# The nociceptive response during adult cardiac surgery measured by the qNOX index: A feasibility study

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**Background.** Monitoring nociception during general anaesthesia remains a substantial challenge. The Conox monitor uses two EEG indices, the qCon and the qNox. The qNox refers to the probability that a nociceptive stimulation triggers a movement of the patient and the response probability of reaction to nociceptive stimulation. We decided to test the feasibility of monitoring the qNOX index during adult cardiac surgery and to investigate whether this index correlates with hemodynamic and hormonal signs of nociceptive stimulation.

**Method.** We enrolled 19 patients undergoing elective cardiac surgery. These were randomised to 2 groups receiving different doses of sufentanil via target controlled infusion: group A (n=9) 0.25 ng/mL and group B (n=10) 0.75 ng/mL. All patients were maintained at the same depth of anaesthesia. We recorded the Conox monitor indices (qNOX, qCON, electromyographic), hemodynamic variables and plasmatic levels of cortisol and noradrenaline.

**Results.** There was significantly higher blood pressure ($P$=0.013) and plasmatic cortisol ($P$=0.003) in group A and a significant increase in plasmatic noradrenaline with increasing intensity of surgical stimulation in both groups: A ($P$=0.001), B ($P$=0.008). We found no significant corresponding changes in the qNOX index. There was a positive correlation between qNOX and hemodynamic signs of stimulation ($P$=0.012) and between the qNOX and EMG indices ($P$=0.013) after endotracheal intubation, but not later after EMG index dropped.

**Conclusion.** Our results do not support the assumption that signs of nociceptive stimulation during adult cardiac surgery will be reflected by the qNOX index. This may be related to compounding of qNOX processing and use of muscle relaxants. Further investigation on this field is needed.

**Key words:** nociception, general anaesthesia, cardiac surgery, noradrenaline, cortisol, Conox

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## INTRODUCTION

Anaesthesia during cardiac surgery represents specific challenges for anaesthetists in terms of maintaining adequate anaesthesia and analgesia. Cardiac surgery is historically burdened with one of the highest incidences of per-operative awareness during anaesthesia and, at the same time it is one of the most stimulating procedures with extensive nociceptive potential and relatively high doses of opioid administered[1].

While existing technology to monitor the depth of anaesthesia is fairly advanced and methodology has become widely accepted, measurement of response to nociceptive stimulation remains problematic[2].

Nociceptive stimulation during general anaesthesia provokes the sympathoadrenal stress response which can be detected by clinical signs and hormonal activity.

Clinical signs of increased per-operative sympathetic outflow as higher heart rate, increased peripheral vascular resistance, increased blood pressure and dilatation of pupils are usually considered signs of nociceptive stimulation and insufficient analgesia. There are a number of limitations which can compromise the reliability of these signs especially in settings of cardiac surgery – concomitant use of betablockers, sympathomimetics, calcium blockers, vagolytics, vasodilatators and the presence of hemodynamic instability caused by hypovolaemia, vasoplegia, low cardiac output etc.

Per-operative activation of sympathoadrenal stress response can be also detected as increased plasma levels of stress hormones such as cortisol, noradrenaline, adrenaline and adrenocorticotropin[3-6].

Laboratory analysis of plasmatic levels of hormonal responses is not feasible for use as a per-operative feedback for analgesic management.

There are several commercially produced devices claiming to reflect intensity of nociceptive stimulation during operation performed under general anaesthesia. Non of the existing technologies has been proved to have satisfactory level of specificity and sensitivity and thus are lacking potential for general use in wide range of clinical settings in patients undergoing procedure under general anaesthesia[2].

One of the promising technologies is used by monitor Conox (Quantum Medical, Barcelona, Spain). Technology is based on direct measurement of electrical brain activity of frontal region. EEG is processed into numerical indexes qCON and qNOX, where index qCON is related to depth of anaesthesia and index qNOX is declared to be responsive to probability of nociceptive stimulation. While index qCON has been successfully compared with other methods of monitoring of depth of anaesthesia, the clinical role of index qNOX remains less established. There are some results supporting qNOX's responsiveness in predicting nociceptive stimulation and sensitivity to changes in opioid concentrations[7-10].

Since index qNOX is not based on measurements of autonomic activation it should not be, in comparison to other technologies, influenced by cardiovascular status and/or cardiovascular medication. Based on this assumption index qNOX might represent an interesting potential especially during cardiac surgery.

In our study we decided to investigate the feasibility of using this method during adult cardiac surgery and investigate whether index qNOX correlates with selected physiological and hormonal signs of nociceptive stimulation.

Some publications were dealing with the question of whether the depth of anaesthesia technologies based on EEG analysis could have been affected by simultaneous use of non-depolarising muscle relaxants. The frequency band associated with EMG activity can be close to or be partially overlapped with that of the EEG[11-12]. According to other authors both indexes of monitor Conox qCON and the qNOX could be affected by use of muscle relaxants[13].

## METHOD

The study obtained the approval of the Ethics Committee of the University Hospital Kralovske Vinohrady in Prague, ID:EK-VP/041012. Written informed consent for participation was obtained from 21 adult patients scheduled for cardiac surgery. Two were excluded due to exclusion criteria (administration of corticoids and development of acute coronary ischaemia with signs of cardiac failure). Thus there were finally 19 patients enrolled in the study which was conducted from July to November 2020.

Exclusion criteria were also as follows: non-elective procedure, expected difficult airway, LV ejection fraction below 40%, signs of hemodynamic instability, sepsis, signs of renal or liver impairment, insufficiently compensated diabetes mellitus, corticoid treatment, administration of noradrenalin, suprarenal gland disease, use of etomidate, hypoalbuminaemia below 25 g/L, BMI above 40.

All patients underwent elective cardiac surgery and all were monitored using the Conox(Quantum Medical, Barcelona, Spain). This technology is based on measurement of electrical brain activity scanned by an electrode placed above the frontal region. The EEG signal is processed through the Adaptive Neuro Fuzzy Inference System (ANFIS) and two main indices, qCON and qNOX are generated as an output. Different EEG frequency bands are used to process each of the two indices. These are expressed on a scale of 0–99. Index qCON is related to the depth of anaesthesia: a qCON of 99 means full awareness, while 0 indicates no detected cortical activity. Index qNOX is claimed to be related to the probability of reaction to nociceptive stimulation, the higher the index is, the higher is the probability of reaction. According to the manufacturer qNOX above 60 is connected with very high probability of reaction, qNOX below 40 means very low probability of nociceptive responsiveness.

The Conox monitor also measures EMG activity. The EMG index is derived from electromyographic signals of facial muscles and ranges from 0 to 100, where 0 refers to electromyographic activity detected.

The night before surgery, patients were given orally, benzodiazepine alprazolam 0.25 mg (body weight below 75 kg) or 0.5 mg (body weight above 75 kg).

All were anaesthetised using a standardised anaesthetic protocol. Patients were randomised to two groups, based on different doses of TCI sufentanil: group A (n=9) TCI of 0.25 ng/mL, group B (n=10) 0.75 ng/mL. Sufentanil TCI was started just before administration of general anaesthetics and maintained at the same rate until the end of time T4 (15 min after sternotomy). For TCI administration we used a B Braun Space perfusor with pharmacokinetic model of Gepts[14].

After the start of sufentanil TCI, induction to general anaesthesia was performed by i.v. administration of midazolam 0.075 mg/kg, propofol 0.75 mg/kg and inhalation of sevoflurane with an end tidal concentration 1–2 %. When qCON fell below 60, muscle relaxant rocuronium in a dose of 1.0 mg/kg was administered and endotracheal intubation under direct laryngoscopy was performed. General anaesthesia was then maintained with continuous propofol infusion (1 mg/kg/h) and inhalation of sevoflurane (ET 1–2%) with the aim of maintaining all patients at the same depth of anaesthesia which was monitored using the Conox and the qCON index was maintained within the range 30–50. Muscle relaxant rocuronium was administered in a continuous infusion of 0.4 mg/kg/h.

Hemodynamic management was focused on maintaining the mean arterial pressure within 20% change from pre-induction baseline. Boluses of vasopressor or vasodilator were used if needed. We avoided use of noradrenalin. Phenylephrine in boluses of 100 mcg was used instead. Glyceryl trinitrate in boluses of 100 mcg was used as vasodilator. We recorded the time of administration of vasoactive drug for each patient. There were several reasons why our investigation was focused on the pre-bypass phase of operation: surgical stimulation is increasingly extensive, dilution effect of cardiopulmonary bypass priming on plasma concentrations of drugs and hormones was avoided as were the effects of hypothermia on pharmacokinetics and pharmacodynamics.

We defined four points of time in the pre-bypass phase: T1 – immediate pre-induction, T2 – just after endotracheal intubation, T3 – just after sternotomy, T4 – 15 min after sternotomy, when the chest was already spread and manipulation inside the chest had started. Intensity

of nociceptive stimulation therefore was increasing from time T1 to T4.

We recorded values of qCON, qNOX and hemodynamic variables as heart rate, systolic, diastolic and mean arterial blood pressure. In addition we obtained blood samples at defined points of time. The blood samples were cooled to a temperature of 4 °C and sent out to a laboratory for analysis of plasma concentrations of cortisol and noradrenaline.

Plasmatic cortisol level analysis was performed on the immunochemical module of the Atellica Solution analyzer (Siemens, Erlangen, Germany). The Atellica IM Cortisol (Cor) method is a competitive immunoassay using direct chemiluminescence technology.

Samples for noradrenaline level analysis were prepared with Chromsystems assay kit and analysed by system of High Performance Liquid Chromatography with electrochemical detector HPLC-ECD (ESA Biosciences, Inc., Chelmsford, Massachusetts, USA).

All data were statistically analysed by an independent institution. The data associated with the paper are not publicly available but are archived and available from the corresponding author on reasonable request.

### Statistical analysis

Continuous data are presented as arithmetic means and standard deviations (SD). Two-sample t-test and Mann-Whitney test were used to test differences between groups. Within-group changes over time were analysed using linear mixed-effects regression model. Spearman's rank correlation coefficient $r_s$ was used to measure and test the degree of association between continuous variables. All 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, U.S.A.).

## RESULTS

Basic demographic data of patients from both groups are presented in Table 1. There were no significant differences in main characteristics.

Analysis of blood pressure data showed that there were no significant differences between the groups at time T1 – pre induction to general anaesthesia. There was significantly higher mean arterial pressure in group A at time T2 and at T4. Significant differences of blood pressure found in between both groups at corresponding points of time are summarised in Table 2.

The use of vasoconstrictor phenylephrine and vasodilator glyceryl trinitrate, was sporadic and statistical analysis found no significant difference between two groups of patients.

Data sets of plasmatic levels of cortisol and noradrenaline were analysed by t-test and Mann-Whitney test. There was significantly higher plasmatic cortisol found in group A at time T4 ($P$=0.003). Data of plasmatic cortisol levels are graphically presented in Fig.1.

As for plasma levels of noradrenalin there were no significant differences between the two groups. In both groups though the plasmatic level of noradrenalin significantly rose over time from time T1 to time T4: $P$=0.001 (for group A), $P$=0.008 (for group B), respectively. Development is graphically presented in Fig.2.

Development of index qNOX was analysed in both groups. We compared values of qNOX at corresponding times (T2, T3, T4) and also cumulative values of qNOX of corresponding intervals of time which we called qNOX50 and qNOX60. We defined qNOX50 as a percentage of time when qNOX was equal or above 50, qNOX60 then as a percentage of time when qNOX was equal to or above 60 within the interval. Values of qNOX for T1 were not included in the analysis, because T1 was defined as the time before induction to general anaesthesia and so be-

**Table 1.** Comparison of basic demographic data.

| Group | Age (y) | | Weight (kg) | | BMI | | EFLV (%) | |
|---|---|---|---|---|---|---|---|---|
| | AM | SD | AM | SD | AM | SD | AM | SD |
| A | 69 | 7.9 | 86.9 | 18.4 | 29.5 | 6.5 | 55 | 8.3 |
| B | 65.7 | 7.9 | 89.7 | 9.4 | 29.8 | 3.8 | 61 | 6.9 |
| P | 0.375 | | 0.425 | | 0.915 | | 0.114 | |

AM, arithmetic mean; BMI, body mass index; EFLV, left ventricle ejection fraction; *P*, *P* value; SD, standard deviation.

**Table 2.** Significant differences of blood pressure.

| Group | BPS2 (mm Hg) | | BPM2 (mm Hg) | | BPM4 (mm Hg) | | BPD2 (mm Hg) | | BPD4 (mm Hg) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | AM | SD | AM | SD | AM | SD | AM | SD | AM | SD |
| A | 140 | 35 | 97 | 78 | 97 | 12 | 74 | 14 | 76 | 11 |
| B | 112 | 14 | 74 | 67 | 79 | 19 | 57 | 12 | 60 | 18 |
| P | 0.036 | | 0.014 | | 0.024 | | 0.013 | | 0.028 | |

AM, arithmetic mean; BPD2, diastolic arterial blood pressure at time T2; BPD4, diastolic arterial blood pressure at time T4; BPM2, mean arterial blood pressure at time T2; BPM4, mean arterial blood pressure at time T4; BPS2, systolic arterial blood pressure at time T2; *P*, *P* value; SD, standard deviation.

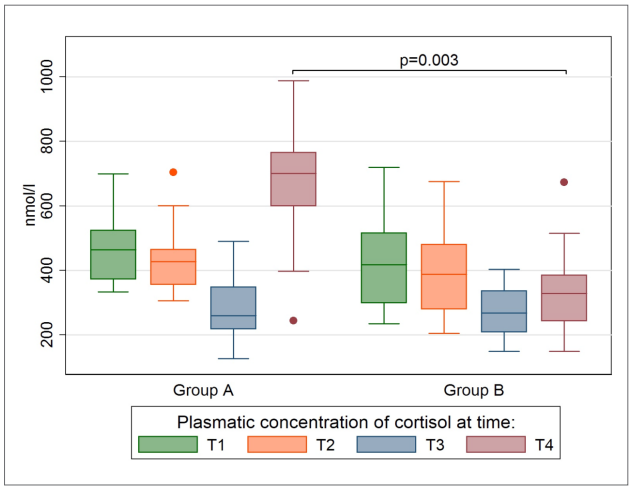


**Fig. 1.** Plasmatic concentrations of cortisol. There was significantly higher plasmatic cortisol found in group A at time T4.
Group A, patients receiving TCI sufentanil 0.25 ng/mL; group B, patients receiving TCI sufentanil 0.75 ng/mL; *P*, *P* value; T1, immediate pre-induction; T2, just after endotracheal intubation; T3, just after sternotomy; T4, 15 min after sternotomy.

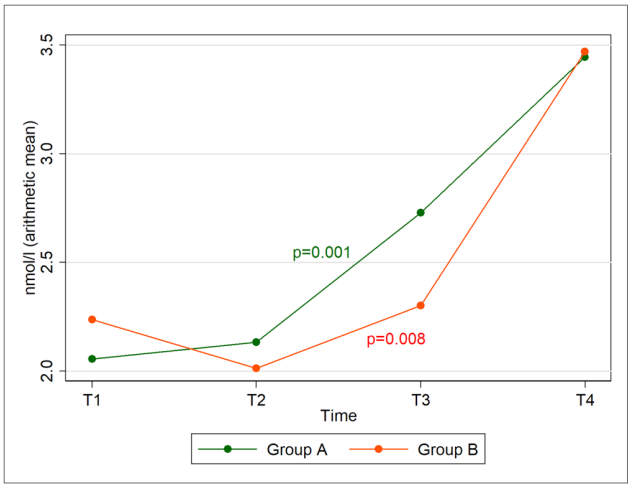


**Fig. 2.** Plasmatic concentrations of noradrenaline. In both groups the plasmatic level of noradrenalin significantly rose over time from time T1 to time T4.
Group A, patients receiving TCI sufentanil 0.25 ng/mL; group B, patients receiving TCI sufentanil 0.75 ng/mL; *P*, *P* value; T1, immediate pre-induction; T2, just after endotracheal intubation; T3, just after sternotomy; T4, 15 min after sternotomy.

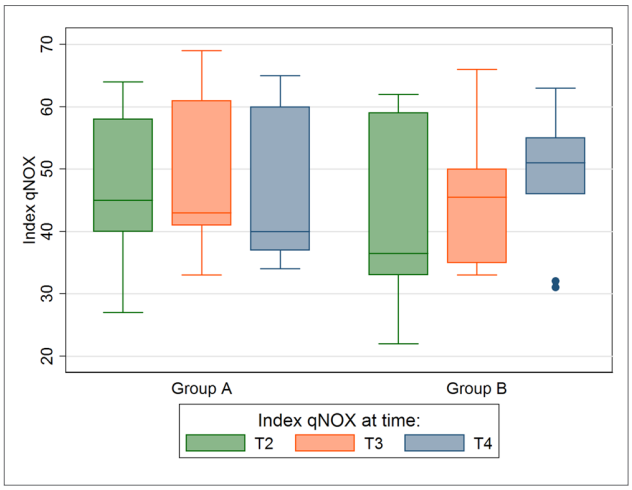


**Fig. 3.** Values of index qNOX. Values of qNOX for T1 were not included in the analysis, because T1 was defined as the time before induction to general anaesthesia and so before any surgical stimulation had started.
Group A, patients receiving TCI sufentanil 0.25 ng/mL; group B, patients receiving TCI sufentanil 0.75 ng/mL; T2, just after endotracheal intubation; T3, just after sternotomy; T4, 15 min after sternotomy.

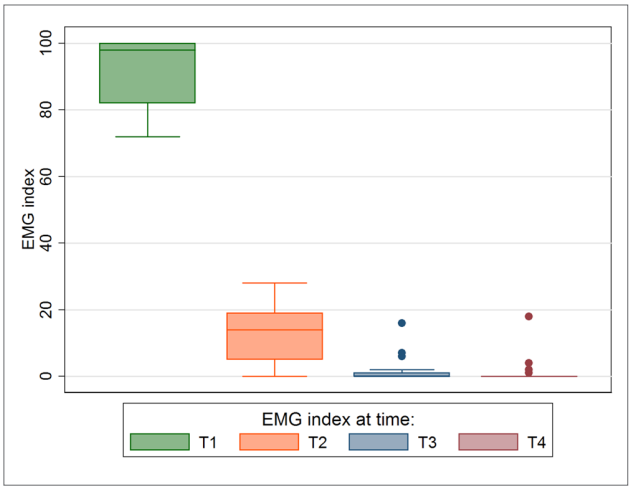


**Fig. 4.** Development of EMG index in time. EMG index of all patients significantly decreased from time T1 to T2 (*P*=0.0001) and from T2 to T3 (*P*=0.001) and T4 (*P*=0.001). Muscle relaxant was used in both groups at the same dose and dosing regimen, and therefore patients were pooled in this analysis.
T1, immediate pre-induction; T2, just after endotracheal intubation; T3, just after sternotomy; T4, 15 min after sternotomy.

fore any surgical stimulation was started. The statistical analysis showed no significant differences in values of indices qNOX, qNOX50 or qNOX60 between groups at corresponding times and intervals (*P* values from 0.380 to 0.998). Values of index qNOX are graphically presented in Fig.3

When we analysed the data of all patients (n=19) we found that index EMG significantly decreased from time T1 to T2 (*P*=0.0001), from T2 to T3 (*P*=0.001) and T4 (*P*= 0.001). This fading of the EMG index is seen because of the use of muscle relaxant. Decrease of EMG index at T2 was sudden but not as low as at T3 and T4 when it was close to isoelectric line. Development of EMG index is presented in Fig.4.

We subsequently analysed changes of qNOX and changes of EMG between different times and we found significant positive correlation between the two in interval T1-T2 ($r_S$=0.560, *P*=0.013) but not in other intervals. At time T2 we also found significant positive correlation of qNOX and diastolic ($r_S$=0.564, *P*=0.012) and mean

arterial pressures ($r_S$=0.487, *P*=0.036) and pulse rate ($r_S$=0.566, *P*=0.012). No similar relationship was detected at times T3 and T4.

## DISCUSSION

Our main objective was to investigate the reactivity of index qNOX to changes in variables associated with nociceptive stimulation.

All our patients were anaesthetised using a standardised anaesthetic protocol and maintained within the same adequate depth of anaesthesia monitored. by index qCON. The two groups of patients differed by different dose of TCI sufentanil.

Our data suggest that we were able to detect hemodynamic and hormonal signs related to peroperative nociceptive stimulation. Patients in group A expressed significantly higher levels of blood pressure at time T2 and T4 and significantly higher level of plasmatic cortisol at time T4. We can assume that patients in group A receiving a lower dose of sufentanil, expressed significantly higher evidence of signs related to nociceptive stimulation than patients in group B, who were receiving a higher dose of sufentanil.

We also found significant increase in plasma levels of noradrenalin in both groups of patients over time with increasing intensity of surgical stimulation.

We also found no significant differences in absolute or cumulative values of index qNOX between groups or any significant development of index qNOX at any defined points of time or time intervals.

As a secondary result we found significant development related to the EMG index in all our patients from both groups. EMG index was significantly lower at time T2 compared to time T1 but still significantly higher than at times T3 and T4.

Sudden drop of EMG index below baseline at time T2 (just after direct laryngoscopy and endotracheal intubation) can be explained by administration of an initial bolus of rocuronium, Some EMG index activity at time T2 remained. At times T3 and T4 the EMG index was already close to the isoelectric line. This can be explained by ongoing infusion of rocuronium when steady state of muscle paralysis had been already achieved.

Subsequent analysis found significant relationship/positive correlation between qNOX and EMG index at time T2. There was also significant positive correlation between qNOX and blood pressure and between qNOX and heart rate at time T2. None of these correlations were found at times T3 and T4.

These results indicate two possible conclusions. First. Index qNOX showed some reactivity to stimulation during direct laryngoscopy and endotracheal intubation, but reactivity of qNOX was limited to the situation when some residual EMG activity was still detected. Second. Index qNOX showed certain relationship with the EMG index and its' reading and/or processing might be influenced by simultaneous use of muscle relaxants.

## CONCLUSION

We were able to demonstrate that group of patients receiving a lower dose of sufentanil presented significantly higher incidence of hemodynamic and hormonal signs related to nociceptive stimulation. However, we found no corresponding changes in the qNOX index between the groups.

We found that the plasma noradrenaline level rose over time with increasing intensity of surgical stimulation in both groups but there were no corresponding changes in the qNOX index at defined times or intervals of times.

Our overall results do not support use of the qNOX index for monitoring response to nociceptive stimulation in adult patients undergoing elective cardiac surgery.

As a secondary finding we detected clear reactivity of index qNOX in relation to direct laryngoscopy and endotracheal intubation. This was limited to the situation when EMG index was still presented but was not detectable as it approached the isoelectric line. Our secondary conclusion supports the assumption that the qNOX index might be affected by simultaneous use of muscle relaxants.

However, we still can recommend the use of index qCON as an equivalent of depth of anaesthesia, as this index reacted sensitively and predictably to anaesthetic dose and clinical situation.

Further studies of larger groups of patients should be carried out to establish the validity and role of monitoring the qNOX index and its relation to simultaneous use of muscle relaxants.

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