Appropriate Thresholds of Systolic Blood Pressure and R–R Interval for Assessment of Baroreflex Sensitivity by the Sequence Method during Sevoflurane Anesthesia

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Background: The sequence method of determining baroreflex sensitivity (BRSSEQ) has been reported to correlate poorly with the phenylephrine method of determining BRS in individuals with attenuated BRS. Inhalation anesthetics are also known to decrease BRS. We therefore assessed the effect of varying the systolic blood pressure (SBP) and R–R interval (RRI) thresholds on BRSSEQ values and compared these results with the BRS obtained by the modified Oxford technique (BRSMODEX).

Methods: The average number of valid sequences and BRSSEQ values were derived by varying the SBP threshold from 0.5 to 2.5 mmHg and the RRI threshold from 1 to 6 ms, and the relation of BRSSEQ values to BRSMODEX values using sequential administration of nitroprusside and phenylephrine was assessed in 40 healthy individuals during sevoflurane anesthesia.

Results: Increasing either the SBP thresholds or RRI thresholds resulted in a decrease in the number of valid sequences. As the SBP thresholds were decreased and the RRI thresholds were increased, BRSSEQ values increased. When the SBP threshold exceeded 1 mmHg, no significant correlations were observed between BRSSEQ and BRSMODEX values. Significant correlations between the two methods were observed for an SBP threshold of 0.5 mmHg and RRI thresholds of 1, 2, 3 and 4 ms. Biases between the two methods were 2.1, 2.1, 0.4, and 0.4 ms/mmHg for 0.5 mmHg and 1, 2, 3 and 4 ms.

Conclusions: These findings suggest that adjusting the SBP threshold to 0.5 mmHg and the RRI threshold to 3 or 4 ms may improve BRSSEQ validity during sevoflurane anesthesia, when compared to BRSMODEX. (Korean J Anesthesiol 2007; 52: S 1–8)

Key Words: anesthesia, baroreflex sensitivity, modified Oxford technique, sequence method, thresholds.

INTRODUCTION

Volatile anesthetics influence the hemodynamic stability by impairing autonomic nervous function, and, at clinically relevant concentrations, they can depress baroreflex control of heart rate.1–3) During general anesthesia, the cardiac baroreflex function, which plays a role in controlling the neural system that maintains cardiovascular homeostasis in humans, has been known to be an important negative feedback reflex to correct fluctuations in arterial blood pressure (ABP).4–6)

Baroreflex sensitivity (BRS) has been assessed primarily by analyzing the heart rate response to changes in blood pressure induced by vasoactive drugs.5–9) However, because administration of these drugs may not be appropriate in some individuals, methods have been developed to estimate BRS by analyzing spontaneous fluctuations of cardiovascular variables. Among the various techniques used to measure spontaneous BRS is the sequence method (BRSSEQ),10–13) a noninvasive method that analyzes the continuous relationship between beat-by-beat fluctuations in systolic blood pressure (SBP) and R–R interval (RRI), using the conventional thresholds of 1 mmHg for SBP and 4 to 6 ms for RRI.12,14–17) However, the RRI and SBP thresholds for BRSSEQ are arbitrary, and it is not known whether the thresholds used are optimal, especially in anesthetized individuals with attenuated BRS due to inhalation anesthetics.

On the basis of these considerations, we tested that the hypothesis that sequence method using the conventional thresholds of 1 mmHg for SBP and 4 to 6 ms for RRI do not...
evaluate appropriately BRS in a situation of impaired baroreflex function induced by general anesthesia. This hypothesis was tested in 2 ways. First, we evaluated the effect of varying the SBP and RRI thresholds on the average number of valid sequences and BRSSEQ values. Second, we analyzed the correlation between BRSSEQ values and the BRS values obtained by the modified Oxford technique (BRSMOX) using sequential administration of nitroprusside and phenylephrine, which is thought to be a means to provoke and characterize human baroreflex responses, during sevoflurane anesthesia.

**MATERIALS AND METHODS**

**Patients**

The study population consisted of 40 healthy individuals (24 males, 16 females; age, 19-41 yr; weight, 60-83 kg; height, 165-178 cm) scheduled for hepatic lobectomy as liver transplantation donors under general anesthesia. Donors with abnormal heart rhythms were excluded. All donors were free of cardiovascular or autonomic disorders, and none had taken any regular medication for 1 yr prior to surgery. All donors received written explanations of the protocol and signed a written consent form approved by the Institutional Review Board for Protection of Human Subjects at Asan Medical Center.

**Study protocol and measurements**

All donors were placed in the supine position in a quiet operating room with an ambient temperature ranging from 24 to 26°C before induction of anesthesia. A standard three-lead electrocardiogram (ECG) was used to collect data, and the radial artery was cannulated with a 20-gauge catheter with a local anesthetic. Beat-by-beat ECG and ABP were monitored continuously (VSM 5°, PHYSIO-CONTROL CO. USA).

Anesthesia was induced with 5 mg/kg thiopental. Vecuronium was administered for neuromuscular block, and no anticholinergic agent was used. As soon as the trachea had been intubated, anesthesia was maintained with sevoflurane in oxygen and air (fractional inspired oxygen tension, 0.4). Breath-by-breath end-tidal sevoflurane concentration and carbon dioxide tension were measured by a gas analyzer (S/5, Datex-Ohmeda, Finland), which was calibrated before each use. Lungs were mechanically ventilated (tidal volume, 6-8 ml/kg at a respiratory rate of 15 breaths/min), and end-tidal carbon dioxide tension was maintained around 32-35 mmHg. Esophageal temperature was monitored continuously to ensure normothermia. To collect stable data with no surgical stimuli, all experiments were performed during the approximately 30 min waiting period for confirmation of liver biopsy results in donors anesthetized with 1.5 minimum alveolar concentration end-tidal sevoflurane. The 6-8 min interval prior to measuring BRSMOX was used for sequence method analysis in this period.

**Data analysis**

ECG and ABP signals were digitalized and collected at 500 samples/sec using an on-line personal computer that interfaced with an analog-to-digital converter (DI-720U, DATAQ Instruments, USA). R waves and ABP peaks were identified to provide beat-by-beat RRI, heart rate, and SBP. Commercially available softwares (Windaq, DATAQ Instruments, USA; DAD-iSP, DSP Development, USA; Baroreflex sensitivity analysis, Nevrokard, Slovenia) were used for artifact detection, signal conditioning, and data analysis.

**Sequence method**

Sequences in which RRI or SBP increased or decreased concurrently over 3 or more beats were identified, and the regression slope was calculated in those sequences with correlation coefficients of > 0.85. BRSSEQ was defined as the average value of the individual slopes occurring within this
Herein, thresholds, minimum change of SBP or RRI to each beat, are needed to analyze sequences. The average number of valid sequences and BRSSEQ values were obtained by varying the SBP threshold from 0.5 to 2.5 mmHg and the RRI threshold from 1 to 6 ms, and BRSSEQ values were compared with BRSMODOX values.

**Modified Oxford technique**

Baroreflex responses were provoked by intravenous bolus injections of sodium nitroprusside (100μg or 150μg) followed 60 sec later by phenylephrine hydrochloride (150μg or 200μg) (Fig. 2). This was repeated twice, with at least 10 min between trials. Drugs were administered to elicit a 15-25 mmHg reduction in SBP and subsequent increases in baseline levels. Beat-by-beat values were averaged over 2-mmHg pressure increments. BRSMODOX was defined as the slope of the linear portion of the RRI-SBP relation from the nadir to the peak SBP response (Fig. 2C). To obtain a robust curve fit, a sigmoid fit was applied to the binned data to identify the linear portion of the baroreflex curve (TableCurve 2D, SPSS Inc., USA), and data points clearly falling in either the threshold or saturation region were manually removed from the analysis. The correlation coefficients (r²) for linear gain estimates ranged from 0.80 to 0.98 (mean, 0.92 ± 0.04). For each individual, the gains for two trials were averaged to provide a single value for BRSMODOX.

**Statistical analysis**

All data are presented as mean ± SD. Normality of the data was examined using the Kolmogrov-Smirnov test (SigmaStat, Systat software, USA). Correlations between the variables were performed with Pearson’s product moment for analysis of normally distributed data. Bland-Altman method was used to compare BRSSEQ and BRSMODOX during general anesthesia. Hypothesis testing for the bias (null hypothesis: bias = 0) was performed by the one-sample t test. A P value > 0.05 was required to accept the null hypothesis.

**RESULTS**

The effect of different thresholds on the number of valid sequences in 40 healthy individuals anesthetized with 1.5 minimum alveolar concentration end-tidal sevoflurane is depicted in Fig. 3. Increasing either the SBP thresholds or RRI thresholds resulted in a decrease in the number of valid sequences. Especially, the number of valid sequences at a 2.5 mmHg SBP threshold was insufficient, and ranged from 1 to 6. The effect of modifying SBP and RRI thresholds on BRSMDOX in 40 individuals is shown in Fig. 4. As the SBP thresholds were decreased and the RRI thresholds were increased, BRSMDOX values increased.
We observed moderate correlations between BRSSEQ and BRSMODEX at a 0.5 mmHg SBP threshold and 1, 2, 3 and 4 ms RRI thresholds (Fig. 5). However, there were no significant correlations between BRSSEQ and BRSMODEX at a 0.5 mmHg SBP threshold and 5 and 6 ms RRI thresholds, and at 1, 1.5, 2, and 2.5 mmHg SBP thresholds and 1, 2, 3, 4, 5, and 6 ms RRI thresholds, respectively.

The average values of BRSMODEX and BRSSEQ for an SBP threshold of 0.5 mmHg and RRI thresholds of 1 to 4 ms are summarized in Table 1. The average estimate of BRSMODEX was 5.6 ± 2.4 ms/mmHg, which was greater than the values of BRSSEQ (3.4 ± 1.9 ms/mmHg for 0.5 mmHg and 1 ms, 3.5 ± 1.9 ms/mmHg for 0.5 mmHg and 2 ms, 5.3 ± 2.4 ms/mmHg for 0.5 mmHg and 3 ms, and 5.3 ± 2.4 ms/mmHg for 0.5 mmHg and 4 ms).

The correlation between BRSSEQ values and BRSMODEX values and the relationship between the average of the two estimates and their difference are shown in Fig. 5. The results of Bland-Altman analysis showed that the bias (BRSMODEX – BRSSEQ) did not differ from 0 when SBP threshold was 0.5 mmHg and RRI thresholds were 3 and 4 ms (bias = 0.4 ms/mmHg, P > 0.05 vs. 0 for 0.5 mmHg, 3 ms: bias = 0.4 ms/mmHg, P > 0.05 vs. 0 for 0.5 mmHg, 4 ms).

In the present study, due to a lack of spontaneous sequences, BRSSEQ could not be measured in 1 individual at an SBP threshold of 0.5 mmHg and RRI thresholds of 1 and 2 ms, and in 6 individuals at an SBP threshold of 0.5 mmHg and RRI thresholds of 3 and 4 ms.

**DISCUSSION**

The major finding of the present study is that alteration of the SBP and RRI thresholds affected not only the number of valid sequences, but also the values of BRSSEQ. Additionally, the present data showed that, in healthy individuals anesthetized with 1.5 minimum alveolar concentration end-tidal sevoflurane, BRSSEQ using the conventional thresholds of 1 mmHg for SBP and 4 to 6 ms for RRI did not correlate with BRSMODEX, but that, by adjusting the SBP threshold to 0.5 mmHg and the RRI threshold to 3 or 4 ms, BRSSEQ could be correlated with BRSMODEX.

The effects on the cardiovascular system of inhalation anesthetics commonly used for general anesthesia may be related to their effects on the autonomic nervous system, as well as to their direct effects on cardiac function and the peripheral vessels. Inhalation anesthetics especially depress the arterial baroreflex function, an important contributor to short-term blood pressure regulation and to cardiovascular variability pattern.21-22) Sevoflurane,13 desflurane,21 enflurane,21 and isoflurane22 all attenuate baroreflex function, and these volatile anesthetics cause concentration-dependent attenuation of BRS.22 It is therefore important to evaluate and maintain...
Fig. 5. Relationship between BRS_{MOODX} and BRS_{SEQ} using the Bland-Altman analysis. (A) BRS_{MOODX} vs. BRS_{SEQ} (0.5 mmHg for SBP, 1 ms for RRI), (B) BRS_{MOODX} vs. BRS_{SEQ} (0.5 mmHg for SBP, 2 ms for RRI), (C) BRS_{MOODX} vs. BRS_{SEQ} (0.5 mmHg for SBP, 3 ms for RRI), (D) BRS_{MOODX} vs. BRS_{SEQ} (0.5 mmHg for SBP, 4 ms for RRI). Dashed lines indicate the mean difference (bias). BRS_{MOODX}: baroreflex sensitivity obtained by the modified Oxford pharmacologic technique, BRS_{SEQ}: baroreflex sensitivity determined by the sequence method, SBP: systolic blood pressure, RRI: R-R interval.
failure rate in individuals with attenuated BRS, thus limiting its use in clinical practice. In the present study, we also found that the BRSSEQ values obtained using the thresholds of 1 mmHg and 4 ms were not correlated with BRSMODOX in healthy individuals anesthetized with sevoflurane. Thus, similar to earlier report, RRI and SBP thresholds of BRSSEQ need to be changed to optimize its validity in humans with attenuated BRS.

In the present study, interestingly, changing the RRI and SBP thresholds of BRSSEQ during sevoflurane anesthesia has a great influence on the number of valid sequences and values of BRSSEQ. Valid sequences at 0.5 and 1 mmHg SBP thresholds had sufficient number, but they were markedly diminished at 2 and 2.5 mmHg SBP thresholds. Also, the average values of BRSSEQ increased as the RRI thresholds were increased from 1 to 6 ms and the SBP thresholds were decreased from 2.5 to 0.5 mmHg. Although the precise mechanisms remain unknown, this finding is in line with the earlier study by Davies et al., who reported that there was an obvious dependence of measured BRS values on the thresholds of RRI and SBP in patients with congestive heart failure.

Our findings, however, differ from the earlier study suggesting that spontaneous indices are inadequate estimates of, and are inconsistent with, the pharmacological baroreflex gain during sevoflurane anesthesia. This discrepancy is likely due to differences in methodology, as we previously described. Specifically, the earlier study measured results obtained by up and down sequences separately, whereas we did not, primarily because we did not detect a discrepancy between the up and down slopes of the sequence method, as was previously noted. In addition, in the earlier report, the pressor and depressor drugs were administered separately, whereas we injected vasoactive drugs sequentially to reveal the entire sigmoid nature of arterial baroreflex function. Furthermore, the

### Table 1. Comparisons between BRSSEQ and BRSMODOX

<table>
<thead>
<tr>
<th>Thresholds of BRSSEQ</th>
<th>BRSSEQ (ms/mmHg)</th>
<th>BRSMODOX (ms/mmHg)</th>
<th>Bias (ms/mmHg)</th>
<th>LOA (ms/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, 0.5 mmHg; RRI, 1 ms</td>
<td>3.4 ± 1.9</td>
<td>5.6 ± 2.4</td>
<td>2.1</td>
<td>-2.3 to 6.6</td>
</tr>
<tr>
<td>SBP, 0.5 mmHg; RRI, 2 ms</td>
<td>3.5 ± 1.9</td>
<td>5.6 ± 2.4</td>
<td>2.1</td>
<td>-2.3 to 6.6</td>
</tr>
<tr>
<td>SBP, 0.5 mmHg; RRI, 3 ms</td>
<td>5.3 ± 2.4</td>
<td>5.6 ± 2.4</td>
<td>0.4</td>
<td>-4.2 to 5.1</td>
</tr>
<tr>
<td>SBP, 0.5 mmHg; RRI, 4 ms</td>
<td>5.3 ± 2.4</td>
<td>5.6 ± 2.4</td>
<td>0.4</td>
<td>-4.2 to 5.1</td>
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</table>

All values are reported as mean ± SD. BRSSEQ: baroreflex sensitivity determined by the sequence method, BRSMODOX: baroreflex sensitivity obtained by the modified Oxford pharmacologic technique, LOA: limits of agreement, SBP: systolic blood pressure, RRI: R-R interval.
SBP and RRI thresholds of BRS_{SEQ} in anesthetized individuals were not altered in the earlier report.

Several potential limitations should be considered in interpreting the results of the present study. First, a comparison between spontaneous sequence method and modified Oxford technique for assessing BRS is complex. Fundamentally, two methods evaluate different aspects of baroreceptor cardiac reflex function. The sequence method investigates the RRI reflex changes in response to spontaneous SBP fluctuations of small magnitude, but the pharmacologic technique evaluates the RRI reflex changes in response to large SBP fluctuations provoked by vasoactive drugs. Therefore, the disparity in the values of BRS_{SEQ} and BRS_{MODOX} may be expected, and this disparity may be wider during anesthesia than conscious state. Second, we assessed BRS in individuals anesthetized with only 1.5 minimum alveolar concentration end-tidal sevoflurane. Thus, further studies are needed to establish the effect of various concentrations of inhalation anesthetics and other anesthetic agents (e.g., isoflurane, desflurane, propofol, etomidate) on the most appropriate RRI and SBP thresholds for BRS_{SEQ}. Third, the results of the present study were obtained in only young healthy individuals. Thus, further studies are also required to evaluate BRS values provided by the two methods in the old or subjects with cardiovascular disease, diabetes mellitus, or renal disease. Fourth, although recording was made for assessing of BRS_{SEQ} in the earlier many investigations,\(^{25,26,30,31}\) it is possible that the 6-8 min period in the present study is not great enough to give a reliable assessment of human baroreceptor cardiac reflex function. Lastly, surgery, which may influence or damage to vessels, nerves, and organs in abdomen, may be associated with autonomic dysfunction, but we consider that there was little influence on our results because our data were collected in individuals not subjected to surgical stimuli and the resultant fluctuations of ABP and heart rate.

In conclusion, we have shown here that the number of valid sequences and BRS_{SEQ} values are highly sensitive to changes in the selected thresholds for SBP and RRI, and that the spontaneous sequence method, using the conventional thresholds of 1 mmHg for SBP and 4 to 6 ms for RRI to evaluate BRS in healthy individuals anesthetized with 1.5 minimum alveolar concentration end-tidal sevoflurane, may be not appropriate. Our findings suggest that an SBP threshold of 0.5 mmHg and an RRI threshold of 3 or 4 ms would be appropriate for measuring BRS_{SEQ} during sevoflurane anesthesia, when compared to BRS_{MODOX}.

REFERENCES


