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Correlation of surgical plethysmographic index and entropy with hemodynamic changes in laparoscopic cholecystectomy

[1]Dr. Allenki Prashanthi, [2]Dr. Nirmala Jonnavithula, [3]Dr. Karri Pavani, [4]Dr. Narmada Padhy

[1]MD, Assistant Professor, Department of Anaesthesiology and Intensive Care, Mamatha Academy of Medical Sciences, Hyderabad, Telangana, India
[2]MD, Professor, Department of Anaesthesiology and Intensive care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India
[3]MD, Department of Anaesthesiology, Mamatha Academy of Medical Sciences, Hyderabad, Telangana, India
[4]MD, Associate Professor, Department of Anaesthesiology and Intensive Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Corresponding Author:
Dr. Allenki Prashanthi (prashu9allenki@gmail.com)

Abstract

Background: The stress response to surgery is an unconscious response to tissue injury and refers to autonomic, hormonal and metabolic changes that follow injury or trauma. Excessive intraoperative stress evoked by surgical nociceptive stimulation may influence patient's outcome, length of hospital stay and overall costs of hospital care. Traditionally, clinical signs like somatic or autonomic responses are used to evaluate whether analgesia is adequate. It has been proved to be unreliable demonstrating low specificity. In the present study hemodynamic changes are correlated with changes in surgical plethysmographic index (SPI) and entropy at the time of stress.

Methods: A prospective non-randomised observational study was conducted in the patients posted for elective laparoscopic cholecystectomy. Hundred ASA physical status I and II patients aged between 18 to 60 years belonging to both the gender scheduled for elective laparoscopic cholecystectomy were enrolled in the study.

Results: According to the correlation coefficient values SPI values are correlating with changes in heart rate, systolic blood pressure and diastolic blood pressure at the time points of 5 min after intubation, 10 mins after intubation and before inflation. Entropy values does not correlate with SPI as entropy indicates hypnosis level where as SPI is based on sympathetic and parasympathetic stimulation. State entropy correlates with changes in systolic and diastolic blood pressure at the time points of before inflation, 30 min after inflation and deflation. However state and response entropy correlates with each
Other. Response entropy correlates with changes in systolic and diastolic blood pressure at the time points of 5 mins after intubation and before inflation.

Conclusion: We conclude that SPI correlates moderately with heart rate, systolic blood pressure and diastolic blood pressure at the times of stressful periods during surgery.

Keywords: Correlation, surgical plethysmographic index, response entropy, state entropy, laparoscopic cholecystectomy

Introduction

The stress response to surgery is an unconscious response to tissue injury and refers to autonomic, hormonal and metabolic changes that follow injury or trauma [1]. The activation of the sympathetic neural and autonomic humoral pathways causes changes in heart rate, blood pressure and blood circulation. Excessive intraoperative stress evoked by surgical nociceptive stimulation may influence patient's outcome, length of hospital stay and overall costs of hospital care [2]. To achieve adequate analgesia, it is crucial to use an ideal variable for assessing the stress level or perhaps more accurately the balance of nociception – antinociception. Stress-free anaesthesia, with measurement-based control of analgesia and hypnosis, would improve postoperative outcome [3].

Traditionally, clinical signs like somatic (movement) or autonomic (tachycardia, hypertension, sweating, and tearing) responses are used to evaluate the adequacy of analgesia. It has been proved to be unreliable demonstrating low specificity [4].

Surgical plethysmographic Index (SPI) is a novel multivariate index. It is developed using two continuous cardiovascular variables, the normalized heart beat interval and the normalized pulse wave amplitude. It quantifies the intraoperative stress level or nociception during general anaesthesia [5].

Degree of hypnosis and the management of analgesia are not represented by direct monitoring. They are represented indirectly by the pathophysiological secondary response. Entropy is a measuring tool for the level of hypnosis [6]. During general anaesthesia, electroencephalogram (EEG) changes from irregular to more regular patterns as anaesthesia deepens. Similarly, facial electromyogram (FEMG) quiets down as the deeper parts of the brain are increasingly saturated with anesthetics. The entropy module measures these changes by quantifying the irregularity of EEG and FEMG signals [7]. In adults, the entropy range guideline reflects a general association between the patient's clinical status and entropy values [8].

Titration of anesthetics to entropy guideline should be done in context of patient status and treatment plan. Individual patients may show different values. In the present study hemodynamic changes are correlated with changes in surgical plethysmographic index and entropy at the time points of stress during laparoscopic cholecystectomy procedures. The hallmark of laparoscopy is the creation of pneumoperitoneum with carbon dioxide which results in pathophysiological changes. The changes are characterized by increase in arterial pressure and systemic and pulmonary vascular resistance early after the beginning of intra-abdominal insufflation. A 10% to 30% reduction in cardiac output has been reported in most studies [9]. We hypothesized that SPI, entropy correlates with changes in hemodynamic variables that occur at standard stress point of time like intubation, surgical stress response, pneumoperitoneum and extubation.

Aim of the study: Correlation of surgical plethysmographic index and entropy with hemodynamic changes at the standard stress points of time in laparoscopic cholecystectomy.

Material and Methods

The prospective non-randomised observational study was carried out after obtaining approval from the NIMS institutional ethical committee, EC/NIMS/1865/2017 and 21th ESGS Number 435/2017. We obtained written informed consent from patients and also registered the trial with Clinical trial registry of India with CTRI number CTRI/2017/03/008097**.**

Power calculations suggested that a minimum of 85 subjects are required to study the

correlation with and α error of 0.05 and β error of 0.2 [10]. A sample size of 100 was taken as some cases may get converted to open procedure or otherwise.
Hundred ASA physical status I and II patients aged between 18 to 60 years belonging to both the gender scheduled for elective laparoscopic cholecystectomy were enrolled in the study. Exclusion criteria: ASA III,IV, Laparoscopy converted into open cholecystectomy, Patients with coagulation disorders, BMI > 30 kg/m^2, Sepsis, excessive bleeding during the procedure, Surgery > 3 hours, Delayed recovery or requiring postoperative ventilation, unwillingness to give consent.

Anaesthetic management

All the patients were premedicated with tab. alprazolam 0.25mg and ranitidine 150mg night before and on the morning of surgery. Standard general anaesthesia technique was followed for all the patients. In the operating room, baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), Saturation (Spo_2), temperature, state entropy (SE), Response entropy (RE), SPI were monitored and noted down. After obtaining IV access, Inj. glycopyrrolate 0.1mg and inj. fentanyl 2mcg/kg were given intravenously 5 minutes before induction of anaesthesia. All the patients were preoxygenated with 100% oxygen for 3 minutes. Standard induction of anesthesia included Inj. Propofol IV till the loss of response to verbal contact and intubation was facilitated with muscle relaxant inj. atracurium 0.5 mg/kg IV. All the patients were intubated with an appropriate size oral cuffed portex endotracheal tube and maintained with sevoflurane and nitrous oxide in oxygen in a ratio of 60:40 and sevoflurane tailored to the patients' need. Atracurium and fentanyl in a ratio of 1:1 was given as infusion to maintain relaxation and analgesia uniformly. Inj. ketorolac 30 mg was administered IV to all the patients at the beginning of the surgery. HR, SBP, DBP, MAP, SE, RE, SPI values were recorded at the following times-base line, 1, 5 and 10min after intubation, before inflation of peritoneum, 30 mins after inflation, after deflation and after extubation. At the end of surgery all the patients were reversed with 0.04-0.07 mg/kg neostigmine and 0.4mg glycopyrrolate and extubated after meeting the criteria for extubation and good recovery.

Statistical analysis

Statistical analysis was performed using the software Statistical Package for the Social Sciences (SPSS) Version 17.9 (Chicago IL). The descriptive analysis for continuous data was expressed as mean with standard deviation, ordinal data was expressed as median with Inter quartile range (IQR). The nominal data was expressed as frequency with percentages. The correlation of the variables with events was performed using Spearman's correlation. The correlation between the variables at different time periods was performed using person's correlation. A p value of < 0.05 is considered for significant correlation.

Results

The data was collected for all the 85 patients included in the study and the final analysis was done. The mean age of the patients was 40 years and the mean duration of the surgery was 106 minutes. Mean and standard deviation of the clinical parameters required in perioperative period were shown in table 1. Mean and Standard deviation of the variables at different time periods were presented in table 2.
Mean of all the parameters at different time periods was presented in figure 1.
Correlation between SPI values and haemodynamic changes at the time of stressful events and SPI with entropy were presented in table 3. According to the correlation coefficient

values SPI values were correlating with changes in HR, SBP and DBP at the time points of 5 min after intubation, 10 mins after intubation and before inflation. SPI values were not correlating with the values of SPO_2. Entropy values does not correlate with SPI as entropy indicates hypnosis level where as SPI is based on sympathetic and parasympathetic stimulation.

Correlation of SE with haemodynamic parameters and SPI is presented in table 4. State entropy correlates with changes in SBP and DBP at the time points of before inflation, 30 min after inflation and deflation. However SE and RE correlates with each other. Correlation of response entropy with haemodynamic parameters and SPI is presented in table 5. Response entropy correlates with changes in SBP and DBP at the time points of 5 mins after intubation and before inflation.

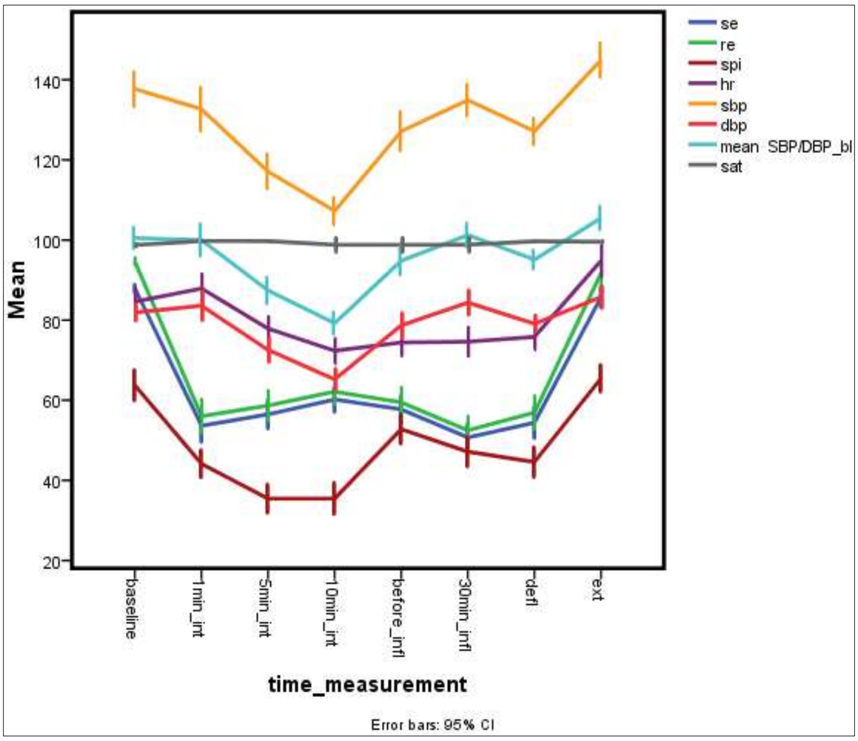

Fig 1: Mean of the variables at different time periods.

Fig 1: Mean of the variables state entropy(se), response entropy(re), surgical plethysmography index (SPI), heart rate(hr.), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure(mean SBP/DBP), saturation(sat) at the time of stress periods-baseline, 1min after intubation(1min-int), 5min after intubation(5min-int),10min after intubation(10min-int), before inflation(before-infl), 30min after inflation(30min-infl), deflation (DEFL), extubation (EXT).

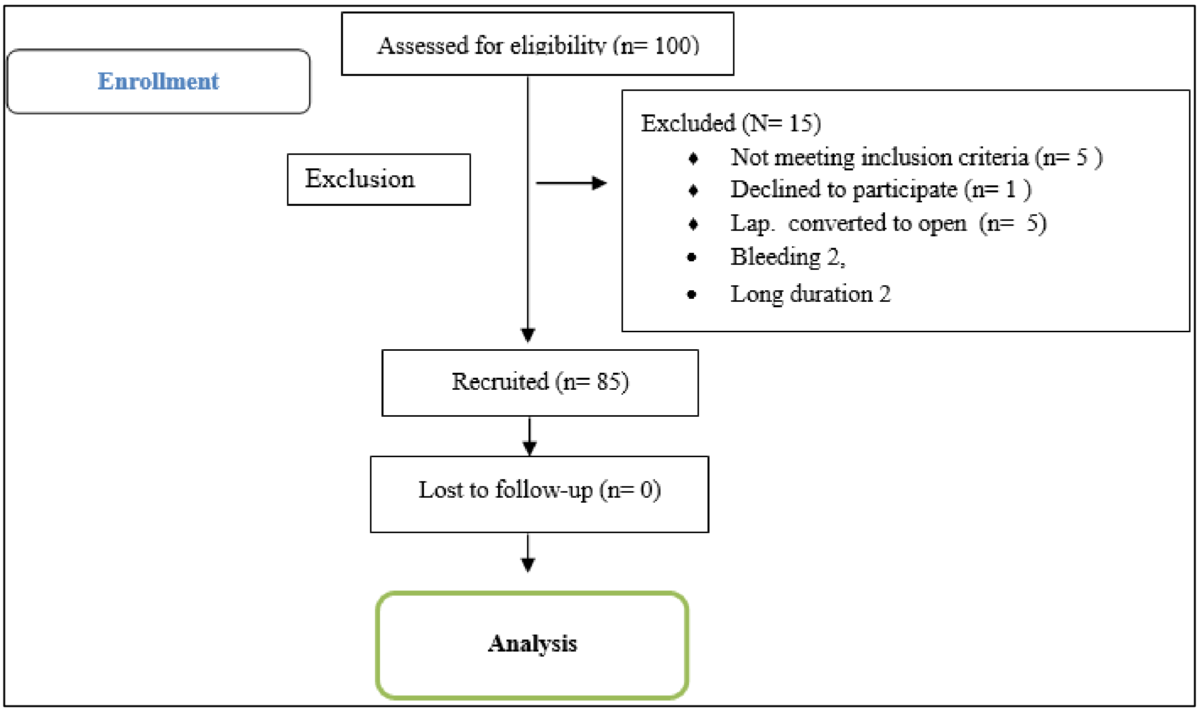

Fig 2: Consort diagram

Table 1: Mean and Standard deviation of the variables and clinical parameters.

Variable	Mean ± Standard Deviation
Age (in years)	40.06 ± 10.828
Duration of surgery (in mins)	106.37 ± 33.885
Fentanyl requirement in Intraoperative period in micro grams(µgm)	20.95 ± 31.04
Fentanyl requirement in Postoperative period in micro grams(µgm)	0.70 ± 3.555
Sevoflurane requirement in millilitres.	28.79 ± 16.701

Table 2: Mean and Standard deviation of the variables at different time periods.

Time intervals	SE	RE	HR	SBP	DBP	MAP	SpO_2	SPI
Baseline	87.90 ± 5.155	94.64± 4.241	84.60 ± 17.495	137.70 ± 21.637	81.90 ± 10.549	100.50 ± 13.077	98.75 ± 1.452	63.75± 19.162
1 min after intubation	53.64 ± 20.429	56.04 ± 20.788	87.91 ± 17.903	132.70 ± 27.168	83.61 ± 18.494	99.97 ± 19.91	99.75 ± 0.796	44.14 ± 17.523
5 min after intubation	56.48 ± 17.748	58.69 ± 18.520	77.89 ± 14.765	117.09 ± 21.575	72.56 ± 15.408	87.40 ± 16.33	99.73 ±0.802	35.43 ±17.991
10 min after intubation	60.18 ± 15.790	62.16 ± 16.545	72.36 ± 15.054	107.26 ± 16.511	65.22 ± 13.207	79.23 ±13.31	98.80 ± 9.003	35.46 ±19.770
Before inflation	57.72 ± 17.544	59.47 ±18.700	74.43 ± 16.123	127.16 ± 24.042	78.68 ± 15.633	94.83 ± 17.37	98.80 ± 9.035	52.79 ±18.226
30 min after inflation	50.72 ± 17.06	52.49 ± 17.387	74.61 ± 17.843	134.94 ± 19.544	84.38 ± 15.636	101.23 ± 14.83	98.82 ± 8.992	47.15 ± 18.521
Deflation	54.41 ± 19.673	59.63 ± 20.692	75.83 ± 14.841	127.16 ± 16.232	79.09 ± 10.734	95.11 ±11.469	99.67 ± 0.739	44.59 ± 18.895
Extubation	85.75 ± 13.334	91.96 ± 13.592	94.83 ± 19.235	144.96 ± 20.977	85.77 ± 13.752	105.50 ±14.33	99.58 ± 1.130	65.49 ± 17.011

Table 2: SE-State Entropy, RE-Response Entropy, HR-Heart Rate, SBP-Systolic Blood Pressure, DBP –Diastolic Blood Pressure, MAP-Mean Arterial Pressure, SpO_2-Oxygen Saturation, SPI-Surgical Plethysmographic Index.

Table 3: Correlation coefficient of all the parameters at different time intervals in relation to SPI

Time intervals	SE	RE	HR	SBP	DBP	MAP	SpO_2
Baseline	0.48	0.53	.321**	- 0.056	-0.002	0.0	0.244*
1 min after intubation	-0.077	-0.037	-0.016	-0.036	0.017	-0.005	-0.100
5 min after intubation	0.171	0.123	0.143	0.325**	0.289**	-0.005	0.139
10 min after intubation	0.051	0.026	0.210*	0.388**	0.408**	0.272**	-0.100
Before inflation	0.000	0.077	0.252*	0.295**	0.371**	0.030	0.155
30 min after inflation	0.101	0.146	0.205*	0.070	0.087	-0.087	-0.195
Deflation	0.224*	0.298**	-0.039	0.183	0.160	0.186	0.227*
Extubation	0.044	0.168	0.081	0.114	0.004	0.058	0.052

SE-State Entropy, RE-Response Entropy, HR-Heart Rate, SBP-Systolic Blood Pressure, DBP – Diastolic Blood Pressure, MAP-Mean Arterial Pressure, SpO_2-Oxygen Saturation, SPI-Surgical Plethysmographic Index.

* - Correlation is significant at $p<0.05$ level,

**- Correlation is significant at $p<0.01$ level

Table 4: Correlation coefficient of all the parameters at different time intervals in relation to SE

Time intervals	SPI	RE	HR	SBP	DBP	MAP	SpO_2
Baseline	.048	0.259**	-0.122	.107	.024	.061	.121
1 min after intubation	-0.077	.942**	.075	.033	-0.079	-0.047	.020
5 min after intubation	.171	.973**	-0.169	-0.088	-0.246*	-.005	.227*
10 min after intubation	.051	.942**	-0.064	-0.084	-0.174	-0.082	.120
Before inflation	.000	.952**	-0.171	-0.267**	-0.305**	-0.252*	-0.094
30 min after inflation	.101	.969**	-0.023	-0.201*	-0.365**	-0.182	-0.040
Deflation	.224*	.944**	-0.007	-0.152	-0.275**	-0.243*	.127
Extubation	0.044	.893**	-0.065	.028	.081	.065	.036

SE-State Entropy, RE-Response Entropy, HR-Heart Rate, SBP-Systolic Blood Pressure, DBP – Diastolic Blood Pressure, MAP-Mean Arterial Pressure, SpO_2-Oxygen Saturation, SPI-Surgical Plethysmographic Index

* - Correlation is significant at $p< 0.05$ level

**- Correlation is significant at $p<0.01$ level

Table 5: Correlation coefficient of all the parameters at different time intervals in relation to RE.

Time intervals	SPI	SE	HR	SBP	DBP	MAP	SpO_2
Baseline	.053	.259**	.016	-0.013	-0.105	-0.052	.091
1 min after intubation	-0.037	.942**	.068	.053	-0.061	-0.014	-0.009
5 min after intubation	.123	.973**	-0.148	-0.051	-0.277**	-0.028	.165
10 min after intubation	.026	.942**	-0.013	-0.082	-0.174	-0.095	.120
Before inflation	.077	.952**	-0.126	-0.282**	-0.311**	-0.288**	-0.083
30 min after inflation	.146	.969	.088	-.144	-.318	-.127	-.038
Deflation	.298**	.944**	.017	-0.107	-0.236*	-0.198*	.155
Extubation	.168	.893**	-.037	.068	.072	.079	.057

SE-State Entropy, RE-Response Entropy, HR-Heart Rate, SBP-Systolic Blood Pressure, DBP – Diastolic Blood Pressure, MAP-Mean Arterial Pressure, SpO_2-Oxygen Saturation, SPI-Surgical Plethysmographic Index

* - Correlation is significant at $p<0.05$ level

**- Correlation is significant at $p<0.01$ level

Discussion

In the present study we investigated the correlation of SPI and Entropy with hemodynamic changes during the periods of stress in laparoscopic cholecystectomy. SPI is a non-invasive variable. It uses pulse plethysmography and photoplethysmography obtained from pulse oximetry monitoring, to provide an index of nociception-antinociception balance [11]. It correlates with surgical stimuli and dosage of analgesic and predicts the effect of pain stimuli and analgesic therapy with greater certainty than common clinical parameters [12, 13].

In our study we found that SPI values are correlating moderately with the changes in heart rate, systolic blood pressure and diastolic blood pressure at the time points of 5 min, 10 mins after intubation and before inflation. SPI reflects a change of the autonomic nervous system balance in body. The increase of the sympathetic activity increases SPI. Potentially, any medication or therapy that affects the sympathetic nervous system balance is reflected in the value of the SPI [14]. Bonhomme and Hans *et al.* [15, 16] have studied SPI, HR and Mean arterial pressure (MAP) during neurosurgery using standardized noxious stimulus and fluid challenge as interventions and found that the interpretation of SPI, HR, and MAP is affected by the status of the patient's intravascular blood volume and chronic history of hypertension. Hence in our study SPI is correlating with changes in HR and BP. So monitoring SPI can predict hemodynamic changes. Mustola *et al.* [17] noted that sometimes with poor plethysmographic signal in elderly patients at low blood pressure below MAP 60 mmHg and in the absence of stimulation, SPI increased and NIBP decreased. This paradoxical response was reversed by Ethyl phenylephrine 2 mg IV. Poor signal and weak plethysmographic pulse may thus confound the interpretation of the SPI values. To overcome this bias in our study we included only ASA grade I and II patients and of age between 18 and 60 years. Ilies *et al.* [18] investigated the effect of posture on SPI. The posture of a patient shifts the balance of the autonomic nervous system, and therefore has a marked effect on the absolute value but does not suppress the reactivity of the SPI. This might be the reason why SPI is correlating with hemodynamic variables only at certain stress time points.

SPI can be used in outpatient anaesthesia. It reduces the consumption of both remifentanil and propofol. These patients awaken faster and can be extubated sooner [11]. Another study [19] has compared SPI guided analgesia with conventional analgesia practices in children. The conclusion of the study was SPI guided analgesia resulted in lower fentanyl consumption but less stable hemodynamics during surgery and increased postoperative pain and emergence agitation, resulting in higher postoperative analgesic requirements compared with conventional analgesia practices in children. In children, the vascular walls have a lower collagen–elastin ratio and percentage of smooth muscle cells compared with adults, who show increased collagen and muscle cells with age [20,21]. Basal catecholamine concentration and resting muscle sympathetic nerve activity increase in children with age, leading to enhanced stimulation of vascular smooth muscle and vasoconstriction [22]. Sarkola *et al.* [23] in their study demonstrated that children had lower vascular wall stress and higher distensibility compared with adolescents and adults, which can have an impact on SPI as it depends on vascular wall distensibility and intravascular pulse pressure [24]. In our study we included patients of age between 18-60years, so that we were able to overcome the bias.

Regarding hypnosis levels, two non-invasive methods are presented in the literature, one is bispectral index (BIS) and the other is entropy. Both methods are based on the electroencephalographic -based monitor. According to the studies one of the most specific methods is entropy, determined by SE and RE [25-27]. Balci *et al.*, have also shown that SE and RE values were lower than the BIS level, concluding that entropy has higher sensibility and sensitivity in comparison to BIS. [28] Hence we used the non-invasive method, entropy with higher sensitivity in our study to overcome the limitations of the previous studies.

We found that there was no correlation of SPI and SpO_2. SPI algorithm has been developed for finger measurement and cannot be used on other sites such as ear or toe. The change of the SpO_2 probe between fingers may also change SPI values, but will maintain the responsiveness of the measurement to stimulation and analgesic medications. As conclusion, after a change of the SpO_2 probe site or after removing and re-attaching the probe on the same site, the SPI value may shift to a slightly different level without a change in the nociception-anti-nociception balance [14].

Conclusion

We conclude that SPI correlates moderately with heart rate, systolic blood pressure and diastolic blood pressure at the times of stressful periods during surgery and it is not correlating with entropy as entropy is based on level of hypnosis. Our results may guide future research for developing new algorithms of antinociception assessment.

References

1. Huiku M, Uutela K, Van Gils M, Korhonen I, Kymalainen M, Merilainen P, *et al.* Assessment of surgical stress during general anaesthesia. Br J Anaesth. 2007;98(4):447-55.
2. Xinzhong Chen, Carsten Thee, Matthias Gruenewald, Christoph Ilies, Jan H¨ocker, Robert Hanss, *et al.* Correlation of Surgical Pleth Index with Stress Hormones during Propofol-Remifentanil Anaesthesia. The Scientific World Journal. 2012.
3. MMRF Struys, Vanpeteghem C, Huiku M, Uutela K, Blyaert NBK, Mortier EP. “Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion”, Br J Anaesth. 2007;99(3):359-367.
4. Rantanen M, Yli-Hankala A, van Gils M. “Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia,” Br J Anaesth, 2006;96(3):367-376.
5. Huiku M, Uutela K, van Gils M. “Assessment of surgical stress during general anaesthesia”, Br J Anaesth. 2007;98(4):447-455.
6. Liu Q, Chen YF, Fan SZ, Abbod MF, Shieh JS. EEG signals analysis using multi-scale entropy for depth of anesthesia monitoring during surgery through artificial neural networks. Comput Math Methods Med. 2015;2015:232381.
7. Viertiö-Oj. Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiologica Scandinavica48, 2004;2:154-161.
8. Vakkuri. Time-frequency balanced spectral entropy as a measure of anaesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiologica Scandinavica. 2004; 48(2):145-153.
9. Rajdip Hazra, Manjunatha SM, Babrak Manuar MD, Rajarshi Basu, Sisir Chakraborty. Comparison of the effects of intravenously administered dexmedetomidine with clonidine on hemodynamic responses during laparoscopic cholecystectomy. Anaesth Pain & Intensive Care. 2014;18(1):25-30.
10. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB, Designing clinical research: an epidemiological approach.4thedition. Philadelphia PA: Lippincott Williams and Wilkins. 2013, 79.
11. Bergmann I, Go¨hner A, Crozier TA, Hesjedal B, Wiese CH, Popov AF, *et al.* Surgical pleth index-guided remifentanil administration reduces remifentanil and propofol consumption and shortens recovery times in outpatient anaesthesia Br J Anaesth. 2012;1-7.
12. Huiku M, Uutela K, van Gils M. Assessment of surgical stress during general anaesthesia. Br J Anaesth 2007;98:447-55.
13. McCartney CJ, Brull R, Chan VW. Early but no long-term benefit of regional compared with general anesthesia for ambulatory hand surgery. Anaesthesiology. 2004;101:461-7.
14. Ledowski T. Monitoring of intra-operative nociception: skin conductance and surgical stress index versus stress hormone plasma levels Anaesthesia. 2010;65:1001-1006.

15. Bonhomme V. Comparison of the Surgical Pleth Index™ with haemodynamic variables to assess nociception-antinociception balance during general anaesthesia Br. J. Anaesth. 2011;105:101-11.
16. Hans P. Effect of a fluid challenge on the Surgical Pleth Index during stable propofol-remifentanil anaesthesia Acta Anaesthesiol Scand. 2012;56:787-796.
17. Mustola S. Performance of Surgical Stress Index during Sevoflurane-Fentanyl Anesthesia Anesthesiology Research and Practice 2010, 5.
18. Ilies C, The effect of posture and anaesthetic technique on the surgical pleth index Anaesthesia. 2012; 67:508-513.
19. Ji Hye Park, MD, Byung Gun Lim, M.D., Ph.D., Heezoo Kim, M.D., Ph.D., Il Ok Lee, M.D., Ph.D., Myoung Hoon Kong, M.D., Ph.D., Nan Suk Kim, M.D., Ph.D. Comparison of Surgical Pleth Index–guided Analgesia with Conventional Analgesia Practices in Children Anesthesiology. 2015;122:1280-7.
20. Sheykhzade M, Simonsen AH, Boonen HC, Outzen EM, Nyborg NC Effect of ageing on the passive and active tension and pharmacodynamic characteristics of rat coronary arteries: Age-dependent increase in sensitivity to 5-HT and K+. Pharmacology 2012;90:160-8.
21. Popescu MR, Zugun FE, Cojocaru E, Tocan L, Folescu R, Zamfir CL. Morphometric study of aortic wall parameters evolution in newborn and child. Rom J Morphol Embryol 2013;54:399-404
22. Dinenno FA, Dietz NM, Joyner MJ.Aging and forearm post junctional alpha-adrenergic vasoconstriction in healthy men. Circulation 2002; 106:1349–54.
23. Sarkola T, Manlhiot C, Slorach C, Bradley TJ, Hui W, Mertens L, Redington A, Jaeggi E, Evolution of the arterial structure and function from infancy to adolescence is related to anthropometric and blood pressure changes. Arterioscler Thromb Vasc Biol 2012;32:2516.
24. Dorlas JC, Nijboer JA: Photo-electric plethysmography as a monitoring device in anaesthesia. Application and interpretation. Br J Anaesth. 1985;57:524-30.
25. Balci C, Karabekir H, Sivaci R. Determining entropy values equivalent to the Bispectral Index values during sevoflurane anaesthesia. Arch Med Sci. 2010;6(3):370-4.
26. Anderson RE, Barr G, Öwall A, Jakobsson J. Entropy during propofol hypnosis, including an episode of wakefulness. Anaesthesia. 2004;59:52-6.
27. Vakkuri A, Yli-hankala A, Sandin R, *et al.* Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol nitrous oxide-alfentanil anesthesia. Anesthesiology. 2005;103(2):274-9.
28. Balci C, Karabekir H, Sivaci R. Determining entropy values equivalent to the Bispectral Index values during sevoflurane anaesthesia. Arch Med Sci. 2010;6:370-4.