Baroreflex control of heart rate during and after propofol infusion in humans

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Background. This study was designed to determine cardiovagal baroreflex gain during propofol infusion and to characterize its recovery profile using the pharmacological and spontaneous sequence methods in 13 healthy volunteers without cardiovascular or autonomic disorders.

Methods. After an 8- to 10-h fast and no premedication, measurements of RR intervals obtained from the electrocardiogram and non-invasive beat-to-beat systolic blood pressure (SP) were made at conscious baseline, at 60 and 120 min after induction of general anaesthesia using propofol, and at 20, 60, 120 and 180 min after emergence from anaesthesia. During propofol anaesthesia, ventilation was mechanically controlled to maintain normocapnia and calculated propofol concentration was adjusted by a TCI system at 5 \( \mu \text{g} \text{ ml}^{-1} \). Baroreflex responses were triggered by bolus i.v. injections of phenylephrine and nitroprusside to alter SP by 15–30 mm Hg. The linear portions of the baroreflex curves relating RR intervals and SP by least-square regression analysis were determined to obtain pharmacological gains. In addition, spontaneous sequence baroreflex gains were calculated from spontaneously fluctuating SP and RR intervals.

Results. Baseline pressor and depressor test gains before propofol anaesthesia were 29.1 (SD 14.9) and 12.5 (7.8) ms mm Hg\(^{-1}\), respectively. They were significantly depressed by 65–73% during propofol infusions. Similarly, baseline up- and down-sequence baroreflex gains were 33.8 (28.9) and 27.3 (19.8) ms mm Hg\(^{-1}\), respectively, and were significantly depressed by 71–87% during propofol anaesthesia. Pressor test and up-sequence baroreflex gains returned to the baseline values 20 min after emergence from propofol anaesthesia, but depressor test and down-sequence baroreflex gains did not recover until 60 min after emergence.

Conclusions. We conclude that heart rate responses to both lowering and elevating blood pressure were depressed by propofol anaesthesia, and 60 min was required for their full recovery after discontinuation of propofol infusion.

Keywords: anaesthesia, general; anaesthetics i.v., propofol; heart, heart rate; nervous system, autonomic; nervous system, parasympathetic; reflexes, baroreceptor

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Arterial baroreflex function is an important short-term neural control system for maintaining cardiovascular stability. Volatile anaesthetics such as isoflurane, sevoflurane and desflurane exert concentration-dependent inhibitions of baroreflex control of heart rate (HR) to a similar extent in humans,\(^1\) but exhibit different characteristics of recovery of baroreflex function.\(^2\) Propofol, an i.v. anaesthetic that can be used for both induction and maintenance of anaesthesia, has shown either no effect or attenuation of cardiac baroreflex function depending on its concentration in blood.\(^6\)–\(^11\) However, the recovery characteristics of baroreflex responses after propofol anaesthesia have not been investigated. In the light of the increasing number of outpatient surgical procedures, it is important to know how much time is required for full recovery of baroreflex function after propofol infusion in humans.

Accordingly, this study was designed to test the hypothesis that a relatively high blood propofol concentration (\(5 \mu \text{g} \text{ ml}^{-1}\)) would result in baroreflex inhibition. In addition, we have determined the recovery characteristics of cardiac baroreflex responses assessed by the Oxford pharmacological method and the spontaneous sequence technique after propofol anaesthesia in healthy young volunteers. To isolate the effects of propofol and eliminate possible confounding factors affecting baroreflex responses, no other anaesthetics, opioids or sedative premedications were administered during the entire course of the study.
Methods

The study protocol was approved by the human research committee of Akita University School of Medicine, and written informed consent was obtained from each subject. We studied 13 ASA I volunteers aged between 22 and 37 yr. Subjects who drank alcoholic beverages daily, those with a history of cardiovascular, pulmonary or neurological disorders, or those who had taken any medication in 2 weeks before the study were excluded. They were not allowed to take any caffeine for at least 24 h before the study. All subjects arrived at the operating room without premedication after a fast of 8–10 h.

All subjects were placed in the supine position, and a 22-G i.v. catheter was inserted using local anaesthesia into an antecubital vein for drug injection. Acetate Ringer’s solution i.v. catheter was inserted using local anaesthesia into an antecubital vein for drug injection. Acetate Ringer’s solution was administered at a rate of 2 ml kg\(^{-1}\) h\(^{-1}\) throughout the study. Arterial pressure was determined non-invasively by radial arterial tonometry (Nihon Colin, Jentow-7700\(^{TM}\), Aichi, Japan). RR intervals were determined using an electrocardiography lead with a high signal-to-noise ratio (EKG, Hewlett Packard, Viridia CMS 2000\(^{TM}\), Boeblingen, Germany).

Tympanic temperature was measured in each subject and whole-body forced-air warming was used to maintain conscious baseline temperature during and after anaesthesia. The ambient temperature was set to 20\(^\circ\)C before and 25–30\(^\circ\)C during and after anaesthesia to avoid shivering. Subjects were allowed to rest in the supine position for at least 20 min in a quiet environment before initiation of the study.

To assess baroreflex control of HR, pressor and depressor tests were performed using i.v. bolus injections of phenylephrine (50–300 \(\mu\)g) and nitroprusside (50–300 \(\mu\)g) to increase and decrease systolic pressure (SP) by 15–30 mm Hg, respectively. A period of stabilization (usually 5 min) between the pressor and depressor tests allowed HR and SP to return to within ±5% of pretest values. To determine spontaneous sequence baroreflex gains, recordings of spontaneous RR intervals and SP were made over a period of 5 min. During this period, patients were in the supine position and were breathing spontaneously in a quiet environment.

 Oxygen was given for 3 min via a facemask. Then general anaesthesia was induced using a TCI pump (TERUMO, TE-371\(^{TM}\), Tokyo, Japan) with propofol 10 \(\mu\)g ml\(^{-1}\) as the target blood concentration. After a laryngeal mask airway was inserted, the lungs were mechanically ventilated with air and oxygen (tidal volume 8–10 mg kg\(^{-1}\) at a ventilatory frequency of 8–10 breaths min\(^{-1}\); \(F_{1\text{O}_2}=0.34\) to maintain end-tidal carbon dioxide tension at 4.7 kPa throughout the anaesthesia period. The second and third sets of the depressor and pressor tests were performed, and recordings of spontaneously fluctuating SP and RR intervals were made for 5 min in a similar manner after maintaining the calculated blood propofol concentration at 5 \(\mu\)g ml\(^{-1}\) by the TCI system for 60 min and 120 min after induction (Anaesthesia 60 and Anaesthesia 120, respectively). Propofol administration was then discontinued. After confirming the return of adequate spontaneous respiration and appropriate responses to verbal commands, the laryngeal mask airway was removed. Subjects were left undisturbed with supplemental oxygen 2 l min\(^{-1}\) via a facemask. The depressor and pressor tests were repeated at 20, 60, 120 and 180 min after the removal of the laryngeal mask airway (Recovery 20, 60, 120 and 180, respectively). Recordings of SP and RR intervals for determinations of spontaneous baroreflex gains were also made at these intervals.

Arterial BP and RR intervals were determined beat-to-beat, digitized, stored at a sampling rate of 200 Hz in a computer and subsequently analysed off-line. A custom program was developed to process the digitized data using a 16-bit analog–digital converter (AD7120; ATM Communications, Tokyo, Japan) which detected R waves to determine RR intervals from ECG signals. The recordings were also observed on an oscilloscope during transfer for elimination of non-sinus or artefactual signals caused by unanticipated movement of the study subjects. Digital files were thus generated, with each column consisting of SP, diastolic BP, mean BP and RR interval values for every cardiac cycle. These files were used for calculations of the pharmacological and spontaneous sequence baroreflex gains. Arterial baroreflex gain was determined by least-squares regression analysis on the linear portion of the sigmoid relation between SP and RR interval, when each RR interval was plotted as a function of the preceding SP (one-offset). Estimation of spontaneous sequence baroreflex gain was based on a spontaneous sequence of containing three or more beats relating RR intervals and progressively changing SP in the same direction using linear regression analysis. Up-sequence and down-sequence were defined as continually increasing and decreasing sequences, respectively. Only sequences where successive pressure pulses differed by at least 1 mm Hg were selected. Correlation coefficients (\(R\)) of pharmacological and spontaneous sequence gains >0.8 were accepted for subsequent data analyses.

Power analysis based on a previous similar study and our pilot study revealed that at least 12 patients would provide a power >0.8 (\(P=0.05\)) for 30% difference in temporal changes in baroreflex gains.\(^2\) Changes in haemodynamic, baroreflex and other variables over time were first analysed by one-way analysis of variance for repeated measurements, and if a significant difference was detected with respect to time, it was followed by paired \(t\)-test with Bonferroni’s correction. All data are presented as mean (SD), and \(P<0.05\) is considered statistically significant.

Results

Ten male and three female volunteers completed the study. Their mean age, weight and height were 26 (22–37) yr, 62 (9) kg and 170 (9) cm, respectively. After general
anaesthesia induction, SP decreased significantly and returned to the baseline value after emergence from general anaesthesia, while HR and tympanic temperature remained unchanged throughout the study period. Estimated blood propofol concentrations, maintained at 5.0 (0.0) μg ml⁻¹ during anaesthesia, decreased gradually after discontinuation of anaesthetic (Table 1).

Phenylephrine pressor and nitroprusside depressor test gains before propofol anaesthesia were 29.1 (14.9) ms mm Hg⁻¹ and 12.5 (7.8) ms mm Hg⁻¹, respectively. Both pharmacological gains were significantly depressed during propofol anaesthesia compared with the baseline values (Fig. 1). However, pressor test gain recovered 20 min after emergence from anaesthesia, while depressor test gain returned to the baseline value 60 min after emergence from propofol anaesthesia.

### Discussion

A major finding of our study is that cardiovagal baroreflex function in humans is depressed by propofol alone when its calculated blood concentration was 5 μg ml⁻¹ by the TCI system. The effects of propofol on baroreflex function have shown controversial results previously, but appear to be dose-related. Cullen et al. studied propofol infusion rates of 54 and 108 μg kg⁻¹ min⁻¹ supplementing 66% nitrous oxide in oxygen in spontaneously breathing healthy

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**Table 1** Pretest systolic blood pressure, heart rate, estimated blood propofol concentration and tympanic temperature before, during and after propofol anaesthesia. Values are mean (sd). *P<0.05 vs awake values.

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>Pretest</th>
<th>Anaesthesia 60</th>
<th>Anaesthesia 120</th>
<th>Recovery 20</th>
<th>Recovery 20</th>
<th>Recovery 120</th>
<th>Recovery 180</th>
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<td>Pretest SP (mm Hg)</td>
<td>111 (9)</td>
<td>95 (11)*</td>
<td>106 (9)*</td>
<td>124 (14)</td>
<td>115 (16)</td>
<td>111 (11)</td>
<td>117 (13)</td>
<td></td>
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<tr>
<td>Pretest HR (beats min⁻¹)</td>
<td>69 (10)</td>
<td>69 (12)</td>
<td>71 (14)</td>
<td>68 (11)</td>
<td>62 (11)</td>
<td>62 (9)</td>
<td>62 (10)</td>
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<tr>
<td>Propofol concentration (μg ml⁻¹)</td>
<td>0.0 (0.0)</td>
<td>5.0 (0.0)*</td>
<td>5.0 (0.0)*</td>
<td>1.3 (0.3)*</td>
<td>0.7 (0.1)*</td>
<td>0.4 (0.1)*</td>
<td>0.3 (0.1)*</td>
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</tr>
<tr>
<td>Temperature (°C)</td>
<td>35.7 (0.6)</td>
<td>35.6 (0.6)</td>
<td>35.8 (0.6)</td>
<td>35.9 (0.4)</td>
<td>35.9 (0.4)</td>
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**Fig 1** Percentage change relative to awake baseline value (100%) of (A) the phenylephrine pressor and (B) the nitroprusside depressor test gains of healthy volunteers before (Awake), during (Anaesthesia) and after (Recovery) propofol anaesthesia (n=13). Values are mean (sd). *P<0.05 vs Awake values.
patients, and found that phenylephrine pressor and nitroprusside depressor tests were unaffected. Similarly, Samain et al.7 showed in spontaneously breathing patients that propofol infusions of 100 and 200 μg kg\(^{-1}\) min\(^{-1}\), which resulted in blood propofol concentrations of 3 μg ml\(^{-1}\) and 4.5 μg ml\(^{-1}\), respectively, did not affect phenylephrine pressor test gain. On the other hand, Ebert et al.10 demonstrated that induction with propofol 2.5 mg kg\(^{-1}\) i.v. followed by propofol 200 μg kg\(^{-1}\) min\(^{-1}\) infusion resulted in significant reduction of cardiac baroslope in mechanically ventilated patients.

This is the first study to demonstrate that attenuated baroreflex response persists after discontinuation of propofol in humans. In rabbits, depressed baroreflex response was seen 30 min after discontinuation of propofol 500 μg kg\(^{-1}\) min\(^{-1}\), but not after propofol 200 μg kg\(^{-1}\) min\(^{-1}\), suggesting that the degree and duration of baroreflex depression after propofol infusion is dose related. Therefore recovery of baroreflex function in our study might have been faster if anaesthesia had been maintained at a lower propofol concentration. Although statistically significant differences in recovery characteristics of baroreflex responses were detected between pressor and depressor perturbations, the overall pattern of all the responses appear similar, and recovery occurred within 60 min of emergence from anaesthesia. On the other hand, 60–120 min was required until full recovery of cardiac baroreflex function took place after 1 MAC of isoflurane or sevoflurane anaesthesia lasting for a similar period in healthy volunteers.13 14 However, since propofol and volatile-anaesthetic-based techniques are not directly comparable, further comparative studies under strictly equi-anesthetic concentrations are warranted.

Our results should be interpreted with some caution. First, SP was not determined by the intra-arterial catheter. However, tonometric SP values correspond well to the intra-arterial SP in normotensive subjects for the range of pressures seen in our study.15 We have no reason to question the reliability of tonometric BP in healthy individuals with no evidence of peripheral vascular abnormalities. Furthermore, arterial tonometry has been used successfully for assessing pharmacological and sequence gains in humans.16 Secondly, we did not determine the concentration–response relationship. To eliminate any confounding effect affecting baroreflex responses, any other adjuvant, such as nitrous oxide, sedative or opioid had to be avoided. Blood propofol concentrations <5 μg ml\(^{-1}\) resulted in frequent untoward movements in our pilot study, and thus a relatively higher blood concentration was required. More importantly, opioid, other i.v. anaesthetic agents and/or epidural analgesia should be concomitantly administered for surgical anaesthesia. Since these drugs/techniques may alter baroreflex responses or cardiac autonomic activity,17–19 their combined effects with propofol on cardiovagal function should be evaluated. Lastly, since median performance error for blood propofol concentration calculated by the TCI system was reported to be 16.1% higher than the directly measured concentration,20 the median blood propofol concentration in our subjects could have been ~5.8 μg ml\(^{-1}\).

In conclusion, cardiac baroreflex responses assessed by pharmacological and spontaneous sequence techniques were depressed during propofol anaesthesia at a calculated blood concentration of 5 μg ml\(^{-1}\) in healthy humans. Attenuated baroreflex function persists after discontinuation of propofol, and 60 min was required for its full recovery. Further study is warranted to determine the combined effects of propofol and other adjuvants, such as opioid and/or i.v. anaesthetic agent, on cardiac baroreflex function in actual clinical situations.

**Fig 2** Percentage change relative to awake baseline value (100%) of (a) the up-sequence and (b) the down-sequence baroreflex gains of healthy volunteers before (Awake), during (Anaesthesia) and after (Recovery) propofol anaesthesia (n=15). Values are mean (SD). *P<0.05 vs Awake values.

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Acknowledgements
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References