Assessment of heart rate variability at different depths of anaesthesia during surgery

Papaioannou Vasilios MD, PhD, Kostoglou Christos, MD, Papagiannopoulou Pinelopi MD, PhD, Georgiadou Theodora, MD, Kanakoudis Fotios MD, PhD

ABSTRACT
Assessment of heart rate variability at different depths of anaesthesia during surgery
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General anaesthesia is associated with a reduction in heart rate variability (HRV) compared to awake situation. In this study the hypothesis of reduction in HRV was tested in two different levels of anaesthesia depth. Forty six patients were randomly allocated in two groups, where anaesthesia was maintained with sevoflurane (n=23) or propofol (n=23). Administration of both anaesthetics was regulated in order to achieve a BIS value 25±5, followed by an increase to 55±5, both being stable for 5 min. HRV analysis included low frequency (LF), high frequency (HF) and total power (TP) measurements during the two levels of BIS. Estimated Normalized Values and LF/HF ratio were analyzed as well. Both logarithms of LF, HF and the Total Power values were changed in a statistically significant way from state of anaesthesia with BIS 25±5 to BIS 55±5 within each group of patients (0.24±0.53 vs 0.80±0.58, -0.73 ± 0.53 vs -0.17 ± 0.58, 5.16±5.49 vs 13.93±14.41 respectively for sevoflurane group, t-paired test p<0.05, 0.36±0.36 vs 0.76±0.43, -0.62 ± 0.35 vs -0.23 ± 0.36, 4.50±7.13 vs 10.40±14.38 respectively for propofol group, Wilcoxon test p<0.05). Normalized values and LF/HF ratios did not differ significantly, indicating similar sympathovagal balance between different levels of hypnosis. No difference between the two groups was found in terms of all HRV metrics with BIS values either 25±5 or 55±5. Conclusively, maintenance of anaesthesia with either propofol or sevoflurane affects HRV in a BIS dependent way without significant difference between them, but sympathovagal balance seems to remain unchanged.

Analysis of heart rate variability (HRV), that is the variability of R-R in the electrocardiographic (ECG) signal, has been widely used as a measure of activity of the sympathetic and parasympathetic components of the autonomous nervous system [1,2]. Surgical stress stimulates the sympathetic nervous system and in some cases the parasympathetic as well. Suppression of this stimulation routinely is achieved by opioids during general anaesthesia, which markedly depresses HRV and therefore it has been suggested as a measure of depth of anaesthesia [3-5]. It may be surmised that changes in HRV that occur during general anaesthesia could reflect more closely the brainstem anaesthesia effect. In contrast, EEG indices (Bispectral index, 95% spectral edge frequency) measure cortical effects [6].

Many authors have observed that induction of anaesthesia with both propofol and sevoflurane is associated with a reduction in HRV compared to preanaesthetic values, although there are
some conflicting data regarding the effects of these two anaesthetics on cardiac sympathetic or parasympathetic tone [7-10]. However, there are still some questions to be answered, such as what happens during surgery under general anaesthesia? Is the reduction in HRV, because of anaesthesia, capable to suppress or modify the stimulation of autonomic nervous system because of surgical stress? Therefore, the first goal of this study was to test the hypothesis that general anaesthesia with propofol or sevoflurane would affect HRV in a way depending on the depth of anaesthesia as it is expressed by Bispectral Index (BIS), during surgical operation with the surgical stress factor included. The second goal of the study was to investigate if there is a difference between propofol and sevoflurane anaesthesia in relation to HRV changes during high and low BIS values.

Methods

Forty six patients of good physical status (ASA I and II), scheduled for various types of elective lower abdominal surgery, were studied after approval by the Institutional Ethics Committee and written informed consent was obtained. Patients were studied during reconstruction phase, after resection phase was finished. Patients with diabetes mellitus, quadriplegia or other major neurological disorders, ischemic heart disease, congestive heart failure or hypertension were excluded from the study. None of the patients was taken medications that affect autonomic or cardiovascular function. No premedication was given before surgery.

On arrival to the operating room, the patient’s vital signs were monitored using leads II and V5 of ECG, non-invasive arterial blood pressure (determined by automated oscillometry at 3 min intervals), capnography and arterial oxygen saturation (SpO2). BIS values were measured continuously on a monitor (Model A1050 version 3.4; Aspect Medical Systems, Natick, MA). Before induction of anaesthesia, patients were randomly allocated in two groups (P and S) by use of a random number generator program (EXCEL XP® Microsoft). General anaesthesia was induced with propofol 2 mg Kg⁻¹, remifentanil 1µg Kg⁻¹ and cisatracurium 0.15 mg*Kg⁻¹, for both group of patients, followed by tracheal intubation. Anaesthesia was maintained in the group P (n=23) with propofol infusion at a rate of 50-300 µg*Kg⁻¹*min⁻¹ and 60% nitrous oxide in oxygen. In the group S (n=23) anaesthesia was maintained with sevoflurane at 0.5-2 minimal alveolar concentration (MAC) inspiratory concentration and 60% nitrous oxide in oxygen as well. In both groups there was a continuous infusion of remifentanil in standard rate of 0.1 µg*Kg⁻¹*min⁻¹ with ANNE® ABBOTT Infusion pump. After tracheal intubation neuromuscular block was maintained with cisatracurium with repeated bolus doses according to patient needs (clinical criteria). The lungs were ventilated mechanically at a rate of 8 breaths per minute (Julian® Dräger, Germany) and tidal volume was set to maintain end-tidal carbon dioxide tension at 4.0-5.0 kPa (about 8-10 ml*kg⁻¹). Blood pressure was controlled within the range of ±25% of baseline (preanaesthetic) values with intravenous fluids or phenylephrine administration.

After the major surgical stress (resection phase) had been stabilized, the propofol infusion rate or the % inspiratory concentration of sevoflurane were changed in order to reach BIS values within a range of 25±5. After 5 minutes of steady state (BIS25), ECG data were

Table 1. Patient characteristics. Demographic data of the patients studied and type of operations. Values are expressed as mean±SD or absolute numbers.

<table>
<thead>
<tr>
<th>Operation</th>
<th>Sevoflurane (N=23)</th>
<th>Propofol (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>13/10</td>
<td>14/9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54±17</td>
<td>60±14</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>81±15</td>
<td>76±11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1.70±0.09</td>
<td>1.67±0.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operation</th>
<th>10</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bladder removal</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Sigmoidectomy</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 2. Hemodynamics during anesthesia with BIS values 25±5 and 55±5 using sevoflurane or propofol.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (N=23)</th>
<th>Propofol (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIS 25±5</td>
<td>BIS 55±5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>65±12</td>
<td>68±11</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120±14</td>
<td>136±24</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>65±12</td>
<td>72±12</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83±13</td>
<td>93±13</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
BIS=bispectral index, HR=heart rate, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure.

Table 3. Frequency Domain Parameters of HRV for the two study groups during two different times, with BIS values 25±5 and 55±5.

<table>
<thead>
<tr>
<th></th>
<th>Group S (N=23)</th>
<th>Group P (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIS 25</td>
<td>BIS 55</td>
</tr>
<tr>
<td>LogLF (msec²/Hz)</td>
<td>0.24±0.53</td>
<td>0.80±0.58*</td>
</tr>
<tr>
<td>LogHF (msec²/Hz)</td>
<td>-0.73 ± 0.53</td>
<td>-0.17 ± 0.58*</td>
</tr>
<tr>
<td>LFn (LF/TP)*100</td>
<td>99.1±98.1</td>
<td>207.2±319.5</td>
</tr>
<tr>
<td>HFn (HF/TP)*100</td>
<td>10.0±8.9</td>
<td>21.5±33.7</td>
</tr>
<tr>
<td>Total power (TP, msec²)</td>
<td>5.16±5.49</td>
<td>13.93±14.41*</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>9.29±1.36</td>
<td>9.53±1.58</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. * p<0.05 within the group

obtained from the monitor (Vitara, Julian, Dräger, Germany), recorded and digitized onto a personal computer via an appropriate software (PROTO version 5.2, Dräger, Germany), where the signals of the electrocardiogram (ECG) were A/D converted at a frequency of 640Hz. Then, the R wave of the signal of the ECG was detected by a peak detection method and finally time series of 1/RR were low pass filtered and an instantaneous heart rate (HR) time series was sampled at 1Hz. The duration of recording was 5 minutes and all recorded data were used for off-line analysis. The same procedure was performed when the propofol infusion rate or the % inspiratory concentration of sevoflurane were changed, in order to accomplish BIS values in the range of approximately 55±5 for a period of 5 min at least (BIS55).

Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency [11]. An open-source software was used via the Web Site Physionet that is a public service of the Research Resource for complex physiologic signals and is funded by the National Center for Research Resources of the National Institutes of Health. Nonparametric methods (fast Fourier transform) for the calculation of PSD were applied, using an epoch length of 2 s (=512=2⁹ data points). The spectral power of each spectrum (msec² /Hz) was calculated at high frequency (HF, 0.15 - 0.4 Hz) and low frequency (LF, 0.04 - 0.15 Hz) after data had been read into a MATLAB format in a MATLAB version 5.3 environment, according to Moody and Kaplan [12,13]. The total energy (msec²) was considered equal to the variance of the signal and was calculated with the same algorithm as a measure of the total power (TP) of the signal [13]. LF and HF normalized values (LFn=LF/TP*100, HFn=HF/TP*100) were used to assess sympathetic and vagal modulation of heart rate respectively.
and the ratio LF/HF was used as an index of sympathovagal balance.

**Statistical Analysis**

Because of the big range of values, heart rate power data were logarithmically transformed to fulfil the requirements of normal data distribution. A normal distribution of log power spectra at each phase was confirmed by the Kolmogorov-Smirnov test. A Wilcoxon test or t-paired test for variables with normal distribution was used for comparison, at times with the two different BIS values within the same group. Comparisons of HRV data between the two groups of patients during the two different states of hypnosis with BIS values 25±5 and 55±5 were made with Kruskal-Wallis test and one-way analysis of variance (ANOVA) test for continuous variables with normal distribution. We decided that a minimal 10% difference in percentage changes of HRV parameters between the two levels of BIS would be important. Therefore, n=21 patients in each group would be necessary to detect such a difference if α=0.05 and β=0.1. Probability values less than 0.05 were considered significant. Calculation was performed with the SPSS software version 8. Data are expressed as mean±SD.

**Results**

One-way analysis of variance (ANOVA) did not reveal any significant difference in demographic data of the two groups in terms of age, weight, height and kind of operation (table 1). Circulatory system condition as it is expressed by heart rate (HR), systolic (SBP), diastolic (DBP) and mean blood pressure (MAP) was

![Figure 1](image-url)
clinically comparable, either within groups for BIS25 and BIS55, or between groups (table 2). Logarithmically trans-formed LF and HF values (logLF and log HF), normalized values (LFn and HFn), Total power (TP), and LF/HF ratio of the two study groups in two different times, with BIS values in the range of 25±5 and 55±5, are shown in table 3. Differences between BIS25 and BIS55 within the groups were significant for logLF, logHF and TP (p<0.05). No statistically significant differences were detected between HRV parameters of the two groups (sevoflurane or propofol) during either of the two study periods of BIS25 or BIS55 (table 3).

Figure 1 shows in a bar chart the significant changes of logLF (1A), logHF (1B), and TP (1C) between and within the two study groups in two different times (BIS25, BIS55). Both logarithms of LF, HF and the Total Power (TP) change in a statistically significant way from state of anaesthesia with BIS25 to BIS55 within the same group of patients (p<0.05 t-paired test and Wilcoxon test respectively). The mean of total power (TP) seems to be slightly smaller during BIS25 and greater during BIS55 for the group P compared to the group S, but this was not of statistical significance (p=0.09 Kruskal-Wallis test).

Figure 2 shows in a bar chart the non-significant changes of LFn (2A), HFn (2B), LF/HF ratio (2C) between and within the two study groups in two different times (BIS25, BIS55).

Discussion

All components of the HRV power spectra decrease during and increase after general anaesthesia [4,7]. Kanaya et al observed a BIS-dependent decrease in the power of HF but not of LF band, in patients receiving propofol for induction of anaesthesia, indicating that propofol reduces cardiac parasympathetic tone depending on the depth of anaesthesia. Contrary, se-
A cardiac vagal tone caus es an increase in the LF/HF ratio [16,20], different authors have reported that controlled mechanical ventilation produces an increase in HF component and may also lead to a reduction in LF band [16,20]. The authors of present study did not study preoperative HRV status of patients, because there was interested in BIS-dependent HRV changes related to propofol or sevoflurane anaesthesia, under deep (BIS25) versus moderate hypnosis (BIS55). Nevertheless, as respiratory rate, tidal volume and end-tidal carbon dioxide tension were similar between groups, the differences observed in spectral power were likely not influenced by differences in the respiratory pattern.

The continuous infusion of same dose of remifentanil intraoperatively in both groups of patients could have decreased, even more, the effect of respiratory frequency on HRV metrics. The authors are not aware of any study investigating remifentanil effects on HRV analysis, but Latson et al have shown that a potent opioid such as sufentanil decreased absolute power measurements of vagally mediated HRV, and increased corresponding normalized measurements of vagally mediated HRV, offsetting by this way any influence on HF from controlled mechanical ventilation [21].

In both study groups, induction of anaesthesia was performed with propofol. The high lipid solubility of propofol results in an onset of action that is almost as rapid as that of thiopental. Awakening from a single bolus dose is also rapid due to a very short initial distribution half-life ($t_{1/2a} = 2-8$ minutes). The exceptionally high clearance rate probably contributes to relatively quick recovery after a continuous infusion [22].

Induction and maintenance of anaesthesia included nitrous oxide and opioid infusion in both study groups. Nitrous oxide administration produces signs of mild sympathomimetic stimulation that may be resulted, according to Naito and Gillis from an inhibition...
of norepinephrine uptake by the lungs, making more neurotransmitter available to receptors [23]. However, the inhalation of nitrous oxide in the presence of opioids results in a centrally mediated inhibition of its sympathomimetic effects, as Stoelting and Lappas have proven since 1973 and 1975 respectively [24,25]. In the present study all patients had the same influence by these drugs, as they all were administered the same remi-fentanil infusion and nitrous oxide inhalation.

Although LF and HF normalized values were not significantly different between groups, we could say that the total power, that is the measure of the variability of the ECG signal, was greater in sevoflurane group than in patients received propofol, probably because of the lower cardiovascular depression that is induced by sevoflurane related to propofol. The central nervous system depression is quite high during BIS values of 25, so we can suppose that the difference in total power is not due to centrally triggered HRV alterations. At the same time, the LF/HF ratio was approximately the same between groups, indicating similar sympathovagal balance. It is important to note again that HRV measures fluctuations in autonomic inputs to the heart rather than the mean level of autonomic status [26].

The total power difference between groups was not significant, and LFn, HFn, LF/HF ratio were approximately equal. This could be attributed to different depth of anaesthesia at the same BIS value between propofol and sevoflurane anaesthesia. Ibrahim et al have pointed out, that the BIS demonstrate significant variability among anesthetics through unknown mechanisms [27]. Since there was no indication of increased sympathetic tone such as heart rate or blood pressure alterations, these changes cannot be attributed mainly to different impact of propofol or sevoflurane on HRV dynamics at the level of heart tissue per se. Despite the different cardiovascular depression effects of propofol and sevoflurane, propofol has a profile of central nervous system depression that differs from other anesthetic drugs, because uniformly depresses central nervous system (CNS) structures, including subcortical centers [28]. The authors of present study don’t know how these differences can be translated in terms of HRV analysis.

The analysis of HRV metrics between BIS25 and BIS55 within groups revealed significant increase of logLF, logHF and total power for both groups of patients, approximately the same LF/HF ratio and insignificant changes of normalized values of frequency components. That means that the transition from BIS25 to BIS55 leads to a decrease of both anesthetic effects on HRV, resulting to a greater variability of ECG signals. Nevertheless, it is not known at what level this happens and it can not be certain about the exact effects of anesthetics to central nervous system, peripheral receptors or heart tissue per se through autonomic nervous system. The fact that LF/HF ratio and normalized values did not change significantly within groups could support the hypothesis that HRV dynamics was mainly altered due to different anaesthesia effects on a central level.

In summary, there is no difference between propofol and sevoflurane groups in a statistically significant way in terms of HRV metrics during general anaesthesia in two levels of BIS values (25±5 or 55±5). Although logLF, logHF and total power were significantly different between BIS25 and BIS55 within groups, normalized values and LF/HF ratios were approximately the same, indicating similar sympathovagal balance between different levels of hypnosis for both groups of patients. One of the limitations of this study is that it is impossible to have exactly the same degree of surgical stress. Although this may be somehow confounding regarding the interpretation of the results, this is the routine clinical practice and we have to accept it. Nevertheless, despite different effects of propofol or sevoflurane on cardiovascular system it seems that variability of CNS depression is the major mechanism of different aspects of HRV dynamics between groups, even if this could be resulted from different depth of anaesthesia at the same BIS values between propofol and sevoflurane.

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References


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