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Signa Vitae

ORIGINAL RESEARCH

Lower dose of sufentanil was associated with higher plasmatic level of cortisol in patients undergoing elective cardiac surgery at the same depth of anaesthesia: a prospective randomised pilot study. Do we overlook "stress under the surface"?

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Abstract

Objective monitoring of per-operative nociception remains an unanswered challenge. Anaesthetists still mostly rely on signs of activation of the sympathetic nervous system, *e.g.*, an increase in heart rate and blood pressure. These signs can be often blurred in cardiac surgery because of medication influencing heart rate and blood pressure or by severe hemodynamic disturbances. Such conditions create the potential for incompletely checked nociception which can lead to unrecognised "under the surface" stress reaction. We decided to investigate whether patients undergoing cardiac surgery maintained at the same level of monitored depth of anaesthesia would express differences in plasmatic level of stress hormone cortisol when given a different dose of opioid sufentanil. Nineteen patients undergoing elective cardiac surgery were included in our prospective randomised trial. All patients were anaesthetised by a standardised protocol (using midazolam, propofol, sevoflurane, sufentanil and rocuronium) and were maintained within the same range of anaesthetic depth monitored by monitor Conox (qCON 30–50). Patients were randomised in two groups. Group LS (lower sufentanil), n = 9, recieved TCI (target controlled infusion) sufentanil in dose of 0.25 ng/mL, group HS (higher sufentanil), n = 10, in dose of 0.75 ng/mL. 15 minutes after sternotomy we took blood samples for analysis of plasmatic levels of cortisol. Group LS had significantly higher plasmatic cortisol levels, median 700 nm/L, than HS, median 328 nm/L (p = 0.006). We conclude that a lower dose of sufentanil was associated with higher plasmatic level of cortisol and thus more significant activation of hypothalamic–pituitary–adrenal axis stress response. We emphasise that activation of stress response can be underestimated during cardiac surgery. Our result supports the need for developing an objective monitoring method of per-operative nociception.

Keywords

Cardiac anaesthesia; Analgesia; Nociception; Cortisol; Stress response

1. Introduction

Maintaining adequate depth of anaesthesia and analgesia during surgery is one of the most important goals of per-operative anaesthetic care.

While monitoring depth of anaesthesia has become a widely available and accepted technique of per-operative monitoring, objective monitoring of actual level of nociceptive stimulation remains a mostly unanswered challenge [1].

Anaesthetists still dose opioids relying mostly on signs of activation of a sympathetic nervous system such as an increase in heart rate and/or blood pressure.

Cardiac surgery can represent a special challenge for detecting signs of sympathetic stimulation. These signs can be often mimicked by pre-operative medication involving beta-blockers, calcium blockers, per-operative administration of beta-mimetics, vagolytics, vasoconstrictors or vasodilators. Profound changes in hemodynamics during cardiac surgery can also occur: large and rapid shifts of intravascular volume, vasoplegia, low cardiac output, arrhythmias. These situations can also make assessment of nociception based on sympathetic stimulation impossible. Effective management of nociception should be one of the objectives of anaesthetic care [2].

Where techniques of regional anaesthesia cannot be used, per-operative analgesia is provided mainly by administration of opioids.

Opioids are very potent drugs but have a relatively narrow

therapeutic window and can have serious side effects. Opioids therefore should be titrated to the actual per-operative patient's need, *e.g.*, actual intensity of nociceptive stimulation [3, 4].

There were big differences in the dose of opioids used during cardiac surgery historically-different approaches shifted from the concept of "high dose opioid" or "stress free" [5, 6] anaesthesia to the recently described concept of "opioid free" anaesthesia" [7–9].

Both overdosing and underdosing of opioids can have a specific impact on patients' safety, morbidity and mortality. When given in an insufficient dose, the nociceptive stimulation is not suppressed effectively and can provoke a stress response with many consequences [10–14].

Overdosing of opioids can cause prolonged intubation, ventilation and other complications [15–18].

There are many reasons why per/operative opioid administration should be based on reliable feedback using objective monitoring of nociception in real time. Although there are already several commercially produced devices for the monitoring of nociception, none have been shown to have had a satisfactory level of specificity and sensitivity [19–22].

Recent meta analyses did not bring an unequivocal answer on how useful existing nociceptive monitors are in per-operative management and dosing of opioids [3, 23, 24].

The vast majority of existing technologies are based on the evaluation of changes in the tone of the vegetative nervous system, which represents a fundamental limitation for reliable use during cardiac anaesthesia.

From all the reasons mentioned above, cardiac surgery has a certain possible potential of for creating conditions under which reaction to nociception can be blurred or overlooked. Subsequent stress reaction can be developing unrecognised as "stress under the surface".

The main objective of our study was to verify the hypothesis as to whether patients anaesthetised at the same level of unconsciousness would express different signs of stress response caused by nociceptive stimulation when given a different dose of analgetic.

Patients undergoing cardiac surgery would be randomised in two groups each receiving a different dose of opioid sufentanil. At the same time all patients would be anaesthetised by a standardised anaesthetic protocol and maintained in the same level of monitored depth of anaesthesia. All patients would be managed with the same hemodynamic protocol to maintain mean arterial pressure within the same range. We would also record the total dose of vasoconstrictor and vasodilator used to achieve this goal.

Activation of hypothalamic–pituitary–adrenal axis would be assessed by analysis of plasmatic levels of cortisol.

There were several reasons why we focused our observation on the phase prior to connection to the cardiopulmonary bypass. Firstly, we wanted to avoid the diluting effect of primary filling of the extracorporeal circulation circuit on plasmatic concentration of cortisol. Secondly, we wanted to avoid changes in pharmacokinetics and pharmacodynamics of sufentanil during extracorporeal circulation, caused by the dilution effect of priming as well as by temperature fluctuations. Thirdly, we wanted to avoid the interference of observed hemodynamic parameters with possible hemodynamic fluctuations during the cannulation of large vessels and heart. Last but not least, the initial phase of cardiac surgery is suitable for evaluating the response to nociception due to significant surgical stimulation during the sternotomy and the opening of the chest.

2. Materials and methods

Our prospective randomised observational study was performed from July to November 2020 at the Department of Cardiac Surgery, University Hospital Kralovske Vinohrady and 3rd Faculty of Medicine, Charles University, Prague, Czech Republic.

The exclusion criteria for participation in the study were as follows: previous sternotomy or thoracotomy, signs of hemodynamic or other systemic instability, non-elective procedure, sepsis, signs of renal or liver impairment, expected difficult airway, LVEF (left ventricle ejection fraction) below 40%, diabetes mellitus, corticoid treatment, suprarenal gland disease, use of etomidate, hypoalbuminemia below 25 g/L, BMI (body mass index) above 40.

All patients underwent elective cardiac surgery. All patients came from home and were admitted on the day before surgery. All patient had the standard preoperative fluid and food restriction from midnight and were listed for morning procedure. During the investigation period (ending 15 min after the sternotomy) patients received 250 ml of physiological solution intravenously. There was no hemodilution in the period of our investigation.

Patients were randomised into two groups subsequently receiving different doses of sufentanil TCI (target controlled infusion). Group LS (lower sufentanil), n = 9, received TCI sufentanil of 0.25 ng/mL. Group HS (higher sufentanil), n = 10, received TCI sufentanil of 0.75 ng/mL. The pharmacokinetic model of Gepts was used in both groups [25].

All patients were anaesthetised using the same anaesthetic protocol. The depth of anaesthesia was monitored by index qCON (Quantium Consciousness Index) using the Conox monitor (a non-invasive depth of anaesthesia monitor manufactured by Quantum Medical, Barcelona, Spain). All patients were maintained within the same range of depth of anaesthesia (index qCON: 30–50).

Five minutes before induction to general anaesthesia we took first blood samples for analysis of baseline plasmatic cortisol levels.

After preoxygenation, we started a sufentanil TCI (dose according to randomisation) and subsequently performed an induction to general anaesthesia. Our standardised anaesthetic protocol consisted of i.v. administration of midazolam 0.075 mg/kg, propofol 0.75 mg/kg and inhalation of sevoflurane (end-tidal concentration 1–2%). When index qCON dropped below 60, the muscle relaxant rocuronium was administered in a dose of 1.0 mg/kg and endotracheal intubation was performed. General anaesthesia was then maintained with continuous propofol infusion (1 mg/kg/hr) and inhalation of sevoflurane (ET 1–2%) which was dosed according to index qCON. We maintained the depth of anaesthesia in all patients within the range of index qCON: 30–50. Muscle relaxant rocuronium was administered *via* infusion in a dose of 0.4 mg/kg/hr.

The same protocol of hemodynamic management was used for all patients. We maintained the mean arterial pressure within a range of change of not more than 10% up or down from the pre-induction baseline; in all patients MAP (mean arterial pressure) was maintained within the range 60–80 mmHg. To achieve this goal, boluses of vasopressor phenylephrine or vasodilator glyceryl trinitrate were used if needed, and administrated as a single dose of 50 or 100 mcg each. We recorded the dose of vasoactive medication given to each patient from induction of anaesthesia to the point of blood sampling.

Second blood samples from all patients were obtained 15 minutes after sternotomy. At this time, chest spreader had been applied and surgical manipulation inside the chest had already started. We assumed that this was the most stimulating period of surgery. At this point we also recorded values of systolic blood pressure, pulse rate and depth of anaesthesia index qCON.

2.1 Blood samples analysis

The blood samples were cooled down and at temperature of 4 °C, sent to laboratory. Cortisol concentration analysis was performed on the Atellica Solution analyser (immunoassay and clinical chemistry analyser manufactured by Siemens, Erlangen, Germany) using the method of the Atellica IM Cortisol (Cor) based on a competitive immunoassay using direct chemiluminescence technology.

2.2 Statistical analysis

The collected data was statistically analysed by an independent institution. Central tendency and variability of continuous data is characterized by medians and 25th–75th percentiles. Mann-Whitney test was used to test differences between the groups. Statistical tests were evaluated at a significance level of 0.05. Statistical analysis was performed by statistical software Stata, release 14.2 (StataCorp LP, College Station, TX, USA).

3. Results

There were no significant differences found between LS group (patients receiving lower TCI sufentanil) and HS group (patients receiving higher TCI sufentanil) in the basic demographic data: age, weight, BMI (body mass index), LVEF (left ventricle ejection fraction).

These basic data are presented by median (25th–75th percentile): age (years): 72 (64–75) *vs.* 68 (61–70), $p = 0.217$, weight (kg): 84 (76–95) *vs.* 89.5 (85–101), $p = 0.251$, BMI: 27.6 (25.6–28.7) *vs.* 27.9 (26.9–33.5), $p = 0.720$, LVEF (%): 60 (50–60) *vs.* 63 (55–65), $p = 0.113$. All patients included in our study had normal levels of plasmatic albumin-presented by median (25th–75th percentile): HS group 41.5 (40.2–45.2) g/L, LS group 45.6 (43.8–46.9) g/L.

There were no significant differences found between the groups in the total dose of vasoconstrictor or vasodilator in the period from induction of general anaesthesia to the point of blood sampling. There were no significant differences in systolic blood pressure, pulse rate or index qCON (depth of anaesthesia) between the groups.

There was no significant difference found in the plasmatic level of cortisol at time before induction to general anaesthesia-data are presented by median (25th–75th percentile): LS group had plasmatic level of cortisol 464 nm/L (372–525), HS group had plasmatic level of cortisol 417 nm/L (298–517), $p = 0.624$.

There was a significant difference found in the plasmatic level of cortisol at time after sternotomy. Data are presented by median (25th–75th percentile): LS group had a significantly higher plasmatic level of cortisol 700 nm/L (599–765) compared to the level of HS group 328 nm/L (243–386), $p = 0.006$.

Results are presented in Table 1 and Fig. 1.

4. Discussion

The main finding of our study shows that patients who were receiving a lower dose of sufentanil (TCI 0.25 ng/mL) had a higher level of plasmatic cortisol (700 nm/L; 599–765) compared with patients who were receiving a higher dose of sufentanil (TCI 0.75 ng/mL) and whose cortisol level was (328 nm/L; 243–386); figures are presented as median; 25th–75th percentile. The difference found between the groups was statistically significant; $p = 0.006$. There was no difference between the groups in level of cortisol before induction to general anaesthesia; $p = 0.624$.

Under physiological conditions the plasmatic cortisol levels follow circadian oscillations. In healthy individuals, normal plasmatic concentrations are the highest in the morning (range 250–850 nmol/L) and the lowest at night or early morning (range 110–390 nmol/L). The cortisol levels increases during the stress response to various stimuli including pain perception [26].

Nociceptive stimulation during surgery provokes stress response and is also associated with an increase in plasmatic cortisol levels. It has been documented that plasmatic cortisol during surgery can range from 270 to 1452 nmol/L and that cortisol levels positively correlate with the extensiveness of surgery-major surgery was associated with higher levels of cortisol than the minor surgery [27, 28].

It has also been suggested that a high plasmatic cortisol level correlated with worse outcomes in patients presenting cardiac failure [29].

The interpretation of our findings is that the higher level of cortisol signified a more potent activation of hypothalamic–pituitary–adrenal axis, and thus that patients with a lower dose of opioid experienced a more intense stress reaction to nociceptive stimulation. Our findings are consistent with the results of other authors [27, 28, 30–32].

In our study all patents from both groups were anaesthetised under the same protocol and maintained within the same range of depth of anaesthesia measured by monitor Conox. Index qCON was maintained in a range 30–50. There is convincing evidence that index qCON is reliable in the measurement of depth of anaesthesia when compared with other monitors [33–36].

As one of our secondary findings we can present the fact that there was no significant difference found in index qCON in between the two groups of patients, which is an indication that we succeeded in maintaining the same depth of anaesthesia for patients of the both groups.

At the same time, we found no statistically significant dif-

TABLE 1. Summary of main results.

Variable	Characteristic	LS group	HS group	*p*
Cortisol T0 (nm/L)	median 25th–75th percentile	464 372–525	417 298–517	0.624
Cortisol T1 (nm/L)	median 25th–75th percentile	700 599–765	328 243–386	0.006
BP (mmHg)	median 25th–75th percentile	148 123–150	121 110–140	0.102
PR (beat/min)	median 25th–75th percentile	71 62–91	65 60–73	0.252
qCON	median 25th–75th percentile	43 36–48	40 36–43	0.287
PHE (mcg)	median 25th–75th percentile	200 0–300	200 100–300	0.287
GTN (mcg)	median 25th–75th percentile	0 0–200	100 0–200	0.828

LS group, patients receiving lower TCI sufentanil (0.25 ng/mL); HS group, patients receiving higher TCI sufentanil (0.75 ng/mL); Cortisol T0, plasmatic level of cortisol 5 min before induction to general anaesthesia; Cortisol T1, plasmatic level of cortisol 15 min after sternotomy; BP, systolic arterial blood pressure; PR, pulse rate; qCON, quantium consciousness index; PHE, total dose of phenylephrine given in the period from induction of anaesthesia to 15 min after sternotomy; GTN, total dose of glycerol trinitrate given in period from induction of anaesthesia to 15 min after sternotomy; Cortisol, plasmatic cortisol level in sample taken 15 min after sternotomy; mcg, microgram; nm/L, nanomoles per litre; p, p value.

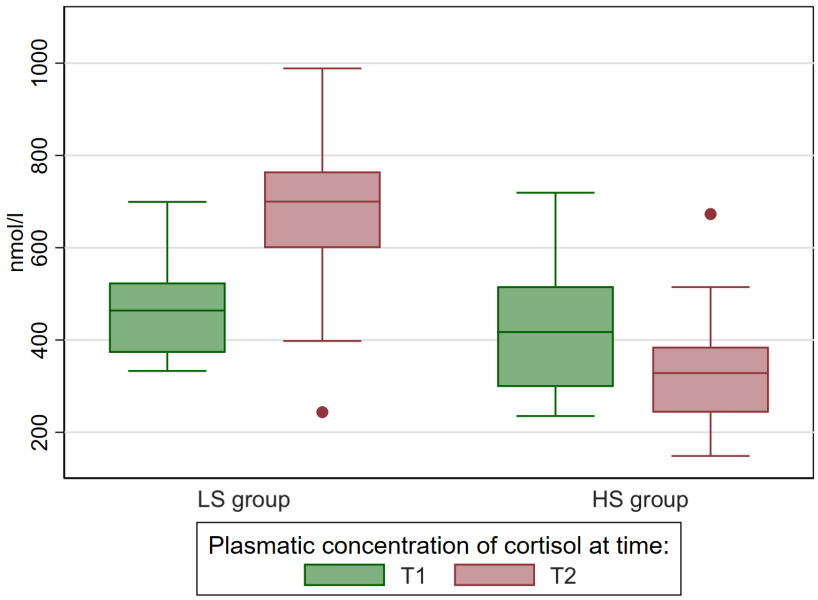

FIGURE 1. Plasmatic levels of cortisol. LS group, patients receiving lower TCI sufentanil (0.25 ng/mL); HS group, patients receiving higher TCI sufentanil (0.75 ng/mL); nm/L, nanomoles per litre; T1, time of the first blood sample—5 min before induction to general anaesthesia; T2, time of the second blood sample—15 min after sternotomy. *p* value for T1 is $p = 0.624$. *p* value for T2 is $p = 0.006$.

ferences between both groups in systolic blood pressure, pulse rate or dose of vasoactive drugs (phenylephrine or glycerol trinitrate).

This secondary finding can be seen as consistent with the specifics of cardiac anaesthesia. Hemodynamic disturbances (change in blood pressure and/or heart rate) are often present during cardiac surgery and can be caused by underlying medication, cardiovascular pathology and impact of the ongoing surgery itself. Cardiac anaesthetists, on the other hand, are skilled and proactive in management of hemodynamic determinants with powerful vasoactive and inotropic drugs when having the objective of maintaining perfusion pressure within the desired range [37–39].

These specific conditions might facilitate situations where classical signs of sympathetic activation (as in an increase of heart rate and/or blood pressure) are blurred and/or missing.

We acknowledge that size of our group of patients might represent one of the limitations of the study.

5. Conclusions

The main findings of our study proved our hypothesis that patients who were receiving a lower dose of the opioid sufentanil presented higher levels of the stress hormone cortisol. More potent activation of the hypothalamic–pituitary–adrenal axis in this group of patients can be explained by a higher intensity of ongoing nociceptive stimulation.

Our study demonstrates, that the signs of ongoing nociceptive stimulation may not be easily visible and/or easily recognised under certain conditions. Patients may then be exposed to an ongoing "under the surface" stress reaction provoked by nociception even when the same patients are being anaesthetised at the right depth of anaesthesia/unconsciousness and maintained within desired hemodynamic parameters.

Cardiac anaesthesia might represent a special case where there is extensive potential for classical clinical signs of nociceptive stimulation to be blurred and/or overlooked. Our results strongly support the need for developing a method of an objective monitoring of nociception.

AVAILABILITY OF DATA AND MATERIALS

The data associated with the paper are archived and can be provided by the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

VR—was the author of the hypothesis, design, protocol and the main investigator; TV—was the main collaborator and advisor; VM—was the scientific advisor; MM—provided an independent statistical data analysis; PK—was the consultant. All authors contributed to the study. All authors read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study obtained the approval of the Ethics Committee of the University Hospital Kralovske Vinohrady in Prague and the approval of University Hospital Kralovske Vinohrady and 3rd Faculty of Medicine, Charles University in Prague, ID: EK-VP/041012, ID: EK-VP/041012. The study was performed in line with the principles of the Declaration of Helsinki. Nineteen adult patients were enrolled after signing informed consent for participation in the trial.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Kelliher LJS, Scott M. Modifying the stress response—perioperative considerations and controversies. Anesthesiology Clinics. 2022; 40: 23–33.

[2] Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA Education. 2020; 20: 321–328.

[3] Funcke S, Pinnschmidt HO, Brinkmann C, Wesseler S, Beyer B, Fischer M, *et al*. Nociception level-guided opioid administration in radical retropubic prostatectomy: a randomised controlled trial. British Journal of Anaesthesia. 2021; 126: 516–524.

[4] Hyland SJ, Brockhaus KK, Vincent WR, Spence NZ, Lucki MM, Howkins MJ, *et al*. Perioperative pain management and opioid stewardship: a practical guide. Healthcare. 2021; 9: 333.

[5] Lowenstein E, Hallowell P, Levine FH, Daggett WM, Austen WG, Laver MB. Cardiovascular response to large doses of intravenous morphine in man. The New England Journal of Medicine. 1969; 281: 1389–1393.

[6] Sebel PS, Bovill JG, Boekhorst RAA, Rog N. Cardiovascular effects of high-dose fentanyl anaesthesia. Acta Anaesthesiologica Scandinavica. 1982; 26: 308–315.

[7] Grant MC, Suffredini G, Cho BC. Is it time to eliminate the use of opioids in cardiac surgery? JTCVS Open. 2021; 7: 247–252.

[8] Goff J, Hina M, Malik N, McLardy H, Reilly F, Robertson M, *et al*. Can opioid-free anaesthesia be personalised? A narrative review. Journal of Personalized Medicine. 2023; 13: 500.

[9] Olausson A, Svensson CJ, Andréll P, Jildenstål P, Thörn S, Wolf A. Total opioid-free general anaesthesia can improve postoperative outcomes after surgery, without evidence of adverse effects on patient safety and pain management: a systematic review and meta-analysis. Acta Anaesthesiologica Scandinavica. 2022; 66: 170–185.

[10] Naguib AN, Tobias JD, Hall MW, Cismowski MJ, Miao Y, Barry N, *et al*. The role of different anesthetic techniques in altering the stress response during cardiac surgery in children. Pediatric Critical Care Medicine. 2013; 14: 481–490.

[11] Li X, Xiang H, Zhang W, Peng C. The effects of remifentanil combined with propofol on the oxidative damage and the stress and inflammatory responses in cardiac surgery patients. American Journal of Translational Research. 2021; 13: 4796–4803.

[12] Yin H, Cao L, Zhao H, Yang Y. Effects of dexmedetomide, propofol and remifentanil on perioperative inflammatory response and lung function during lung cancer surgery. American Journal of Translational Research. 2021; 13: 2537–2545.

[13] Abbott TEF, Pearse RM, Archbold RA, Ahmad T, Niebrzegowska E, Wragg A, *et al*. A rospective international multicentre cohort study of intraoperative heart rate and systolic blood pressure and myocardial injury after noncardiac surgery: results of the VISION study. Anesthesia and Analgesia. 2018; 126:1936–1945.

[14] Agerskov M, Thusholdt ANW, Holm-Sørensen H, Wiberg S, Meyhoff CS, Højlund J, *et al*. Erratum to 'Association of the intraoperative peripheral perfusion index with postoperative morbidity and mortality in acute surgical patients: a retrospective observational multicentre cohort study' (Br J Anaesth 2021; 127: 396–404). British Journal of Anaesthesia. 2022; 128: 744.

[15] Ochroch J, Usman A, Kiefer J, Pulton D, Shah R, Grosh T, *et al*. Reducing opioid use in patients undergoing cardiac surgery—preoperative, intraoperative, and critical care strategies. Journal of Cardiothoracic and Vascular Anesthesia. 2021; 35: 2155–2165.

[16] Urman RD, Seger DL, Fiskio JM, Neville BA, Harry EM, Weiner SG, *et al*. The burden of opioid-related adverse drug events on hospitalized previously opioid-free surgical patients. Journal of Patient Safety. 2021; 17: e76-e83.

[17] Krakowski JC, Hallman MJ, Smeltz AM. Persistent pain after cardiac surgery: prevention and management. Seminars in Cardiothoracic and Vascular Anesthesia. 2021; 25: 289–300.

[18] Rong LQ, Kamel MK, Rahouma M, Naik A, Mehta K, Abouarab AA, *et*

al. High-dose versus low-dose opioid anesthesia in adult cardiac surgery: a meta-analysis. Journal of Clinical Anesthesia. 2019; 57: 57–62.

[19] Hirose M, Okutani H, Hashimoto K, Ueki R, Shimode N, Kariya N, *et al*. Intraoperative assessment of surgical stress response using nociception monitor under general anesthesia and postoperative complications: a narrative review. Journal of Clinical Medicine. 2022; 11: 6080.

[20] Ledowski T. Objective monitoring of nociception: a review of current commercial solutions. British Journal of Anaesthesia. 2019; 123: e312–e321.

[21] Martinez-Vazquez P, Jensen EW. Different perspectives for monitoring nociception during general anesthesia. Korean Journal of Anesthesiology. 2022; 75: 112–123.

[22] Bertolizio G, Garbin M, Ingelmo PM. Evaluation of nociception during pediatric surgery: a topical review. Journal of Personalized Medicine. 2023; 13: 260.

[23] Gruenewald M, Dempfle A. Analgesi/nociception monitoring for opioid guidance: meta-analysis of randomized clinical trials. Minerva Anestesiologica. 2017; 83: 200–213.

[24] Jiao Y, He B, Tong X, Xia R, Zhang C, Shi X. Intraoperative monitoring of nociception for opioid administration: a meta-analysis of randomized controlled trials. Minerva Anestesiologica. 2019; 85: 522–530.

[25] Gepts E, Shafer SL, Camu F, Stanski DR, Woestenborghs R, Van Peer A, *et al*. Linearity of pharmacokinetics and model estimation of sufentanil. Anesthesiology. 1995; 83: 1194–1204.

[26] Mohd Azmi NAS, Juliana N, Azmani S, Mohd Effendy N, Abu IF, Mohd Fahmi Teng NI, *et al*. Cortisol on circadian rhythm and its effect on cardiovascular system. International Journal of Environmental Research and Public Health. 2021; 18: 676.

[27] Khoo B, Boshier PR, Freethy A, Tharakan G, Saeed S, Hill N, *et al*. Redefining the stress cortisol response to surgery. Clinical Endocrinology. 2017; 87: 451–458.

[28] Manou-Stathopoulou V, Korbonits M, Ackland GL. Redefining the perioperative stress response: a narrative review. British Journal of Anaesthesia. 2019; 123: 570–583.

[29] Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M, *et al*. Serum cortisol as a useful predictor of cardiac events in patients with chronic heart failure. Circulation. Heart Failure. 2009; 2: 608–615.

[30] Duncan HP, Cloote A, Weir PM, Jenkins I, Murphy PJ, Pawade AK, *et al*. Reducing stress responses in the pre-bypass phase of open heart surgery in infants and young children: a comparison of different fentanyl doses. British Journal of Anaesthesia. 2000; 84: 556–564.

[31] Weale NK, Rogers CA, Cooper R, Nolan J, Wolf AR. Effect of remifentanil infusion rate on stress response to the pre-bypass phase of paediatric cardiac surgery. British Journal of Anaesthesia. 2004; 92: 187–194.

[32] Naguib AN, Tobias JD, Hall MW, Cismowski MJ, Miao Y, Barry N, *et al*. The role of different anesthetic techniques in altering the stress response during cardiac surgery in children. Pediatric Critical Care Medicine. 2013; 14: 481–490.

[33] Jensen EW, Valencia JF, López A, Anglada T, Agustí M, Ramos Y, *et al*. Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia. Acta Anaesthesiologica Scandinavica. 2014; 58: 933–941.

[34] Müller JN, Kreuzer M, García PS, Schneider G, Hautmann H. Monitoring depth of sedation: evaluating the agreement between the bispectral index, qCON and the entropy module's state entropy during flexible bronchoscopy. Minerva Anestesiologica. 2017; 83: 563–573.

[35] Christenson C, Martinez-Vazquez P, Breidenstein M, Farhang B, Mathews J, Melia U, *et al*. Comparison of the Conox (qCON) and Sedline (PSI) depth of anaesthesia indices to predict the hypnotic effect during desflurane general anaesthesia with ketamine. Journal of Clinical Monitoring and Computing. 2021; 35: 1421–1428.

[36] Pantalacci T, Allaouchiche B, Boselli E. Relationship between ANI and qNOX and between MAC and qCON during outpatient laparoscopic cholecystectomy using remifentanil and desflurane without muscle relaxants: a prospective observational preliminary study. Journal of Clinical Monitoring and Computing. 2023; 37: 83–91.

[37] Vail EA, Shieh M, Pekow PS, Gershengorn HB, Walkey AJ, Lindenauer PK, *et al*. Use of vasoactive medications after cardiac surgery in the United States. Annals of the American Thoracic Society. 2021; 18: 103–111.

[38] Shankar A, Gurumurthy G, Sridharan L, Gupta D, Nicholson WJ, Jaber WA, *et al*. A clinical update on vasoactive medication in the management of cardiogenic shock. Clinical Medicine Insights. 2022; 16: 117954682210750.

[39] Guarracino F, Habicher M, Treskatsch S, Sander M, Szekely A, Paternoster G, *et al*. Vasopressor therapy in cardiac surgery—an experts' consensus statement. Journal of Cardiothoracic and Vascular Anesthesia. 2021; 35: 1018–1029.

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