target controlled infusion (TCI) anaesthesia.

INTERVENTIONS During the calibration phase, investigators evaluated the tetanic stimulus induced NOL index change under standardised TCI remifentanil-propofol anaesthesia during a no-touch period [bispectral index (BIS) between 40 and 60, NOL index under 15]. If the NOL index change was 20 or greater following tetanic stimulation, investigators repeated the tetanus at higher remifentanil concentrations until the response was blunted. Surgeons incised the skin at this remifentanil concentration. The investigators derived a prediction model and in the validation phase calculated, using the NOL response to a single tetanus, the required incision remifentanil concentration for the start of surgery.

MAIN OUTCOME Haemodynamic stability at incision [i.e. maximum heart rate (HR) $<$ 20% increase from baseline, minimum HR (40 bpm) and mean arterial pressure (MAP) $\pm$ $<$20% of baseline].

RESULTS During the calibration phase, no patient had hypertension. Two patients had a HR increase slightly greater than 20% (25.4 and 26.7%) within the first 2 min of surgery, but neither of these two patients had a HR above 76 bpm. Two patients were slightly hypotensive after incision (MAP 64 and 73 mmHg). During the validation phase, neither tachycardia nor hypotension occurred, but MAP increased to 21.5% above baseline for one patient.

CONCLUSION During a no-touch period in patients under steady-state general anaesthesia [propofol effect site concentration (Ce) required for BIS between 40 and 60], the NOL index response to a tetanic stimulus under remifentanil antinociception can be used to personalise remifentanil Ce for the start of surgery and ensure stable haemodynamics.

TRIAL REGISTRATION ClinicalTrials.gov: NCT03324269

Published online xx month 2022

Introduction

Personalising antinociception remains a challenge in perioperative medicine.[1] It is standard care to administer analgesics using empirical models followed by titration based on the patient's haemodynamic response, reflex movement or spontaneous breathing.[2] This 'one-size fits all' approach, however, forces anaesthetists to be one step

*LB and SC are shared co-last authors.

From the Department of Anaesthesia and Resuscitation, Erasme Hospital, Université Libre de Bruxelles, Brussels (LP, IT, IH, LVO, EE, LB, SC), the Department of Anaesthesia, Charleroi University Hospital Centre, Charleroi (MB, SS), EW Data Analysis, Brussels, Belgium (EE), the Department of Anaesthesiology and Intensive Care, Université Paris-Saclay, Paul Brousse Hospital, Assistance Publique Hôpitaux de Paris, Villejuif, France (SC), Outcomes Research Consortium, Cleveland, OH, USA (SC)

Correspondence to Sean Coeckelenbergh, Department of Anaesthesia and Resuscitation, Erasme Hospital, Université Libre de Bruxelles, Brussels 1070, Belgium
E-mail: sean.coeckelenbergh@gmail.com

DOI:10.1097/EJA.0000000000001751

behind nociception and predisposes patients to the adverse effects of excessive or inadequate antinociception. On the one hand, excessive antinociception eliminates sympathetic tonus, which leads to hypotension with the risk of decreased myocardial perfusion,[3] while on the other, inadequate antinociception during a noxious stimulus leads to an excessive sympathetic response that causes tachycardia and hypertension. The latter may lead to acute cardiac events, especially in patients suffering from ischaemic heart disease.[4] Both extremes of antinociception could be associated with postoperative adverse events.[5–7]

A recently developed monitor, the PMD-200 (Medasense, Ramat Gan, Israel), measures the NOL index and has shown considerable potential in optimising antinociception.[8] This is the first index to measure the nociception-antinociception (NAN) balance that derives from multiple parameters. The NAN combines information from pulse wave variations, galvanic skin responses, peripheral temperature and heart rate (HR) variability. The NAN has been shown to be useful in guiding remifentanil administration[9–12] and was associated with decreased intra-operative hypotension,[13] as well as improved postoperative patient comfort.[14]

However, until now, all protocols using the NOL index have been based on a *reactive* algorithm (i.e. the value is assessed after an event occurs and subsequently the opioid dose is modified).[13–15] A standard reproducible noxious stimulus, such as tetanic stimulation applied superficial to the ulnar nerve, has been shown to be well tolerated, equivalent to the noxious stimulus of a surgical incision, and useful in assessing a patient's response to nociception.[16,17] Furthermore, a response to tetanic stimulation at a remifentanil effect site concentration (Ce) of $4\,ng\,ml^{-1}$ has been detected with a nociception monitor, with minimal haemodynamic changes.[18] We therefore aimed to determine if a NOL index change (**Δ** NOL) during a single standard tetanic stimulus performed before surgical incision at a predefined level of EEG depression [bispectral index (BIS) range: 40 to 60] and a remifentanil Ce of $4\,ng\,ml^{-1}$ could predict the personalised remifentanil Ce needed to prevent the haemodynamic response associated with the skin incision during either cardiac or noncardiac surgery. In addition, we also aimed to compare the sensitivity and specificity of the NOL index with other potential indicators of nociception following two noxious events (tetanic stimulation and surgical incision).

Materials and methods

This single-centre prospective interventional study was conducted at the Erasme University Hospital in Brussels, Belgium. The local ethics committee accepted this study (EC Study No. P2017/424, 27 September 2017; ClinicalTrials.gov: NCT03324269, principal investigator Luc Barvais) and informed consent was obtained from all participants. The manuscript adheres to the STROBE reporting guidelines.

This study consisted of two phases. The first phase tested if titration of remifentanil such that the **Δ** NOL was less than 20 after a tetanic stimulus could determine a personalised remifentanil Ce for surgical antinociception (i.e. haemodynamic stability for 2 min from the start of the skin incision). With the data from this first cohort of patients, we then derived a formula that aimed to predict an adequate remifentanil Ce for antinociception at the start of surgery using only a single tetanic test with a remifentanil Ce of $4\,ng\,ml^{-1}$. The second phase then assessed the derived formula's capacity to predict the remifentanil Ce needed for surgical antinociception in a new patient cohort. Included patients were adults undergoing either noncardiac surgery (e.g. thyroidectomy, parathyroidectomy, breast surgery, abdominoplasty) or coronary artery grafting using cardiac bypass (cardiac surgery). For each phase, patients were split into two groups: cardiac and noncardiac surgery patients. Exclusion criteria were as follows: pregnancy, allergy to anaesthetic drugs, illicit substance abuse, pre-operative analgesic drug use, arrhythmia, implanted pacemaker and the use of alpha-2-adrenergic agonists or ketamine. The cohort was purposefully heterogeneous to determine if a single formula could predict remifentanil requirements regardless of age, sex or cardiovascular status.

Anaesthesia protocol

All patients received a standard oral premedication of 0.5 mg of alprazolam 1 h before transfer to the operating theatre, as per institutional protocol. Standard monitoring consisted of pulse oximetry, noninvasive blood pressure (oscillometry, measured immediately preceding and following the noxious event), neuromuscular monitoring (TOFwatch; Idmed, Marseille, France), BIS (Medtronic, Dublin, Ireland) and a 5-lead ECG. All cardiac surgery patients were monitored using arterial cannulation (radial or femoral) and a central venous catheter. The NOL index (PMD-200; Medasense, Israel) was measured with a finger probe placed on the index or middle finger on the side contralateral to the noninvasive blood pressure monitoring cuff or arterial catheter. Additional monitoring modalities were left to the discretion of the attending anaesthesiologist.

Induction and maintenance of anaesthesia was achieved with propofol TCI (Schnider pharmacokinetic model) and remifentanil TCI (Minto pharmacokinetic model): for noncardiac surgery, a computer-controlled infusion system (Toolbox v. 4.0) was used, and for cardiac surgery, two preprogrammed syringe infusion pumps (Agilia SP TIVA; Fresenius Kabi) were used. Propofol was titrated to maintain BIS between 40 and 60 and to avoid burst suppression at all times. Neuromuscular blockade was achieved with rocuronium $0.6\,mg\,kg^{-1}$ for noncardiac surgery and $1\,mg\,kg^{-1}$ for cardiac surgery. Intubation was performed at a remifentanil Ce of $4\,ng\,ml^{-1}$.

Ventilation was initiated at a tidal volume of 7 ml kg^{-1} ideal body weight and at a frequency of 12 per minute. Ventilation parameters were adapted to maintain end-tidal (Et) CO_2 levels between 30 and 36 mmHg or arterial CO_2 at 40 mmHg.

Calibration phase

After at least 10 min following tracheal intubation, the remifentanil Ce remained at 4 ng ml^{-1} and patients underwent a no-touch period during which the NOL index was stabilised at a baseline value under 15 for at least 1 min and propofol was titrated to maintain the BIS between 40 and 60. If the baseline NOL index did not decrease to less than 15 at a remifentanil Ce of 4 ng ml^{-1} after 5 min of no touch, the remifentanil Ce was increased to 5 ng ml^{-1}. Once a baseline NOL value was achieved, a 100 Hz, 50 mA, 30 s tetanic stimulus (TET100) was delivered using two electrodes placed over the ulnar nerve (Algiscan, Idmed, France). A 2-min observation period commenced with the start of the tetanic stimulation. A tetanic stimulus was chosen, as it has been shown to be a reproducible noxious stimulus that is well tolerated during general anaesthesia.[11,16] The trend in the NOL index change was assessed visually and changes that did not follow a steady increase were not considered (abrupt and inconsistent changes were considered as artefacts). The maximum value during these 2 min was noted. If the **Δ** NOL index value increased at least 20, the remifentanil Ce was increased by 1 ng ml^{-1}. Once this Ce was reached, another TET100 was applied and the **Δ** NOL was again assessed. This step was repeated until the **Δ** NOL did not exceed 19. If the **Δ** NOL was less than 20 poststimulation at 4 ng ml^{-1} remifentanil Ce, the remifentanil Ce was reduced by 3 ng ml^{-1} and tested following the same procedure (Fig. 1a). Surgical incision was then performed at the calibrated remifentanil Ce. Using a linear regression model, these data were used to derive a personalised remifentanil Ce for the start of surgery, from the first TET100 at 4 ng ml^{-1}.

Validation phase

In the validation phase, we applied the formula to calculate the remifentanil Ce for the start of surgery in a new cohort of patients (Fig. 1b**)**. Only a single TET100 was applied during the no-touch calibration phase when the remifentanil Ce was 4 ng ml^{-1}. The personalised target remifentanil Ce reached equilibrium at least 2 min before the surgical incision.

Haemodynamic endpoints

The goal of personalising remifentanil Ce was to have optimal personalised NAN balance to avoid haemodynamic instability (hypertension, hypotension, tachycardia and bradycardia) in association with the skin incision. Baseline HR, measured from the pre-operative ECG, and mean arterial blood pressure (MAP), measured non-invasively with oscillometry, were collected at the pre-operative consultation. Haemodynamic instability was defined as a deviation of at least 20% of the patient's baseline MAP (hypertension and hypotension) and an increase of at least 20% of HR (tachycardia). Bradycardia was defined as HR less than 40 bpm.

Prestimulus values were determined during a 1-min period before TET100 and their variation was observed over the 2 min from the start of the stimulus. Some 15 min after this observation period, the pre-incision baseline was obtained and the variation was observed for 2 min from the start of the incision. Delta NOL, delta BIS, delta HR and delta MAP were defined as the difference between their maximum value after the stimulus and their prestimulus value. Data were collected at 30 s intervals using Innovian (Dräger, Lübeck, Germany) intra-operative recording software and at 5 s intervals with the PMD-200 (Medasense, Israel) NOL index monitoring device.

Statistical analysis

Data are presented as the median [IQR] or number of patients. For each of the phases (calibration or validation), MAP, HR, NOL index and BIS were compared between the groups by a Kruskal–Wallis analysis of variance. Within each group, the repeated measures were compared by a Friedman one-way repeated measures test. Multiple comparisons were performed by the Dunn's Multiple Comparison Test. The categorical variables were compared with the χ^2 test. Demographic data were compared by Kruskal–Wallis analysis of variance and Dunn's Multiple Comparison Test or Fisher exact test.

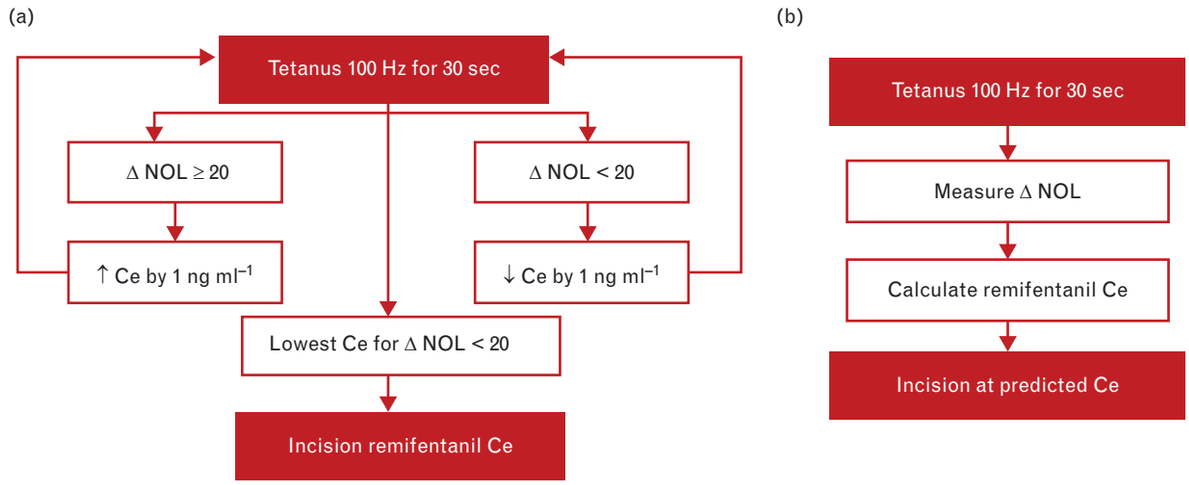
Posthoc analyses receiver-operating characteristic (ROC) curves were plotted for the NOL index, HR, MAP and BIS, to investigate their ability to discriminate between values before and after the start of surgery and before and after tetanic stimulation. In these analyses, patients from the calibration and validation phases were grouped together. The ROC area under curve (AUC) and the mean sensitivity at a working point specificity of 88% (start of surgery) or 85% (tetanic stimulation), and their 95% confidence intervals (95% CI), were calculated. ROC curve comparisons and the comparison of the area under the curve to the value 0.5 were calculated using the DeLong empirical method.

For all tests, P value less than 0.05 was statistically significant. The statistical analysis was performed using the NCSS 20.0.2 statistical package (NCSS, LLC; Kaysville, Utah, USA) for all tests.

Results

A total of 57 patients were screened: from October 2017 to February 2018 for the calibration phase and from October 2018 to February 2019 for the validation phase. Of these, 44 were initially included in the study, but eight were then excluded due to practical and methodological

Fig. 1 (a) Calibration phase algorithm for remifentanil titration based on NOL index change. The remifentanil effect site concentration (Ce) (Minto model) was determined by finding the remifentanil Ce to abolish the NOL index change following a single 100 Hz, 30 s, 50 mA tetanic cutaneous stimulation of the distal ulnar nerve. The initial remifentanil Ce was 4 ng ml^{-1} and propofol Ce (Schnider model) was titrated to maintain Bispectral index between 40 and 60. (b) Validation phase algorithm for remifentanil titration based on NOL index change following a single 100 Hz, 30 s, 50 mA tetanic cutaneous stimulation of the distal ulnar nerve. The remifentanil effect site concentration (Ce) (Minto model) was calculated using the following formula: *RemiCe Inc*= 0.1 Δ NOL + 3.1.



limitations: data were lost for three patients, two patients had signal interference due to electrocautery after incision, one patient was excluded because the protocol was not followed, and two patients had arrhythmias preceding the study intervention. Thus, the final analysis included 36 patients: 16 in the calibration cohort and 20 in the validation cohort. There were significant differences between noncardiac and cardiac surgery patients in terms of the sex, ASA status, age, but these criteria remained similar within each surgical group during the calibration and validation phases (Table 1).

Calibration phase

A total of 16 patients (eight, cardiac surgery; eight, noncardiac surgery) were included in the calibration phase. The remifentanil Ce required to obtain a **Δ** NOL less than 20 after TET100 ranged from 3 to 8 ng ml^{-1} and was significantly different between the cardiac and noncardiac groups. The remifentanil Ce required to limit the NOL response to TET100 was lower in the cardiac group, 4.0 [3.3 to 4.8] vs. 5.5 [5.0 to 7.0] ng ml^{-1}, $P = 0.012$ (Table 1). The NOL index increased significantly in the noncardiac group following TET100 and in both groups at the start of surgery (Fig. 2a). The **Δ** NOL after the first TET100 at a remifentanil Ce of 4 ng ml^{-1} ranged from 4 to 53 and was larger ($P = 0.04$) in the noncardiac group (Table 2). Interestingly, when using the calibrated remifentanil Ce at incision, the median **Δ** NOL was similar in both groups (Table 2). The BIS values did not change significantly following TET100 or incision and were maintained within the recommended range in both groups (Fig. 2b, Supplementary Table 1, http://links.lww.com/EJA/A764). In the cardiac group, HR decreased at induction and then returned to baseline at incision. MAP values in these patients also decreased after induction but remained lower than baseline during TET100. MAP values were comparable to baseline at incision (Fig. 2c and d). In the noncardiac surgery population, HR and MAP remained similar to baseline using the personalised calibrated remifentanil Ce for incision. Two patients, one from each group, had a HR increase more than 20% at incision: a noncardiac surgery patient with a baseline value of 55 bpm whose post incision HR was 69 bpm (25.4% above baseline) and a cardiac surgery patient whose baseline value was 60 bpm and whose post incision value 76 bpm (26.7% above baseline). Two noncardiac surgery patients were slightly hypotensive at incision (64 mmHg, or 73.6% of baseline, and 73 mmHg, or 70.9% of baseline) (Supplementary Table 2, http://links.lww.com/EJA/A764).

Linear regression model for remifentanil Ce prediction

The following equation was derived by plotting the relation between ΔNOL at 4 ng ml^{-1} and the calibrated optimal remifentanil Ce needed to limit the NOL index response during TET100:

RemiCe Inc= 0.069 Δ NOL + 3.1; CI 95% 0.069 (0.03 to 0.11) and 3.1 (2.3 to 4.4).

To facilitate clinical implementation, the equation was rounded up to:

Table 1 Patient characteristics

		Calibration study	Validation study	*P* value within surgical category
Age (years)	Cardiac surgery	77.5 [66.7 to 82.7]	70.5 [54 to 78.5]	0.18
	Noncardiac surgery	47.0 [42.5 to 59.7]	44.5 [23.5 to 60.5]	0.50
	P value between surgical category	0.0022	0.017	
Sex (M/F)	Cardiac surgery	7 / 1	7 / 3	0.76
	Noncardiac surgery	1 / 7	0 / 10	0.88
	P value between surgical category	0.01	0.003	
Heart rate (bpm) at pre-operative consultation	Cardiac surgery	68 [61 to 74]	77 [70 to 91]	0.22
	Noncardiac surgery	74 [68 to 83]	72 [67 to 86]	0.72
	P value between surgical category	0.008	1.00	
Pre-operative mean arterial pressure (mmHg)	Cardiac surgery	93.0 [80.2 to 96.2]	89.2 [86.2 to 95.2]	1.00
	Noncardiac surgery	84.0 [78.5 to 90.7]	83.3 [78.4 to 93.3]	1.00
	P value between surgical category	1.00	1.00	
ASA score (1 to 2/3 to 4)	Cardiac surgery	2 / 6	3 / 7	1.0
	Noncardiac surgery	8 / 0	9 / 1	1.0
	P value between surgical category	0.007	0.019	
Beta blocker or calcium channel blocker (Y/N)	Cardiac surgery	7 / 1	5 / 5	0.24
	Thyroid surgery	3 / 5	1 / 9	0.41
	P value between surgical category	0.11	0.14	
Incision remifentanil effect site concentration	Cardiac surgery	4.0 [3.3 to 4.8]	4.5 [3.4 to 4.8]	1.00
	Noncardiac surgery	5.5 [5.0 to 7.0]	5.4 [5.0 to 6.4]	1.00
	P value between surgical category	0.012	0.017	

Data are median [interquartile range] or number of patients. The categorical variables were compared with the Fisher test and continuous variables by the Kruskal–Wallis test and the Dunn's Multiple Comparison Test.

$$RemiCe\ Inc = 0.1\ \Delta\ NOL + 3.1$$

RemiCe Inc, personalised remifentanil Ce before the start of surgery; Δ *NOL*, maximum NOL – NOL before the stimulus. The stimulus was a 30 s TET100 at a remifentanil Ce of 4 ng ml^{-1}.

This formula was used to calculate the remifentanil Ce target for the start of surgery during the validation phase.

Validation phase

A new cohort of 10 noncardiac and 10 cardiac surgery patients were recruited. During TET100 at a remifentanil Ce of 4 ng ml^{-1}, NOL variations ranged from 0 to 43. The NOL variation following TET100 was lower in the cardiac group (Table 2), and consequently, the personalised remifentanil Ce for incision, calculated from the formula derived during the calibration phase, was also lower in the cardiac group (Table 1). However, there was no difference within the specific surgical cohort for the remifentanil Ce targeted for incision between the calibration and validations phases (Table 1). In both groups, the personalised remifentanil Ce did not block the Δ NOL response following incision (Fig. 3a). Although the Δ NOL to the TET100 in each group at a remifentanil Ce of 4 ng ml^{-1} was different ($P = 0.02$), incision at the personalised remifentanil value led to a similar Δ NOL both groups ($P = 0.76$) (Table 2 and Fig. 3a). The median BIS value increased significantly following TET100 stimulation at a remifentanil Ce of 4 ng ml^{-1} but not following incision (Fig. 3b). After incision at the personalised remifentanil Ce, HR values (Fig. 3c) and MAP values (Fig. 3d) returned to baseline values in both groups. Only one patient in the noncardiac group had hypertension following incision (baseline MAP 79 mmHg, post incision 96 mmHg, 21.5% over baseline), while no cardiac surgery patients had arterial hypertension following incision. No patient was hypotensive or had a HR above 20% of baseline values or below 45 bpm after incision (Supplementary Table 3, http://links.lww.com/EJA/A764).

Sensitivity of monitors to nociceptive stimuli

A ROC curve analysis was carried out to determine the ability of the NOL index, BIS, HR or MAP value variations to detect nociception either during TET100 at a remifentanil Ce of 4 ng ml^{-1} or at incision at the personalised remifentanil Ce (either calibration or validation phase). This analysis shows that the Δ NOL, to both TET100 and incision, was more reliable than the other three parameters at detecting noxious stimuli, as it had a significantly greater AUC when compared with other clinical parameters such as BIS, HR and MAP (Fig. 4).

Discussion

Personalising remifentanil TCI before the start of surgery, based on the change of a sensitive nociception index to a well tolerated noxious stimulus, looks to be clinically feasible. In both cardiac and noncardiac surgery patients, the NOL index response to a tetanic stimulus at a predetermined level of remifentanil-propofol TCI anaesthesia predicted a remifentanil Ce that maintained haemodynamic stability at the start of surgery for the vast

Fig. 2 Calibration outcomes. (a) Nociception level index (NOL). (b) Bispectral index. (c) Heart rate. (d) Mean arterial pressure. The horizontal black line in the boxes represents the median value, the lower and upper box limits are the 25th and 75th percentiles. The whiskers represent the box edge ± 1.5 x inter-quartile range. The circles (severe outliers) represent box edge ± 3.0 x interquartile range. Dunn's Multiple Comparison Test: * $P < 0.05$ vs. baseline value. ** $P < 0.01$ vs. baseline value. *** $P < 0.001$ vs. baseline value. Otherwise, comparison and P value as indicated.

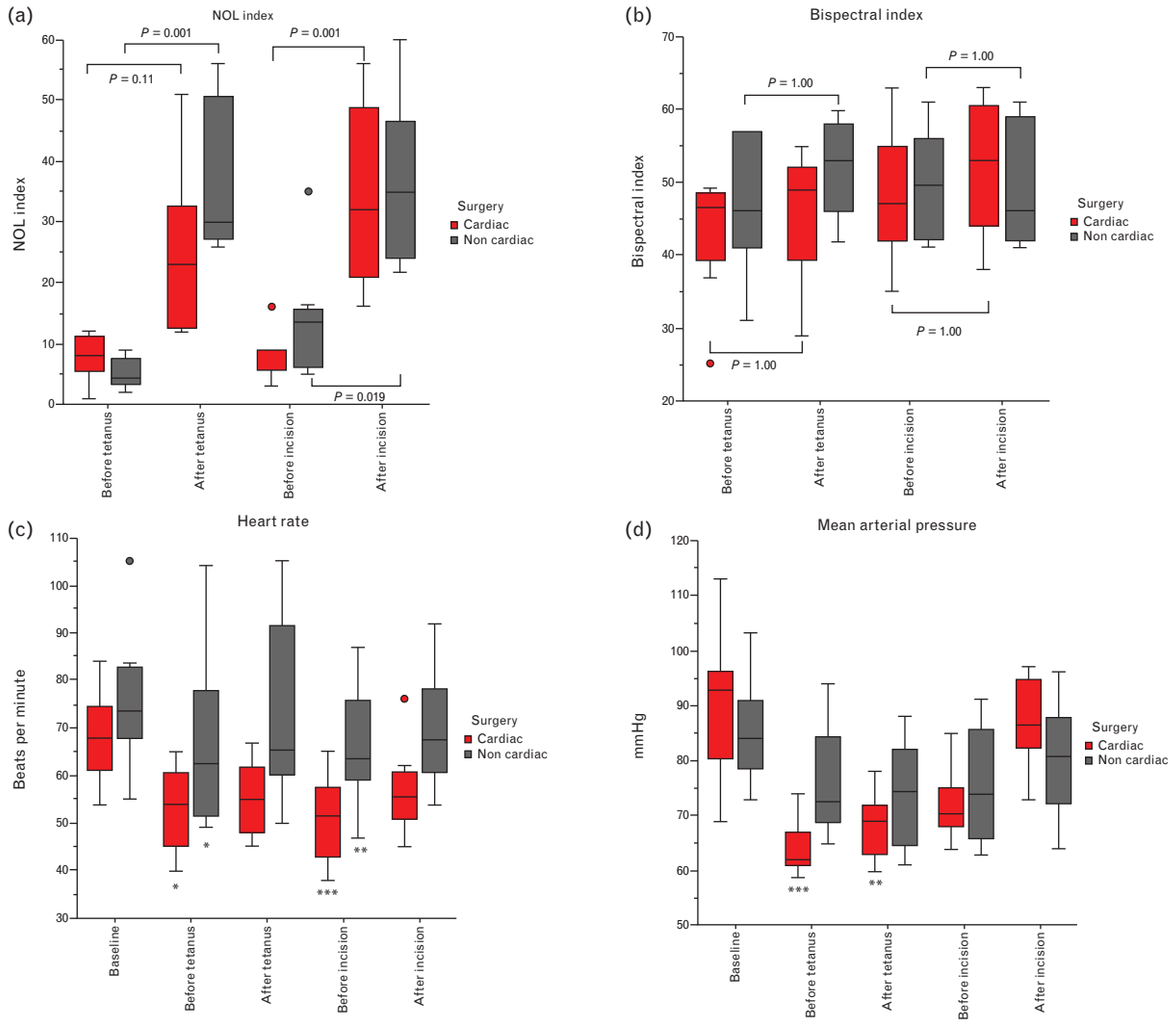
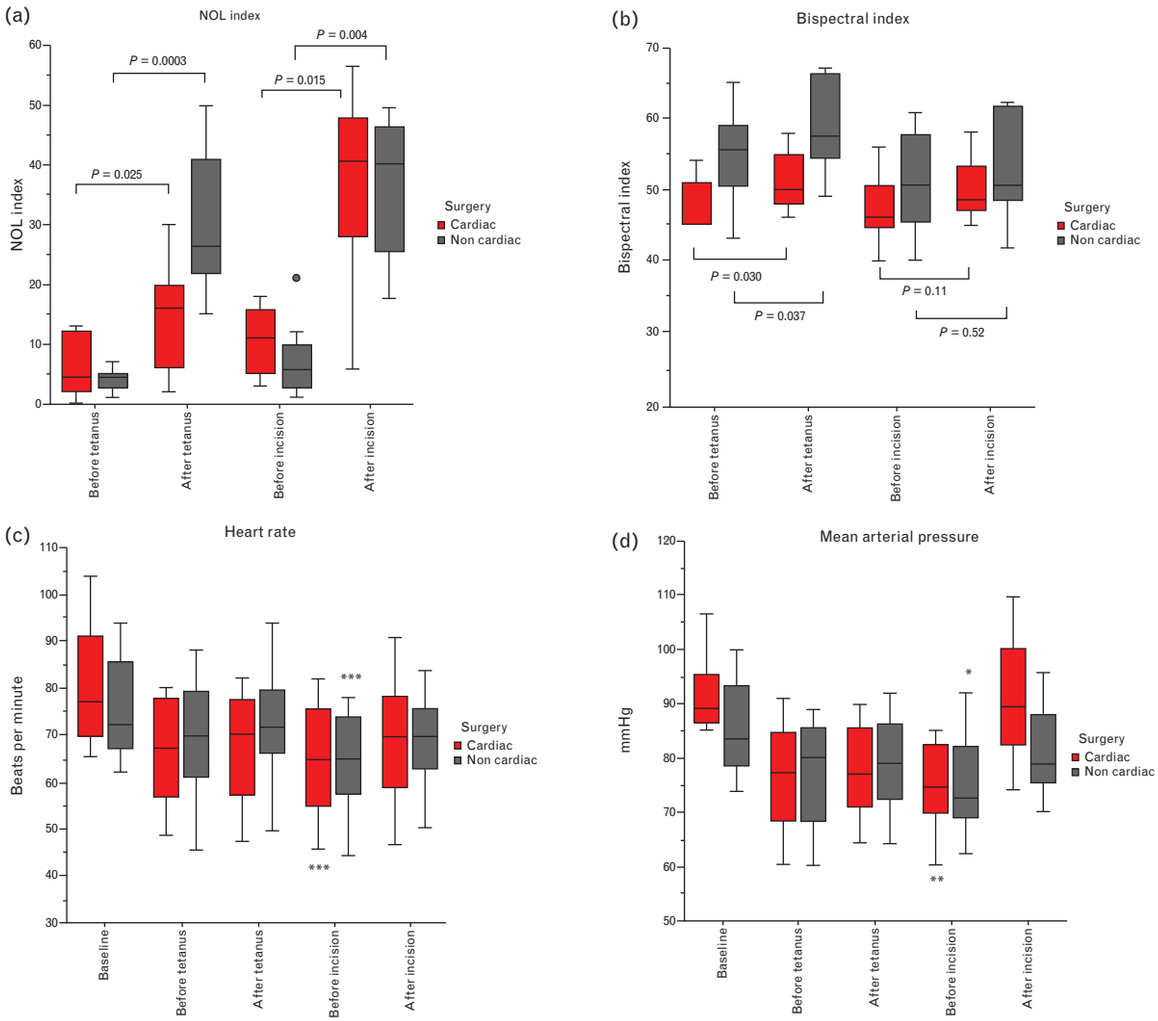


Table 2 Nociception level index change following noxious stimulation

Calibration study	Delta NOL after tetanic stimulation	Delta NOL after incision	Within-group between-times Dunn's Multiple Comparison Test
Cardiac ($n = 8$)	13 [10 to 20]	22 [10 to 29]	$P = 0.64$
Noncardiac ($n = 8$)	25 [20 to 46]	20 [17 to 29]	$P = 0.60$
Between groups Dunn's Multiple Comparison Test	$P = 0.04$	$P = 0.83$	
Validation study	**Delta NOL after tetanic stimulation**	**Delta NOL after incision**	**Within-group between-times Dunn's Multiple Comparison Test**
Cardiac ($n = 10$)	9 [0 to 17]	26 [15 to 35]	$P = 0.024$
Noncardiac ($n = 10$)	24 [19 to 36]	28 [20 to 41]	$P = 0.76$
Between-groups Dunn's Multiple Comparison Test	$P = 0.02$	$P = 0.76$	

Data are median [interquartile range].

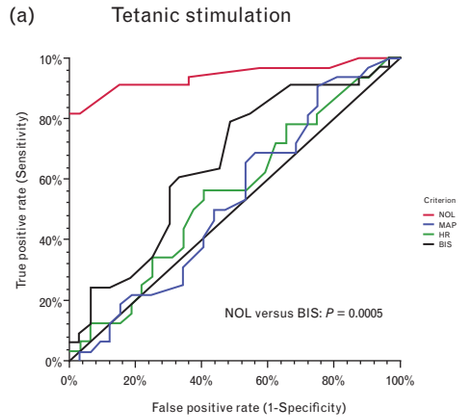
Fig. 3 Validation setting. Outcomes. (a) Nociception level index (NOL). (b) Bispectral index. (c) Heart rate. (d) Mean arterial pressure. The median level with the simultaneous 25 and 75% percentiles (the box limits) is displayed. The whisker boundaries equal the box edge ± 1.5 x inter-quartiles range and the boundaries for the severe outliers (the circles) equal the box edge ± 3.0 x inter-quartiles range. Dunn's Multiple Comparison Test: * $P < 0.05$ vs. baseline value. ** $P < 0.01$ vs. baseline value. *** $P < 0.001$ vs. baseline value. Otherwise, comparison and P-value as indicated.

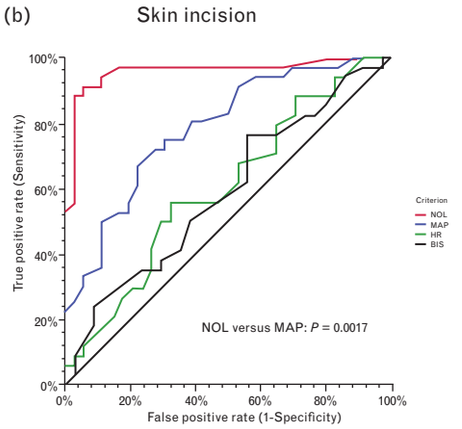


majority of patients. Predicting a remifentanil Ce for skin incision from the NOL index change to TET100 stabilised HR and allowed MAP values at the start of surgery to return to values comparable to pre-operative baseline values. Very few episodes of hypertension and tachycardia occurred. Two different approaches, either a step-by-step algorithm to calibrate nociception or a formula derived from this approach, had similar results. The second approach avoided the titration phase, which can be long and difficult from a haemodynamic point of view. It is important to note that this study only evaluated NAN balance following a tetanic stimulus and the start of surgery. After the 2-min post incision assessment period, the study ended and propofol and remifentanil infusions were titrated using the BIS and NOL values, respectively. Nevertheless, applying such a calibration approach could help anaesthetists to personalise the NAN balance at incision.

Many studies have investigated the potential of nociception monitoring during general anaesthesia, but few have focused on predicting optimal antinociception.[13–15,19–21] As a general rule, these monitors are used to guide reactive algorithms (i.e. to increase or decrease analgesics based on the change in the monitored parameter to surgical stimuli). Nociception monitors may be more sensitive than traditional clinical criteria (tachycardia, hypertension, movement and spontaneous breathing) for guiding antinociception,[8,9] but clinicians still remain one step behind nociception. Several studies have shown the benefits of guiding antinociception with the NOL index. Meijer *et al.*[13] demonstrated that during

Fig. 4 (a) Receiver operating characteristics curve analysis: discrimination of tetanic stimulation from measures before tetanic stimulation. Patients from calibration and validation phases are grouped together. Heart rate and mean arterial pressure did not perform better than random. Nociception level (NOL) outperforms bispectral index ($P = 0.0005$). (b) Receiver operating characteristics curve analysis: discrimination of skin incision from measures before skin incision. Patients from calibration and validation phases are grouped together. Heart rate and bispectral index did not perform better than random. Nociception level (NOL) outperforms mean arterial pressure ($P = 0.0017$).





Receiver operating characteristics curve analysis: discrimination of tetanic stimulation from pre-stimulation period			
Parameter/Index	Area under the curve	95% CI	Upper 1-sided *P*-value to test AUC >0.5
Nociception Level Index	0.94	0.84 to 0.98	<0.00001
Heart Rate	0.55	0.39 to 0.68	0.24
Mean Arterial Pressure	0.53	0.37 to 0.66	0.34
Bispectral index	0.65	0.50 to 0.77	0.011

Receiver operating characteristics curve analysis: discrimination of skin incision from pre-incision period			
Parameter/Index	Area under the curve	95% CI	Upper 1-sided *P*-value to test AUC >0.5
Nociception Level Index	0.94	0.77 to 0.98	<0.00001
Heart Rate	0.61	0.47 to 0.73	0.059
Mean Arterial Pressure	0.79	0.66 to 0.87	<0.00001
Bispectral index	0.59	0.44 to 0.71	0.099

remifentanil-propofol TCI anaesthesia, the NOL index associated with a goal-directed remifentanil titration reduced the incidence of intra-operative hypotension. The same team then showed its potential in personalising antinociception to improve postoperative pain scores.[14] However, predicting adequate antinociception during general anaesthesia by evaluating the change in the NOL response to a standard noxious stimulus has not been shown previously. Such an approach could help anaesthetists anticipate each patient's remifentanil requirement for the start of surgery. Anaesthetists could thus individualise NAN balance before surgery by applying a single validated test rather than their clinical impression. This could avoid the too frequently applied approach of excessively increased antinociception in all patients with the hope of eliminating any haemodynamic response, an approach which, unfortunately, often leads to a loss of sympathetic tonus and hypotension: a known cause of peri-operative morbidity.[22,23] In our study, only two patients, who both underwent noncardiac surgery during the calibration phase, had hypotension (defined by a drop of MAP lower than 80% of baseline) at the start of surgery.

Tetanic stimulation elicits a nociceptive response without any associated adverse effects.[16] We show that this reproducible noxious stimulus does not have clinically dangerous effects on haemodynamics when applied in a heterogeneous population at a remifentanil Ce of $4\,ng\,ml^{-1}$. This confirms earlier reports of the safety and usefulness of this tool.[11,16] However, predicting adequate NAN balance using a tetanic stimulus has its challenges. Defresne *et al.*[21] unsuccessfully attempted to determine if guiding remifentanil administration based on the Surgical Plethysmographic Index response to a tetanic stimulus would lead to a blunted haemodynamic response. In their study, they used arbitrary thresholds to calculate the required remifentanil Ce, and this may have led to their inconclusive results.[21] Our study has two important differences with their work. Firstly, the nociception monitor was different. Secondly, the modifications in remifentanil Ce were not fixed, but based on either a stepwise approach until the Δ NOL response was limited to <20 (calibration phase) or a calculated value based on data from this population (validation phase).

Our ROC curve analysis confirms previous studies and demonstrates the higher sensitivity of the NOL index to detect both tetanic stimulation and incision when compared with changes in HR, MAP and BIS.[9,11] These reports have shown the benefits of nociceptive monitors, but today, clinicians continue to use the haemodynamic responses to surgical stimuli as the main indicator of nociception. Our design, which also investigated HR

and MAP changes as main outcomes, thus further clarifies the ability of the NOL index to detect nociception and demonstrates its clinical utility. Although the NOL index shows considerable potential as both a predictive and reactive tool for guiding antinociception, it is important to underline the fact that it can be affected by multiple factors.[24,25] In our study, arrhythmias and interference from electrocautery led to a loss of signal. Furthermore, using a monitor introduces the need to follow a goal-directed strategy, which is practitioner dependent. Although a closed-loop system could improve compliance, as has been shown with goal-directed haemodynamic therapy[26] or propofol titration using the BIS,[27] the intrinsic limitations of the NOL index monitor should be addressed and compensated. Nonetheless, in controlled situations without arrhythmia or major ventilation changes, this tool has shown its reliability during opioid-based antinociception.[11–13]

Personalising remifentanil TCI is of particular interest because the hypnotic and antinociceptive components of intravenous anaesthesia have synergistic effects[28] and, once excessive, they lead to intra-operative adverse events such as hypotension and burst suppression.[13,29,30] As a combination of hypotension and excessive anaesthetic depth causing burst suppression has been linked to a nearly three-fold increase in the odds of dying,[31] clinicians should be particularly attentive to avoid such events. In the cardiac surgery cohort, no episode of hypotension occurred at the start of surgery thanks to the personalised BIS and NOL guided titrations of propofol and remifentanil. Thus, this optimised NAN balance seems to maintain adequate autonomic nervous system tonus during surgical incision. This study, however, only investigated the capacity of this predicted remifentanil Ce to maintain haemodynamic stability at incision. Maintenance of antinociception after this point was not studied. It is probable that, depending on the stage of surgery, remifentanil Ce would have to be periodically modified to maintain the NOL between 10 and 25.

Limitations

This prospective calibration and validation study has both strengths and limitations. Although the investigation did show the potential of personalising the required remifentanil Ce for individual patients, the population sample is small and heterogeneous. Patient age, ASA score and surgery are the main factors that increase heterogeneity. None of these limitations, however, eliminated the linear relation between the Δ NOL after a tetanic stimulus of 30 s and the required remifentanil Ce for surgical incision. Larger more homogenous studies may offer an even more precise prediction of the personalised remifentanil Ce for specific groups. However, our selected sample has the merit that it includes elderly and cardiac surgery patients, and such patients make up a high-risk group susceptible to excessive anaesthetic depth and haemodynamic instability.[29,30] The patient cohort was chosen on purpose to be heterogeneous so as to establish a model from a large range of remifentanil Ce requirements. As this was an exploratory study, no power analysis was undertaken. Furthermore, we only investigated the capacity of this personalised remifentanil Ce to maintain haemodynamic stability at incision. It is unclear, and seems even improbable, that the predicted Ce could be maintained throughout the surgery. A more reasonable approach would be to incise at the predicted remifentanil Ce and then modify the infusion based on the NOL index changes. Despite these limitations, this study is the first to use the NOL index during cardiac surgery.

Conclusion

During a no-touch period in patients under steady-state general anaesthesia (BIS between 40 and 60), the NOL index response to a tetanic stimulus at a remifentanil Ce of 4 ng ml^{-1} can be used to personalise antinociception for the start of surgery and ensure stable haemodynamics in both noncardiac and cardiac surgery patients. Future larger randomised controlled studies must be performed to determine if this approach, when linked to a goal-directed antinociception strategy, could improve postoperative outcome.

Acknowledgements relating to this article

Assistance with the article: the authors would like to thank the medical and nursing staff of the Erasme University Hospital for their help in carrying out this study.

Financial support and sponsorship: this study was funded solely by departmental resources and the help of the cardiac foundation of the Free University of Brussels.

This manuscript was handled by Esther M. Pogatzki-Zahn.

LB and SC are shared co-last authors.

Conflict of interests: SC has received honoraria from Medasense, Medtronic and Med-Storm.

The other authors state no conflict of interest.

A preliminary account of the results was presented as an abstract at Euroanaesthesia 2019, Vienna, Euroanaesthesia 2021 Munich, as well as during the NOL Webinar – Into the Future of Pain Management (2020).

References

1 Coeckelenbergh S, Richebé P, Longrois D, *et al.* Current trends in anesthetic depth and antinociception monitoring: an international survey. *J Clin Monit Comput Netherlands* 2021; Online ahead of print.
2 Al-Rifai Z, Mulvey D. Principles of total intravenous anaesthesia: practical aspects of using total intravenous anaesthesia. *BJA Educ* 2016; **16**:276–280.
3 Chen A, Ashburn MA. Cardiac effects of opioid therapy. *Pain Med (United States)* 2015; **16**:S27–31.
4 Smit M, Coetzee AR, Lochner A. The pathophysiology of myocardial ischemia and perioperative myocardial infarction. *J Cardiothorac Vasc Anesth* 2020; **34**:2501–2512.
5 Abbott TEF, Pearse RM, Archbold RA, *et al.* A prospective international multicentre cohort study of intraoperative heart rate and systolic blood pressure and myocardial injury after noncardiac surgery: results of the VISION study. *Anesth Analg* 2018; **126**:1936–1945.

6 Abbott TEF, Ackland GL, Archbold RA, *et al.* Preoperative heart rate and myocardial injury after noncardiac surgery: results of a predefined secondary analysis of the VISION study. *Br J Anaesth* 2016; **117**:172–181.
7 Prys-Roberts C. Anaesthesia and hypertension. *Br J Anaesth* 1984; **57**:711–724.
8 Ben-Israel N, Kliger M, Zuckerman G, *et al.* Monitoring the nociception level: a multiparameter approach. *J Clin Monit Comput* 2013; **6**:659–668.
9 Edry R, Recea V, Dikust Y, Sessler DI. Preliminary intraoperative validation of the nociception level index: a noninvasive nociception monitor. *Anesthesiology* 2015; **3**:524–534.
10 StÖcKle PA, Julien M, Issa R, *et al.* Validation of the PMD100 and its nol index to detect nociception at different infusion regimen of remifentanil in patients under general anesthesia. *Minerva Anestesiol* 2018; **84**:1160–1168.
11 Renaud-Roy E, Stöckle PA, Maximos S, *et al.* Correlation between incremental remifentanil doses and the nociception level (NOL) index response after intraoperative noxious stimuli. *Can J Anesth* 2019; **66**:1049–1069.
12 Bollag L, Jelacic S, Delgado Upegui C, *et al.* The nociception level index (NOL) response to intubation and incision in patients undergoing video-assisted thoracoscopic surgery (VATS) with and without thoracic epidural analgesia. A pilot study. [version 1; referees: 3 approved, 1 approved with reserva. *F1000Research* 2022; **7**:875; eCollection 2018.
13 Meijer FS, Martini CH, Broens S, *et al.* Nociception-guided versus standard care during remifentanil-propofol anesthesia: a randomized controlled trial. *Anesthesiology* 2019; **130**:745–755.
14 Meijer F, Honing M, Roor T, *et al.* Reduced postoperative pain using nociception level-guided fentanyl dosing during sevoflurane anaesthesia: a randomised controlled trial. *Br J Anaesth* 2020; **125**:1070–1078.
15 Coeckelenbergh S, Doria S, Patricio D, *et al.* Effect of dexmedetomidine on nociception level index-guided remifentanil antinociception: a randomised controlled trial. *Eur J Anaesthesiol* 2021; **38**:524–533.
16 Funcke S, Sauerlaender S, Pinnschmidt HO, *et al.* Validation of innovative techniques for monitoring nociception during general anesthesia. *Anesthesiology* 2017; **127**:272–283.
17 Rantanen M, Yppärilä-Wolters H, van Gils M, *et al.* Tetanic stimulus of ulnar nerve as a predictor of heart rate response to skin incision in propofol remifentanil anaesthesia. *Br J Anaesth* 2007; **99**:509–513.
18 Gruenewald M, Ilies C, Herz J, *et al.* Influence of nociceptive stimulation on analgesia nociception index (ANI) during propofol-remifentanil anaesthesia. *Br J Anaesth* 2013; **110**:1024–1030.
19 Coeckelenbergh S, Estebe J. Guiding opioid-free intravenous antinociception with the Analgesia Nociception Index: a case report. *Rev Bras Anestesiol* 2020; **70**:678–681.
20 Barvais L, Engelman E, Eba JM, *et al.* Effect site concentrations of remifentanil and pupil response to noxious stimulation. *Br J Anaesth* 2003; **91**:347–352.
21 Defresne A, Barvais L, Clement F, Bonhomme V. Standardised noxious stimulation-guided individual adjustment of remifentanil target-controlled infusion to prevent haemodynamic responses to laryngoscopy and surgical incision: a randomised controlled trial. *Eur J Anaesthesiol* 2018; **35**:173–183.
22 Futier E, Lefrant JY, Guinot PG, *et al.* Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction 6among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* 2017; **10**:1346–1357.
23 Maheshwari K, Turan A, Mao G, *et al.* The association of hypotension during noncardiac surgery, before and after skin incision, with postoperative acute kidney injury: a retrospective cohort analysis. *Anaesthesia* 2018; **73**:1223–1228.
24 Raft J, Coulombe MA, Renaud-Roy E, *et al.* Impact of intravenous phenylephrine bolus administration on the nociceptive level index (NOL). *J Clin Monit Comput* 2020; **34**:1079–1086.
25 Coeckelenbergh S, Vereecke HEM, Richebé P. Nociception level-guided fentanyl titration: potential impact of multimodal anaesthesia and false positives [Comment]. *Br J Anaesth* 2020; **125**:1070–1078.
26 Coeckelenbergh S, Zaouter C, Alexander B, *et al.* Automated systems for perioperative goal-directed hemodynamic therapy. *J Anesth* 2020; **34**:104–114.
27 Joosten A, Rinehart J, Bardaji A, *et al.* Anesthetic management using multiple closed-loop systems and delayed neurocognitive recovery: a randomized controlled trial. *Anesthesiology* 2020; **132**:253–266.
28 Hannivoort LN, Vereecke HEM, Proost JH, *et al.* Probability to tolerate laryngoscopy and noxious stimulation response index as general indicators of the anaesthetic potency of sevoflurane, propofol, and remifentanil. *Br J Anaesth* 2016; **116**:624–631.
29 Soehle M, Dittmann A, Ellerkmann RK, *et al.* Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. *BMC Anesthesiol* 2015; **15**:61.
30 Pedemonte JC, Plummer GS, Chamadia S, *et al.* Electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients mediates postoperative delirium. *Anesthesiology* 2020; **2**:280–292.
31 Willingham M, Ben Abdallah A, Gradwohl S, *et al.* Association between intraoperative electroencephalographic suppression and postoperative mortality. *Br J Anaesth* 2014; **113**:1001–1008.