Autonomic nervous system state: the effect of general anaesthesia and bilateral tonsillectomy after unilateral infiltration of lidocaine†

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Background. Autonomic nervous system (ANS) sensitively responds to intraoperative stress. Several indices characterizing the state and responses of autonomic signs to nociceptive stimuli have been introduced. This study evaluated the behaviour of ANS descriptors after induction, before and during tracheal intubation, and during bilateral tonsillectomies after random and blinded unilateral infiltration of lidocaine 1% until emergence from anaesthesia.

Methods. Twelve patients undergoing bilateral tonsillectomy were anaesthetized with fentanyl and propofol (induction) and sevoflurane (maintenance). All patients were monitored throughout anaesthesia for middle finger temperature, non-invasive arterial pressure, heart rate (HR) and pulse rate (PR), state entropy (SE) and response entropy (RE), and surgical pleth index (SPI). New parameters complementing the above and characterizing the ANS state (ANSS) and responses are pulse-to-pulse interval (PPI), pulse plethysmographic amplitude (PPGA), ANSS, and an index based on maximal ANSS for the subject (ANSSI). Serial data were stored as 10 s averages into a laptop computer.

Results. Anaesthesia induction was associated with an increase in finger temperature to 30.8°C within 10 min, whereas PPGA increased to their maximum levels within 5 min. Laryngoscopy and intubation were associated with transient autonomic responses in most patients. All autonomic signs indicated statistically significant sympathetic activation during saline-infiltrated tonsillectomies when compared with lidocaine-infiltrated sides (P<0.001). Hypnotic measures (SE and RE) and finger temperatures did not differ between the sides.

Conclusions. HR, PPI, PPGA, ANSS, ANSSI, SPI, and RE–SE detect autonomic responses to nociceptive stimuli and differentiate between tonsillectomies on locally anaesthetized tonsils from controls.

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The stress response to surgery is characterized by an increased secretion of pituitary hormones and activation of the sympathetic nervous system (SNS). Hypothalamic activation of the sympathetic autonomic nervous system (ANS) results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. During general anaesthesia, the stress response is blunted by hypnotics and analgesic agents. Heart rate (HR) and the tone of vascular smooth muscle are controlled by the sympathetic cholinergic nervous system. The autonomic fluctuations caused by pain and stressful stimuli are known to decrease the peripheral finger plethysmographic amplitude. Fast SNS responses are mediated neurally while slower, but more sustained sympathetic responses are due to circulating epinephrine and spilled norepinephrine from nerve endings.
Objective and individual methods for reliable detection of states of inadequate analgesia are highly desirable. Monitoring and measurement of patient responses in relation to a variety of nociception–antinociception (NAN) imbalances during general anaesthesia is of great interest. As the ANS steers the function of the heart by accelerating the heart beats (sympathetic nervous or humoral effect) or decelerating them (parasympathetic vagal effect), HR calculated from electrocardiography (ECG) is routinely used for the detection of autonomic imbalance in a variety of clinical situations. Pulse rate (PR) can also be obtained from pulse oximetry. The plethysmographic pulse wave amplitude is often displayed on pulse oximeter screens and contains more relevant information on the state of the circulation during surgery than the ECG. The waveform patterns depend on several factors, such as ventricular contraction force, stroke volume, venous pressure, and sympathetic vasomotor tone of the finger arterioles. Breathing, either spontaneous or by positive pressure ventilation, causes slow periodic fluctuations of the baseline, on which the heart beats are riding, resembling an arterial pressure waveform. The autonomic fluctuations caused by pain, stressful stimuli, and hypovolaemia are known to decrease the peripheral finger plethysmographic amplitude. Pulse amplitude and finger-tip perfusion correlate with finger temperature.

In this study, we wanted to investigate autonomic responses during laryngoscopy and tracheal intubation and whether pre-incisional lidocaine infiltration of one tonsil has an effect on tonsillectomy stress when compared with its pair in the same anaesthesia.

Methods
After approval by the local Ethics Committee and obtaining written informed consent from the participants, 12 adult ASA I and II patients aged 23–38 yr and weighing 54–90 kg were undergoing elective bilateral tonsillectomy because of chronic tonsillitis. Exclusion criteria included age less than 18 or more than 65 yr, central nervous system disease, cardiovascular disease or any disease which is known to affect the ANS (e.g. diabetes), or patients taking drugs affecting the ANS, central nervous system, or cardiovascular system. Exclusion criteria also included a history of alcohol, drug abuse, or psychiatric disease.

Anaesthesia
The patients had fasted from the preoperative evening. No premedication was used. The patients were preoxygenated with 100% O₂ via a face mask. After establishing baseline values, anaesthesia was induced according to normal practice with fentanyl 3 μg kg⁻¹ and propofol 2 mg kg⁻¹ i.v. and deepened first with sevoflurane 8% in oxygen with a fresh gas flow of 5 litre min⁻¹ into a rebreathing circuit with a carbon dioxide absorber. The trachea was intubated without neuromuscular blocking drugs when anaesthesia seemed deep enough, defined as a state entropy (SE) <30. Few patients needed an additional dose of fentanyl 1 μg kg⁻¹ or propofol because of movement in response to laryngoscopy before they could be successfully intubated. The cuff of the tracheal tube was inflated to an intra-cuff pressure of 22 cm H₂O. Anaesthesia was then maintained with sevoflurane in 40% oxygen in air in order to obtain and maintain an SE between 30 and 40. The lungs were normoventilated (t₁₉₀>5.3%). After intubation and placing of the mouth gag, the tonsils were blindly and randomly infiltrated either with 7.5 ml of lidocaine 1% or saline 0.9%. SE was kept at a deep surgical anaesthesia level until the end of surgery, whereafter sevoflurane was discontinued. Extubation was performed gently when the patient started to breathe spontaneously. Monitoring continued until the patients opened their eyes.

Monitoring
Before anaesthesia induction, ECG and entropy sensors were attached according to the manufacturer’s guidelines (S5 Anesthesia Monitor, GE Healthcare, Helsinki, Finland) as reported earlier. A surface temperature sensor was attached to the tip of the left middle finger. A pulse oximeter sensor was placed on the tip of the left thumb. A non-invasive arterial pressure (NIAP) cuff was wrapped around the right upper arm so that the measurements would not interfere with pulse oximetry. An i.v. cannula (20 G) was inserted in the left hand and an ample infusion of room temperature Ringer-Acetate (Vialflo, Baxter, Helsinki, Finland) was started. A laptop computer running a special data collecting software (S5 Collect™, GE Healthcare) program registered all the monitored variables via a serial cable from the S5 Anaesthesia Monitor.

We have developed new descriptors of ANS to complement conventional intraoperative monitoring parameters including the hypnosis parameters SE and response entropy (RE) for the detection of frontal mimic muscle activation. Proposals for quantifying surgical stress have been published recently. Of these, the Surgical Pleth Index (SPI) is based on ‘normalized’ pulse plethysmographic amplitude (PPGA) wave (67% included in the final index) and pulse-to-pulse interval (PPI, 33%), but the algorithm is not available for every researcher, as it has to be processed by the manufacturer. In order to combine the two most interesting sympathetically driven physiological variables HR and PPGA and display them as one index conventional intraoperative monitoring parameters including the hypnosis parameters SE and response entropy (RE) for the detection of frontal mimic muscle activation. Proposals for quantifying surgical stress have been published recently. Of these, the Surgical Pleth Index (SPI) is based on ‘normalized’ pulse plethysmographic amplitude (PPGA) wave (67% included in the final index) and pulse-to-pulse interval (PPI, 33%), but the algorithm is not available for every researcher, as it has to be processed by the manufacturer. In order to combine the two most interesting sympathetically driven physiological variables HR and PPGA and display them as one index.
offline-calculated ANSS index (ANSSI) is the present ANSS as referred to the maximal ANSS in the patient [ANSSI = \(\frac{100 - \text{ANSS}}{\text{ANSS}_{\text{max}}} \times 90\)]. A plug-in program of the Collect software displayed beat-to-beat ANSS on the laptop PC screen. A Marker (‘Take snapshot’ button) was pressed before meaningful events started and precise times were written down. Marker numbers were automatically added to the data sheets into corresponding 10 s average data rows. Collection of the data was terminated when the patients opened their eyes.

After completion of the study, data were analysed and ANSS and ANSSI calculated in MS Excel (Microsoft, Redmond, WA, USA) offline. SPI was calculated from the stored plethysmographic waves at the GE Healthcare factory by one of the co-authors (K.H.U.). The analyses of P–P intervals, PPGAs, and ANSS were enabled by the Collect\textsuperscript{TM} plug-in, where beat-to-beat values during periods of time were stored into a buffer and transferred into Excel for calculation of ANSS.

**Local anaesthesia randomization**

After the mouth gag had been inserted, the superior middle and inferior pole of the right and left tonsillar fossae were randomly infiltrated by the surgeon either with 7.5 ml of normal saline or with lidocaine 1%. An anaesthesia nurse prepared the sterile syringes according to the information inside opaque sealed envelopes numbered 1–12. The surgeon and the investigators were blinded to the drugs. Infiltration was first performed to the right tonsillar fossa. After 3 min from infiltration, surgery was initiated from the right tonsil.

**Statistics**

Data were collected as described previously.\textsuperscript{16} Collect data files (.drc) were translated by the Collect\textsuperscript{TM} software to ASCII or text files and imported into Excel tables, where each parameter including time and Markers formed its own column. Additional columns were inserted for the calculation of parameters, such as PPI, ANSS, and ANSSI\textsubscript{max}.

The data were not, in general, normally distributed. As such, data are expressed as medians (ranges). The first null-hypothesis (H\textsubscript{0}) that anaesthesia was not associated with a change in finger temperatures (\(T\text{\textsubscript{f}}\)) and PPGA was tested on data during induction and emergence using the Mann–Whitney U-test. The second H\textsubscript{0} that laryngoscopy and tracheal intubation did not cause a change in stress-related parameters HR, PPI, PPGA, ANSS, ANSSI, and SPI was tested using Friedman’s repeated measures analysis of variance on ranks on data 1 min before, and 1 and 2 min after (three comparisons) starting to intubate. The third H\textsubscript{0} that the same autonomic signs did not differ during operations on lidocaine- and saline-treated tonsils was tested using the Mann–Whitney U-test. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SigmaStat\textsuperscript{®}, version 3.5 (Systat Software, Inc., Point Richmond, CA, USA) and graphs were designed from the same data using SigmaPlot\textsuperscript{®}, version 10, from the same firm.

**Results**

All null-hypotheses H\textsubscript{01}–H\textsubscript{03} were rejected in this study.

**Induction and emergence of anaesthesia**

Induction of anaesthesia and ample infusion of lactated ringer solution was associated with a statistically significant increase in middle finger-tip temperature from 25.45 (21.79–26.53)\(^\circ\text{C}\) to 32.43 (31.12–34.60)\(^\circ\text{C}\) and PPGA from 0.84 (0.51–1.93)% to 7.11 (3.01–10.97)%, \(P<0.001\) for both changes (Fig. 2). All ANS descriptors responded statistically significantly to laryngoscopy and intubation when data during 1 min before, and 1 and 2 min after starting to intubate were compared (Fig. 3 and Table 1). Figure 4 depicts the beat-to-beat ANSS before and after laryngoscopy (note the vagal slowing of the heart as increasing PPI) and endotracheal insertion of the breathing tube. PPGA and PPI are scaled to enable visual inference. After sevoflurane was turned off, finger temperatures decrease statistically significantly from 32.95 (31.67–34.92)\(^\circ\text{C}\) to 30.18 (27.71–33.16)\(^\circ\text{C}\) and PPGA decreases from 6.74 (2.99–9.76)% to 1.12 (0.54–9.89)%, \(P<0.001\) for both changes.

**Tonsillectomies**

Figure 5 depicts the change of ANS descriptors from 50 s before start of and until the end of operations on

\[\text{Fig 1} \quad \text{Numeric values of ANSS are shown for various combinations of PPGAs and pulse intervals. ANSS data from Figure 4 are also depicted as an example of ANSdot behaviour during laryngoscopy and tracheal intubation.}\]
lidocaine-infiltrated tonsils (filled circles) and saline-infiltrated control tonsils (open circles). Table 2 gives the parameters as medians (ranges) and the statistical significance between the groups during the 5 min operations. Median HR, PPI, ANSSI, and SPI were statistically significantly lower than controls and PPGA and ANSS were statistically significantly higher than controls when lidocaine-treated tonsils were operated on. In addition, RE–SE was higher in the control group, suggesting a more frequent activation of facial mimic muscles.

Discussion

Summary of major findings

Middle finger-tip temperatures increased steadily after anaesthesia induction within 10 min (Fig. 2, upper curves). PPGAs increased also indicating a decrease in the sympathetic tone of the finger-tip arterioles. During laryngoscopic and intubation procedures, PPGA rapidly reacted as transient vasoconstrictive decreases (Fig. 2, lower curves, circles). All ANS descriptors showed statistically significant responses to laryngoscopy and intubation when data during 1 min before, and 1 and 2 min after starting to intubate were compared (Fig. 3, Table 1). At the end, both PPGA and $T_f$ decrease statistically significantly after sevoflurane was turned off.

During tonsillectomies, all ANS descriptors except NIAP showed statistically significant differences in responses when the saline-infiltrated control tonsils were compared with lidocaine-infiltrated tonsils (Table 1 and Fig. 5). Also RE–SE heralded activation of facial mimic muscles during operations on the control tonsil ($P=0.002$).

Uncertainties about the methodology

Our intention to monitor NIAP was met with procedural inconsistencies (auto-measurement with 5 min intervals) and we did not see any consistent or statistically significant results from the effect of these nociceptive manoeuvres on NIAP.

During induction of anaesthesia, we allowed free infusion of Ringer until the finger temperature was $>30^\circ C$ to overcome the compensatory closing of peripheral circulation due to hypovolaemia (fasting). In two patients in Figure 2, the start of free infusion and the warming of the
fingers were delayed. The skin temperature sensors are slow in their response to temperature change, and perhaps therefore, the changes in pulse amplitudes during laryngoscopy and intubation are not seen in finger temperatures (Fig. 2). The effect of volume replacement on finger temperatures in anaesthesia should be studied.
separately in controlled setups. The effect of external warming with warm-air blowers should also be studied.

The stimulus onsets were recorded as Marker # (by pressing ‘Take snapshot’) on the patient monitor. The Marker number is placed in the Collect™ drc-data sheet within the 10 s period of averaged data and is shown in the monitor trends. If the Marker was pressed unluckily during the next 10 s averaging period, all mean parameter values seem to change earlier (Fig. 5). Writing down the exact times of nociceptive procedures did not help, as the responses came as 10 s averages, anyway. This 10 s error in timing did not, however, much affect the trends of the changes of responses, which lasted for clearly longer periods of time.

The SPI value was calculated from the original recorded pulse waveforms and does not have the delay related to the 10 s trends. In order to get a beat-to-beat resolution, we should use one recording channel (e.g. invasive arterial pressure) for precise marking of the stimulus onset. Averaging short episodes within 10 s data tends to round the resulting means. This is particularly regrettable with RE, which expresses means from electromyographic spiky bursts leading to relatively low average values within 10 s periods. However, RE–SE gained statistically significantly higher median values when the control tonsils rather than lidocaine-infiltrated tonsils were operated on. Perhaps, the most significant source of error arises from the pulse oximetry sensor, which is often spring-loaded and causes a gradual lowering of the pulse amplitude, thus mimicking sympathetic activation.9 23

Comparison with previous work
ANS has been studied for more than 100 yr.4 Neukirche and Kienbaum24 evaluated different methods for determination of SNS function and the effects of general anaesthesia on its activation. The skin and muscle sympathetic activities must be studied with needle recordings, while finger pulse plethysmography is virtually non-invasive. The number of fluctuations in skin conductance has been described as a potential tool for monitoring postoperative pain25 and perioperative stress.18

The SPI (formerly surgical stress index) is based on the same variables measured from the plethysmographic pulse wave as ANSS, but includes averaging and learning algorithms and uses a reference population for normalization purposes.9 16 ANSS (=PPGA×PPI, % s) on the ANSdot display (Fig. 1) is calculated after each heart beat and is instantaneous,22 whereas SPI may predict a change and responds after calculations are made. ANSSI [=100−(ANSS/ANSSmax)×90] resembles the SPI, but is devoid of its unpublished averaging and learning algorithms and refers to the patient’s maximal ANS. During relaxation of the sympathetic tone, SPI and ANSSI decrease. For the purpose of this index during clinical anaesthesia, a monitor can continuously define the maximal ANSS for the particular patient and session, since only increasing ANSSI is clinically significant, as it heralds sympathetic activation due to inadequate NAP balance.9

Implications: theoretical, clinical, or both
A parameter which combines two important functions of the heart, time of preloading and filling of the heart and the pulse amplitude after a systole as received by the peripheral tissues, may provide valuable information on the ANSS.

The plain ANSS display indicates early changes in either HR or the tone of the sympathetically guided arteriolar sphincters in the finger14 and, together with SE, will aid in timing of laryngoscopy and tracheal intubation.22 Laryngoscopy seemed to be associated with a brief vagal response causing some bradycardia and an increase in pulse amplitude, which was soon overridden by sympathetic activation, tachycardia, and a decrease in PPGA and ANSS (Fig. 4). The effect of anticholinergic medication on this vagal response may be worth a study. Some patients did not respond to laryngoscopy or surgical intervention because of adequate analgesia. The simple ANSS display could be used during test laryngoscopies to determine the level of antinociceptive medication that allows intubation without autonomic responses seen in Figure 4.

Pulse oximeters emit red and infrared light pulses through the tissues of a finger-tip over 1000 times a second. We used the infrared absorption data as a measure of pulse amplitude. When a finger is placed into the sensor, the basic (minimum) absorption is measured. The basic absorption is caused by the bone, nail, fat, blood, and skin.9 The pulsating component consists of the vascular bed, where arterial pulsation adds to the basic absorption and is expressed as a percentage of it. The
Fig 5 Changes in 10 s means of peak-to-peak pulse intervals (P–Pint), PPGA, autonomic nervous system states (ANSS=P–Pint×PPGA), autonomic nervous system state indexes [ANSSI=100−(ANSS/ANSS\text{max})×90, ANSS\text{max} is the largest ANSS value in each patient] and SPIs during operations on lidocaine- and saline-infiltrated tonsils. The data are normalized to the start of tonsillectomies (0 s). For statistical inference of 5 min operative data, see Table 2.
baseline absorption is affected by venous pulsation that causes some respiratory-related volume-dependent fluctuation of the baseline and waveform variation during the ventilatory cycle. If the sensor is moved in relation to the finger, the basic absorption and also the relative absorption will change resulting into altered plethysmographic amplitude. Movement of the hand will cause motion artifacts and inconsistent amplitude readings. Care must be taken to ensure immobility of the hand during monitoring. Finger temperature monitoring seems a quality assurance; the temperature should be well more than 30°C to ensure good perfusion and pulse.

Conclusion and significance of the findings
All the ANS descriptors (HR, PPI, PPGA, ANSS, ANSSI, SPI, and RE–SE) in this randomized, controlled, and double-blinded study succeeded in detecting the nociceptive stimulus caused by laryngoscopy and tracheal intubation. The descriptors could also differentiate the effect of lidocaine infiltration from saline. To our knowledge, this study can be used to guide the anaesthesia professionals to minimize patient stress responses to nociceptive stimuli. The wide adoption of these established and inexpensive parameters into standard anaesthesia practice may help in improving patient care. Ideally, improvements in outcome will be documented by appropriately designed clinical trials.

Conflict of interest
None declared.

References
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Table 2 ANS descriptors [median (range)] during operations on lidocaine- and saline-infiltrated tonsils were tested using the Mann–Whitney U-test

<table>
<thead>
<tr>
<th>ANS descriptors</th>
<th>Lidocaine-infiltrated</th>
<th>Saline-infiltrated</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>64 (40–85)</td>
<td>65 (36–90)</td>
<td>0.012</td>
</tr>
<tr>
<td>P–Pint (s)</td>
<td>0.909 (0.706–1.500)</td>
<td>0.923 (0.667–1.667)</td>
<td>0.012</td>
</tr>
<tr>
<td>PPGA (%)</td>
<td>7.02 (2.34–10.42)</td>
<td>5.78 (2.53–11.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ANSS (%)</td>
<td>6.473 (13.059–71.962)</td>
<td>43.256 (13.059–71.962)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPI</td>
<td>30 (13–49)</td>
<td>34 (10–53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIAp_syst (mm Hg)</td>
<td>78 (62–111)</td>
<td>81 (66–112)</td>
<td>NS</td>
</tr>
<tr>
<td>SE</td>
<td>25 (17–41)</td>
<td>25 (9–42)</td>
<td>NS</td>
</tr>
<tr>
<td>RE</td>
<td>27 (9–53)</td>
<td>27 (9–53)</td>
<td>NS</td>
</tr>
<tr>
<td>RE–SE</td>
<td>2 (0–14)</td>
<td>2 (0–29)</td>
<td>0.002</td>
</tr>
<tr>
<td>$T_f$ (°C)</td>
<td>32.8 (31.7–34.9)</td>
<td>32.8 (31.8–34.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>


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