Surgical stress index in response to pacemaker stimulation or atropine

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Key points
- Cardiac pacing or administration of atropine in anaesthetized patients resulted in considerable increase of SSI.
- In contrast, arterial pressure and EEG-derived variables (BIS, spectral entropy variables) remained unchanged.
- Recalibration of SSI induced a significant decrease of SSI values only during cardiac pacing.
- After atropine administration, recalibration of SSI had no effect on SSI values.

Background. The surgical stress index (SSI) is a new monitoring tool for the assessment of nociception during general anaesthesia. It is calculated based on the heart beat interval and the pulse wave amplitude. Correlation of SSI with nociceptive stimuli and opioid effect-site concentrations has been demonstrated, but the influence of isolated modulation of heart rate (HR) on SSI is still unclear. The aim of this study was to evaluate the effect on SSI of atropine administration and cardiac pacing.

Methods. In 18 anaesthetized ASA III ICU patients, either repetitive cardiac pacemaker stimulation or administration of atropine (10 μg kg⁻¹) was performed, and the effect on SSI, arterial pressure, spectral entropy, and bispectral index was analysed.

Results. Cardiac pacing at 100 beats min⁻¹ was followed by an increase in SSI from 26 [17–35 (10–41)] to 59 [53–72 (48–78)] (median [inter-quartile range (range)]) (P=0.0006), whereas other variables remained unaffected. Also, atropine administration increased SSI from 27 [20–34 (16–39)] to 58 [48–70 (41–81)] (P=0.007) without significant effect on other variables except HR. A recalibration of SSI during cardiac pacing leads to a significant decrease in SSI to 49 [40–52 (36–57)] (P=0.03), whereas recalibration after atropine administration had no effect.

Conclusions. SSI values measured in patients receiving atropine or in patients with pacemakers should be interpreted cautiously.

Keywords: anaesthesia, depth; anaesthesia, general; equipment, monitors; monitoring, depth of anaesthesia

Accepted for publication: 12 March 2010

Methods

After approval by the local ethics committee of the University Hospital Schleswig-Holstein, Campus Kiel, and written informed consent, 18 patients (ASA physical status III), between 68 and 81 yr, were enrolled in the study. All patients underwent elective aorto-coronary bypass graft surgery and were admitted to the intensive care unit (ICU) after operation. Patients were not included if emergency surgery was performed, if they had a history of severe cardiac arrhythmia, perioperative treatment with β-blockers, or the presence of neurological disease. Only patients in postoperative cardiac sinus rhythm (between 50 and 80 beats min⁻¹) and a norepinephrine infusion ≤0.1 μg kg⁻¹ min⁻¹ were included in the study. No other catecholamine or vasoactive drug was allowed.

Standard ICU protocol

At the end of surgery, every patient received an external cardiac pacemaker (Osypka Pace™ 203H, Osypka Medical,
Berlin, Germany) with internal pericardial electrodes. Then, the anaesthetized, intubated, and mechanically ventilated patients were admitted to the ICU. Standard monitoring including invasive mean arterial pressure (MAP), ECG including heart rate (HR), pulse oximetry, and central venous pressure (all measured by S/5TM Anaesthesia Monitor; GE Healthcare, Helsinki, Finland) was re-established. Sedation was continued with propofol (3–5 mg kg$^{-1}$ h$^{-1}$) and sufentanil (0.2 mg kg$^{-1}$ h$^{-1}$) for $\approx$ 6–8 h until the patients had been rewarmed and were ready to be weaned from the ventilator. All patients received Ringer’s solution (500 ml h$^{-1}$ for the first 4 h) and additional infusion if necessary.

**Study protocol**

Study measurements started 2–3 h after arrival on the ICU. Bispectral index (BIS) (version 4.0) (BIS XpTM sensor electrodes, Aspect Medical Systems, Norwood, MA, USA, and BISTM module, GE Healthcare) and state entropy (SE) and response entropy (RE) (M-entropy moduleTM, GE Healthcare) were applied immediately after arrival on ICU. Sedation was continued with propofol (3–5 mg kg$^{-1}$ h$^{-1}$) and sufentanil (0.2$\mu$g kg$^{-1}$ h$^{-1}$) for $\approx$ 6–8 h until the patients had been rewarmed and were ready to be weaned from the ventilator. All patients received Ringer’s solution (500 ml h$^{-1}$ for the first 4 h) and additional infusion if necessary.

![Fig 1](https://example.com/image1.png) HR (a), MAP (b), BIS (c), SSI (d), RE (i), and SE (i) in anaesthetized, intubated, and mechanically ventilated ICU patients. All patients were temporarily stimulated with an external cardiac pacer with internal pericardial electrodes. D/R, disconnection and recalibration of the SSI monitor and finger clip; I–VII, 5 min study intervals (a detailed description is presented in Methods). (a) I vs III $P<0.001$; IV vs VII $P<0.01$; V vs VII $P<0.05$.

Effect of heart rate on SSI

First, the influence of pacemaker-modulated HR changes on SSI was analysed. The pacemaker—if in use—was switched off and SSI, BIS, and SE and RE values were allowed to stabilize for 5 min until start of measurements. During measurement, SSI, BIS, RE, SE, MAP, and HR were recorded every 1 min manually. These variables were derived from a time period of 10 s (median of five values) at the end of every minute to minimize artifacts. Five minutes after start of measurements without stimulation (interval I), the pacemaker was switched on (80 beats min$^{-1}$, AAI mode) for 5 min (interval II), then HR was increased to 100 beats min$^{-1}$ (AAI mode) for another 5 min (interval III). Afterwards, the pacemaker was switched off again for a 5 min period (interval IV) before it was switched on (100 beats min$^{-1}$) for 15 min (interval V–VII). Twenty-five minutes after the start of measurement, the SSI finger clip was first disconnected from the patient’s finger for 1 min and after reconnection on the patient’s index finger, SSI was allowed to recalibrate for 5 min (interval VI) followed by a final 5 min measuring interval (interval VII) (intervals were also illustrated in Fig. 1a).

Secondly, we investigated the influence of atropine administration on SSI. After a 5 min calibration period,
measurements were started. SSI, BIS, RE, SE, MAP, and HR were recorded manually every 1 min for 5 min, then atropine (10 μg kg⁻¹ i.v.) was administered followed by a study period of 10 min. Then, SSI was disconnected from the patient’s finger for 1 min and recalibrated for 5 min as described above followed by a final study period of 5 min.

Statistical analysis
Data were analysed using commercially available statistics software (GraphPad Prism 5, GraphPad Software Inc., San Diego, CA, USA). Variables before and after electrical or pharmacological intervention were analysed with the Wilcoxon signed-rank test and the Mann–Whitney U-test, as appropriate. A P-value of <0.05 was considered statistically significant. The effect of pacemaker stimulation on SSI was analysed by comparisons of defined time intervals (I vs III, V vs VII, and IV vs VII) (Fig. 1). Corrections for multiple testing were performed. Data are presented as median [inter-quartile, IQR (range)] or mean (SD) as appropriate.

Results
Eighteen patients were enrolled in the study. No patient had to be excluded. Patient characteristics are presented in Table 1.

Influence of cardiac pacemaker stimulation
Before cardiac pacemaker stimulation (interval I), a median [IQR (range)] HR of 71 [62–77 (56–82)] beats min⁻¹ and SSI of 26 [17–35 (10–41)] were recorded (Fig. 1a).

Analysis of SSI, BIS, SE, RE, and MAP during electric stimulation (80 beats min⁻¹) (interval II) revealed a slight but not significant increase in SSI (34 [28–43 (25–47)])], whereas during stimulation at 100 beats min⁻¹ (interval III), the SSI increased significantly (59 [53–72 (48–78)] (P=0.0006). End of stimulation was followed by a decrease in HR to the base level (interval IV) and repeated pacing at 100 beats min⁻¹ (interval V) reproduced a comparable increase in SSI. A disconnection of the finger clip and recalibration of the SSI during continuous pacing at 100 beats min⁻¹ (interval VI) resulted in a decreased SSI of 49 [40–52 (36–57)] (interval VII) compared with the same stimulation rate before (P=0.03). However, SSI was higher than without any stimulation (P=0.004) (interval IV). Although there was a tendency of MAP to increase according to the increase in HR, the EEG-derived parameters SE, RE, and BIS remained completely unchanged (SE: 25 [20–29 (17–31)], RE: 26 [20–30 (18–32)], BIS 34 [27–41 (22–45)] median [IQR (range)]) (Fig. 1).

Influence of atropine
Before atropine administration, HR was 68 [58–73 (53–76)] beats min⁻¹ (median [IQR (range)]). After atropine administration, a significant increase in HR (96 [86–103 (80–107)] beats min⁻¹ (P=0.02)) was observed which remained significant until end of study period after 25 min (Fig. 2a).

The SSI significantly increased after atropine administration from a baseline value of 27 [20–34 (16–39)] to 58 [48–70 (41–81)] during 8–13 min (P=0.007). Recalibration of SSI had no effect. No significant changes were detected in MAP, SE, RE, and BIS. However, a slight increase in SE and RE was detectable 1 min after atropine administration. Values were 33 [26–38 (22–40)] for SE, 34 [26–40 (22–41)] for RE, and 39 [34–45 (32 and 48)] for BIS (Fig. 2).

Discussion
In our prospective observational study, isolated stimulation of HR with a cardiac pacemaker or with atropine in anaesthetized patients resulted in a considerable increase in SSI, whereas MAP and EEG-derived variables SE, RE, and BIS remained unchanged. During pacing, recalibration of SSI induced a significant decrease in SSI, whereas after atropine administration, recalibration had no effect on SSI values.

The SSI was first described by Huiku and colleagues who investigated the index in patients who underwent general anaesthesia with propofol and remifentanil for gynaecological or breast surgery. In comparison with other variables analysed, SSI showed best correlation to actual concentration of remifentanil and intensity of painful stimulation. Therefore, SSI was introduced as a tool for the monitoring of the nociception–anti-nociception balance.

Several studies have investigated SSI during different anaesthetic regimes and patients. Ahonen and colleagues studied 30 women who underwent gynaecological laparoscopy under desflurane/nitrous oxide/fentanyl anaesthesia. The patients received additionally either remifentanil or esmolol during surgery. SSI values in the esmolol group were higher than in the remifentanil group. Interestingly, during the whole study period, HR, systolic arterial pressure, and entropy (SE and RE) were not different between the groups. This indicated a remifentanil-effect on SSI that is independent from isolated HR modulation.

However, the published studies so far investigated only young and healthy patients (mostly ASA physical status I) and—with the exception of Ahonen and colleagues—did not analyse the influence of vasoactive or HR modulating drugs or electric cardiac stimulation on SSI. However,
Effect of heart rate on SSI

Anaesthesia in older patients often requires the administration of vasoactive or HR modulating drugs and in occasional cases the use of a cardiac pacemaker. Therefore, it is important to evaluate and to know possible limitations of this index to avoid misinterpretation of the data obtained.

As might be expected from the SSS algorithm, our results indicate a very strong dependence of SSI on modulation of HR during a largely constant nociception–anti-nociception balance. Recalibration of the device had a differential effect. Recalibration following atropine had no effect on SSI values. In contrast, recalibration during pacemaker stimulation resulted in SSI values that were significantly lower than before at identical HR but significantly higher than at baseline HR. The increase and also the baseline of HR and SSI were comparable in both study groups which otherwise may have affected our findings.

A potential mechanism responsible for this differential effect may be the different HR variability (HRV) which is preserved in the atropine group but nullified in the pacemaker group. Several variables affecting HRV have been identified: depth of anaesthesia and analgesia, nociceptive stimuli, HR, direct cardiovascular drug effects, and individual co-morbidities (e.g. coronary heart disease), but the interaction between these factors is still unclear. A different analysis of a sudden tachycardia dependent on a low or high baseline HR. An HR increase accompanied by a preserved or nullified HRV may help to explain the observed differential effects in our study.

As a result, SSI monitoring in patients with pacemakers should at least be accompanied by repeated recalibration. On the other hand, SSI data in patients receiving HR modulating drugs like atropine should be interpreted cautiously. Recalibration of the device under these circumstances seems not to be a promising strategy.

Several limitations of the present study have to be mentioned. We enrolled only anaesthetized ASA III ICU patients after aorto-coronary bypass graft surgery into our study. All of them had a cardiac pacemaker and were suffering from coronary heart disease, most of them from general atherosclerosis and other co-morbidities. This may affect their reaction to stimulation. Although we adjusted the propofol infusion rate according to a defined BIS target and demonstrated that BIS and spectral entropy values were stable during measurements, we could not guarantee pharmacological steady-state conditions during the study period. Moreover, the individual baseline stress level or pain of every patient could not be quantified but may have influenced the results.

In conclusion, we demonstrated that an increase in HR induced by a cardiac pacemaker or by atropine resulted in a noticeable increase in SSI even without any additional modulation of the nociception–anti-nociception balance. EEG-derived parameters SE, RE, and BIS and also MAP remained constant, indicating deep hypnosis. Therefore, SSI data in patients receiving drugs with pronounced effects on heart rate should be interpreted with caution.

Fig 2 HR (A), MAP (B), BIS (C), SSI (D), RE (E), SE (F) in anaesthetized, intubated, and mechanically ventilated ICU patients before and after administration of atropine (10 μg kg⁻¹ i. v.). D/R, disconnection and recalibration of the SSI monitor and finger clip. (A) 1–5 vs 8–13 min P<0.05; 1–5 vs 21–25 min P<0.05; (C) 1–5 vs 8–13 min P<0.01; 1–5 vs 21–25 min P<0.05.
HR like atropine and in patients with cardiac pacemakers should be interpreted with caution.

Acknowledgement
SSI software was gratefully supplied by GE Healthcare, Helsinki, Finland.

Conflict of interest
None declared.

Funding
Funding was provided from institutional departmental sources.

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