

Differential Effects of Propofol and Sevoflurane on Heart Rate Variability

Noriaki Kanaya, M.D., Ph.D.,* Naoyuki Hirata, M.D.,† Saori Kurosawa, M.D.,† Masayasu Nakayama, M.D., Ph.D.,‡ Akiyoshi Namiki, M.D., Ph.D.§

Background: Propofol is reported to reduce both sympathetic and parasympathetic tone; however, it is not clear whether the changes in heart rate variability are associated with depth of anesthesia. The purposes of the present study were (1) to evaluate the changes in heart rate variability at different depths of hypnosis and (2) to compare the effects of propofol on heart rate variability with that of sevoflurane.

Methods: Thirty patients were randomly allocated into the propofol or sevoflurane for induction of anesthesia. The depth of hypnosis was monitored by the Bispectral Index (BIS). Spectral analysis of heart rate variability using a maximum-entropy method resulted in a characteristic power spectrum with two main regions, a high frequency (HF) and a low frequency (LF). Hemodynamics, entropy, LF, HF, and LF/HF were monitored when the patients were awake and after induction of anesthesia.

Results: Both propofol and sevoflurane decreased blood pressure in a BIS-dependent manner, whereas heart rate showed no significant changes during the study period. In the propofol group, entropy and HF decreased with a reduction in the BIS value. Although LF decreased after induction of anesthesia, propofol caused no further decrease in LF in spite of a reduction in the BIS value. In the sevoflurane group, LF decreased with a reduction in the BIS value. Entropy and HF decreased after induction of anesthesia (BIS at 80); however, no further decreases were observed in spite of a reduction in the BIS value.

Conclusions: Induction of anesthesia with propofol decreased blood pressure, entropy, and HF in a BIS-dependent manner, indicating that propofol reduces cardiac parasympathetic tone depending on the depth of hypnosis. Conversely, sevoflurane did not show the BIS-dependent decreases in heart rate, blood pressure, HF, and entropy, indicating that sevoflurane has little or no effect on cardiac parasympathetic tone.

PROPOFOL is now widely used in clinical practice because of its favorable recovery profile and low incidence of side effects.¹ However, induction of anesthesia with propofol is often associated with a significant decrease in arterial blood pressure and heart rate (HR).^{2,3} The hypotensive effect of propofol has been attributed to a decrease in systemic vascular resistance^{1,4} or in cardiac output⁵ caused by a combination of venous and arterial vasodilation,^{4,6} impaired baroreflex mechanisms,^{7,8} and depression of myocardial contractility.⁹ Although an inhibition of the sympathetic nervous system may explain all the propofol-induced hemodynamic changes,^{6,7} the precise mechanism by which this may occur is unknown. If propofol reduces cardiac sympathetic nerve

activity, it would cause a decrease in HR. However, induction of anesthesia with propofol resulted in relatively large reductions in peripheral sympathetic nerve activity and blood pressure in spite of an increase in HR in humans.^{7,8} In addition, prophylactic anticholinergics did not prevent profound bradycardia and asystole with the use of propofol in healthy adult patients.^{3,10,11} These findings suggest that propofol may have differential effects on the peripheral and cardiac autonomic nervous systems.

Spectral analysis of heart rate variability (HRV) is a widely used, noninvasive technique to assess autonomic indexes of neural cardiac control.¹²⁻¹⁵ The presence of low-frequency (LF) and high-frequency (HF) oscillatory rhythms in the variability of the R-R interval (RRI) is well established. To date, it is believed that LF is mediated by the parasympathetic and sympathetic systems, whereas HF is mediated primarily by the parasympathetic system.

Although there is general agreement that induction of anesthesia with propofol is associated with a reduction in HRV,¹⁶⁻¹⁸ there are some conflicting data regarding the effects of propofol on cardiac sympathetic or parasympathetic tone. Deutschman *et al.*¹⁶ examined the changes in HRV under propofol anesthesia in 10 women undergoing laparoscopy. They observed a significant reduction in total, LF, and HF power after propofol. Addition of opioids and muscle relaxants resulted in further reductions in total and LF, but not HF, power. They concluded that propofol anesthesia reduces parasympathetic tone to a lesser degree than sympathetic tone, resulting in parasympathetic dominance. In contrast, Galletly *et al.*¹⁷ reported that induction of anesthesia with propofol resulted in a greater reduction in HF power than LF power. Similar results were observed after induction of anesthesia with a bolus injection of propofol.¹⁸ The later two reports indicate that propofol anesthesia reduces parasympathetic tone greater than sympathetic tone. At least two factors might be responsible for these conflicting results. First, analysis of HRV is a study of the spontaneous, seemingly random fluctuations about some mean value that are always present when HR is measured on a beat-to-beat basis, even in subjects in a "quiet state." Interpreting information contained in such seemingly chaotic signals is most often provided by mathematical analyses in the time domain, in the frequency domain, or as a measure of entropy.¹²⁻¹⁵ Thus, differences in methods for analyzing HRV may be responsible for these conflicting results. Second, lack of information concerning the depth of anesthesia may present difficulty in interpreting the results. Because HRV is controlled under the central nervous sys-

* Assistant Professor, † Resident, ‡ Instructor, § Professor and Chairman.

Received from the Department of Anesthesiology, Sapporo Medical University School of Medicine, Sapporo, Japan. Submitted for publication April 10, 2002. Accepted for publication July 31, 2002. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Kanaya: Department of Anesthesiology, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo 060-8543, Japan. Address electronic mail to: kanaya@sapmed.ac.jp. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

tem, the depth of anesthesia should be considered to estimate the effects of anesthetics on HRV.

Therefore, the first goal of this study was to test the hypothesis that propofol anesthesia would affect HRV depending on the depth of hypnosis. To assess the depth of hypnosis, we used the Bispectral Index (BIS[®]; Aspect Medical Systems, Inc., Newton, MA), a single composite electroencephalogram measure, which is widely accepted to track electroencephalographic changes associated with different anesthetic states.^{19,20} We used the MemCalc method,²¹⁻²⁴ a combination of the maximum-entropy method for spectral analysis and the nonlinear least squares method for fitting analysis, to assess the HRV. This enabled us to achieve a reliable analysis of HRV over a minimum interval of 30 s.

Sevoflurane is a volatile anesthetic agent with a low blood-gas solubility (0.6). Sevoflurane is now widely used for its desirable properties of rapid induction and emergence and quick control of anesthetic depth.²⁵ It is noteworthy that sevoflurane also has been shown to decrease sympathetic nerve activity in rabbits and appears to reduce myocardial contractility.^{26,27} However, in humans, sevoflurane has little or no effect on peripheral sympathetic nerve activity.²⁸ In contrast, we have reported that ephedrine-induced increase in HR was abolished under sevoflurane anesthesia.²⁹ Because ephedrine acts *via* activation of sympathetic nervous system, our results indicate sevoflurane may have some effects on sympathetic or parasympathetic nerve tone. To our knowledge, published human studies have not examined HRV during sevoflurane anesthesia. Thus, a second goal of the present research was to evaluate the effect of sevoflurane induction on HRV and to compare it with that of propofol.

Materials and Methods

The Institutional Ethics Committee at Sapporo Medical University (Sapporo, Japan) approved this study, and all patients granted their written informed consent. The authors studied 30 patients (American Society of Anesthesiologists physical status class I) scheduled for elective oral surgery. Patients were excluded if they suffered from severe ischemic heart disease, congestive heart failure, diabetes mellitus, or other disorders known to affect autonomic function. None of the patients was taking medications that affect cardiovascular function.

Each patient fasted for at least 11 h prior to testing. On arrival to the operating room, standard monitoring and a BIS[®] monitor were employed. BIS (version 3.4) was measured continuously on an electroencephalogram monitor (Model A1050; Aspect Medical Systems, Natick, MA) using BisSensor strips (Aspect Medical Systems). The strips consisted of three pregelled electrodes, two active and one ground. The impedance of each electrode

was maintained at less than 2 K Ω . Patients were studied while supine. HR was monitored from leads II and V5 of the electrocardiogram. An 18-gauge catheter was inserted into a forearm vein and used for fluid and drug administration. Each subject received 10 ml/kg saline before initiation of the study. The inspired oxygen and end-tidal concentrations of carbon dioxide and sevoflurane were measured continuously with a calibrated infrared gas analyzer. Before induction of anesthesia, patients were randomized to one of two groups by use of flipping a coin. All patients received 100% oxygen *via* face mask for 2 to 3 min prior to induction of general anesthesia, and control recordings were obtained from patients lying quietly in the supine position and breathing spontaneously. In the propofol group, patients received propofol infusion at a rate of 300 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. In the sevoflurane group, anesthesia was induced with 5% sevoflurane in oxygen. Arterial oxygen saturation (SpO₂) and end-tidal carbon dioxide (ETCO₂) were monitored, and normoventilation was maintained with gentle IPPV *via* mask if required. In our preliminary experiment, the BIS decreased gradually after induction of anesthesia in both anesthesia regimens. However, the minimum value of BIS did not reach to 20. Therefore, the hemodynamic and HRV measurements were performed at BIS values of 80, 60, 40, and 30.

Heart Rate Variability Measurements

The fast peaks of R waves on the electrocardiogram were detected, and RRI was measured. The RRI data were analyzed by the maximum-entropy method with high resolution (MemCalc; Suwa Trust, Tokyo, Japan), as described previously.²¹⁻²⁴ In brief, in the program of MemCalc, a time series is assumed to be composed of underlying variation and fluctuating parts; the underlying variation is expressed as the function $x_{uv}(t)$, which can be given by a linear combination of sine and cosine functions

$$x_{uv}(t) = a_0 + \sum_{n=1}^{N_p} [a_n \sin(2\pi f_n t) + b_n \cos(2\pi f_n t)] \quad (1)$$

where f_n is the frequency of the n th component, a_n and b_n are the amplitudes of the n th periodic component, N_p is the total number of components, and a_0 is a constant that indicates the mean value of the time series. The value of f_n is determined by the peaks in the power spectral density. Its estimate, $P(f)$, can be expressed as

$$P(f) = \frac{\Delta t P_m}{\left[1 + \sum_{k=-m}^m \gamma_{m,k} \exp(-i2\pi f k \Delta t) \right]^2} \quad (2)$$

where P_m is the output power of the prediction error filter of the order m , and $\gamma_{m,k}$ is the corresponding filter

Table 1. Demographic Characteristics of Two Anesthetic Groups

	Propofol	Sevoflurane
n	15	15
Sex (male/female)	8/7	8/7
Age (yr)	43 ± 12	44 ± 11
Weight (kg)	60 ± 10	61 ± 11
Height (cm)	161 ± 7	161 ± 8

Values are mean ± SD or number.

coefficient, $m = 0, 1, 2, \dots, M$ ($M =$ optimum filter order). P_m and γ_m are determined by Yule-Walker equations using Burg's algorithm. Ohtomo and Tanaka²¹ demonstrated that equation 1 gives a basis for determining the filter order, and the optimum order should be determined by the condition; the filter order is $> 1/f_{\min}$, where f_{\min} is the minimum among the central frequencies of the components. In this program, the filter order was much higher than those obtained from the first minima of conventional information criteria.³⁰ MemCalc does not cause distortion of the power calculation even if the underlying variation is changed.³⁰

For real-time analysis of HRV, the data on RRI were obtained through on-line computer analysis with 2-ms sampling intervals. The powers of the RRI (ms^2) with LF (0.04–0.15 Hz) and HF (0.15–0.5 Hz) bands were calculated. LF/HF in RRI variability was also assessed. In addition, in the program of MemCalc, an entropy was calculated from pulse time series of 4 RRI. HRV is expressed as randomness of pulse interval. Thus, entropy is expressed as percentage from 0% (pulse series of regular interval, no variability) to 100% (maximal randomness, such as noise).

Data Analysis

Data are expressed as mean ± SD. Mean blood pressure (MBP) was calculated as diastolic blood pressure (DBP) + $\frac{1}{3} \times$ (systolic blood pressure [SBP] – DBP). Changes in LF and HF were expressed as percent change

from baseline (awake) values. LF/HF and entropy were expressed as percentages. We decided that a 10% difference in percentage changes of HRV parameters relative to baseline between the groups would be important. Therefore, $n = 15$ patients in each group would be necessary to detect such a difference if $\alpha = 0.05$ and $\beta = 0.1$. Continuous variables were analyzed using analysis of variance, and the chi-square test was used for descriptive (categorical) variables. Bonferroni correction was used for multiple comparisons between groups and for repeated comparisons over time. P values less than 0.05 were considered statistically significant.

Results

The two study groups were comparable with respect to age, weight, height, and sex (table 1). Baseline values of SBP, DBP, MBP, and HR in awake patients were similar in the both groups (table 2). BIS values at the awake state were 97 ± 2 and 96 ± 3 in the propofol and sevoflurane groups, respectively. Time from induction of anesthesia to BIS values of 30 were 9 ± 2 and 9 ± 3 min in the propofol and sevoflurane groups, respectively.

Administration of propofol resulted in a significant reduction in SBP, DBP, and MBP in a BIS-dependent manner; however, induction of anesthesia with propofol had no significant effect on HR (table 2). In the sevoflurane group, HR did not show any significant change throughout the study period. The inhalation *via* mask of 5% sevoflurane resulted in a significant reduction in MBP at a BIS value of 80, and no further reduction in MBP has been seen at the lower BIS values. Although propofol anesthesia tended to cause a further hemodynamic depression as compared to sevoflurane anesthesia, there were no significant differences in MBP and HR between the propofol and sevoflurane groups.

Changes in HRV parameters during anesthetic induction with propofol or sevoflurane are depicted in figures 1–4. Figure 1 shows the changes in LF during anesthetic

Table 2. Hemodynamics during Induction of Anesthesia with Propofol or Sevoflurane

	Awake	BIS			
		80	60	40	30
Propofol group (n = 15)					
HR (beats/min)	69 ± 14	67 ± 12	65 ± 9	65 ± 10	66 ± 11
SBP (mmHg)	126 ± 16	114 ± 10*	107 ± 11*	102 ± 17*	97 ± 14*
DBP (mmHg)	65 ± 11	62 ± 9	56 ± 11*	50 ± 14*	50 ± 12*
MBP (mmHg)	85 ± 11	81 ± 10*	74 ± 10*	68 ± 13*	66 ± 11*
Sevoflurane group (n = 15)					
HR (beats/min)	73 ± 15	72 ± 11	71 ± 4	72 ± 15	81 ± 20
SBP (mmHg)	139 ± 20	121 ± 15*	112 ± 18*	103 ± 15*	106 ± 13*
DBP (mmHg)	69 ± 13	63 ± 12	59 ± 13*	58 ± 15*	58 ± 13*
MBP (mmHg)	92 ± 13	83 ± 13*	77 ± 11*	72 ± 10*	76 ± 10*†

Values are mean ± SD.

* $P < 0.05$ versus corresponding awake values. † $P < 0.05$ versus propofol group at the same BIS values.

BIS = bispectral index; DBP = diastolic blood pressure; HR = heart rate; MBP = mean blood pressure; SBP = systolic blood pressure.

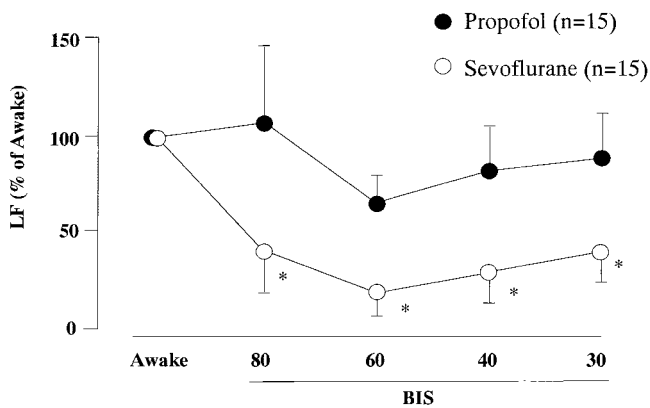


Fig. 1. Changes in low frequency (LF) during induction of anesthesia with propofol or sevoflurane. Values are expressed as mean \pm SD. * $P < 0.05$ versus awake. BIS = Bispectral Index.

induction with propofol or sevoflurane. After administration of propofol, LF showed no significant change from its baseline value except for a transient reduction at BIS value of 60. In contrast, LF markedly decreased after sevoflurane inhalation, and it reached to approximately 40% of baseline value at BIS value of 80. LF further decreased to approximately 20% of baseline value when BIS became 60; however, no further reduction has been seen at the lower BIS values. Figure 2 shows the changes in HF during anesthetic induction with propofol or sevoflurane. HF significantly decreased after propofol administration in a BIS-dependent manner. In contrast, sevoflurane inhalation did not cause any significant changes in HF. Figure 3 shows the changes in entropy during anesthetic induction with propofol or sevoflurane. Propofol anesthesia caused a significant decrease in entropy in a BIS-dependent manner, whereas sevoflurane anesthesia caused a transient decrease in entropy only at the BIS value of 80. Figure 4 shows the changes in LF/HF during anesthetic induction with propofol or sevoflurane. Propofol anesthesia tended to increase LF/HF in a BIS-dependent manner; however, a statistically significance was obtained only at the lowest BIS

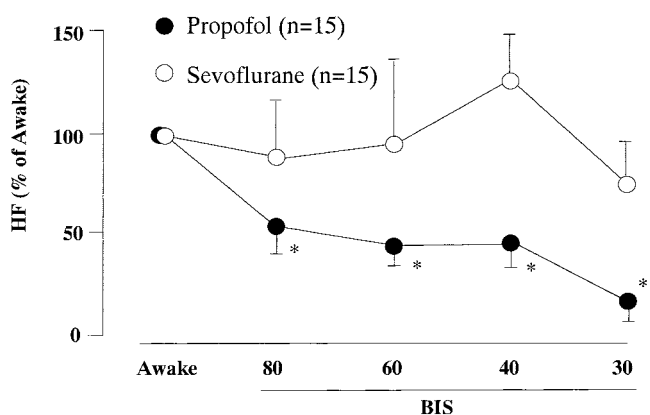


Fig. 2. Changes in high frequency (HF) during induction of anesthesia with propofol or sevoflurane. Values are expressed as mean \pm SD. * $P < 0.05$ versus awake. BIS = Bispectral Index.

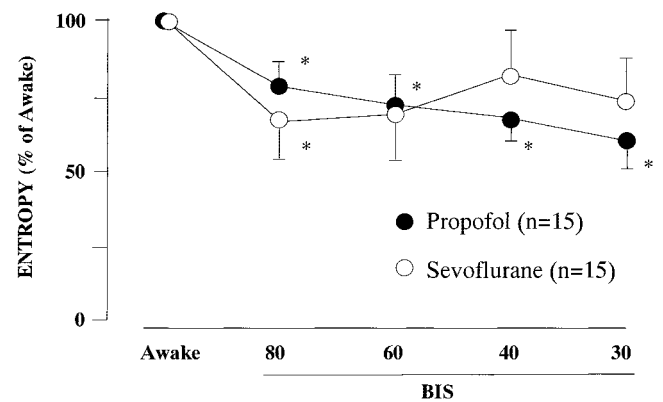


Fig. 3. Changes in entropy during induction of anesthesia with propofol or sevoflurane. Values are expressed as mean \pm SD. * $P < 0.05$ versus awake. BIS = Bispectral Index.

value. In contrast, sevoflurane anesthesia showed basically no effect on LF/HF except for a transient decrease at the BIS value of 40.

Discussion

The major findings of this study were as follows: (1) Induction of anesthesia with propofol was associated with significant decreases in BP, HF or entropy in a BIS-dependent manner, whereas propofol anesthesia basically had no effects on HR or LF. (2) In contrast to propofol, inhalation of sevoflurane *via* mask was associated with decreases in BP or LF independent of the changes in BIS, and sevoflurane anesthesia did not show any significant effects on HR or HF. (3) Both propofol and sevoflurane anesthesia had little effect on LF/HF, except that at the lower BIS values, propofol anesthesia tended to increase LF/HF, whereas sevoflurane tended to decrease LF/HF.

The concept of entropy, as it applies to signals like RRI, is to quantify the repetition of patterns in that signal. Larger values of entropy correspond to greater

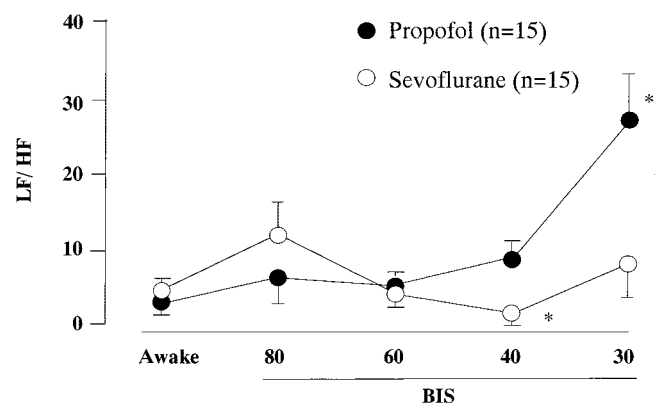


Fig. 4. Changes in low frequency (LF)/high frequency (HF) during induction of anesthesia with propofol or sevoflurane. Values are expressed as mean \pm SD. * $P < 0.05$ versus awake. BIS = Bispectral Index.

apparent randomness or irregularity, whereas smaller values correspond to more instances of recognizable patterns in the data. The entropy calculations, here applied to beat-to-beat HR, can be shown to obliquely provide a positively correlated barometer of the extent of complication of an underlying network model in many diverse systems, with larger values implying a more complex feedback or feedforward system.³¹ In fact, the entropy of RRI is reported to reflect parasympathetic modulation of HR under varying physiologic conditions and in response to pharmacological denervation.¹⁴ This is consistent with our finding that changes in entropy were directionally similar to changes in HF.

Effects of Propofol on Heart Rate Variability

Because the autonomic nervous system, especially the sympathetic nervous system, plays a major role in regulating cardiovascular homeostasis, knowledge of how anesthetic agents modify sympathetic activity is important for understanding subsequent cardiovascular responses. Propofol is known to cause a reduction in BP and HR in humans, and inhibition of sympathetic nerve activity is believed as one major mechanism underlying the propofol-induced hemodynamic depression.^{6,7} In a study measuring the peripheral sympathetic nerve activity, propofol anesthesia is reported to reduce muscle sympathetic nerve activity and renal sympathetic nerve activity in humans and rabbits, respectively.^{7,32} These results indicate that propofol anesthesia reduces sympathetic nerve activity. However, the effect of propofol on parasympathetic nerve activity has not been studied well.

In the present study, propofol anesthesia caused a reduction in HF but not in LF, indicating rapid sequence induction of anesthesia with propofol might reduce a cardiac parasympathetic tone more than sympathetic tone. Similar results were observed after induction of anesthesia with propofol in humans.^{17,18} Galletly *et al.*¹⁷ examined the effect of intravenous propofol anesthesia (2 mg/kg followed by a infusion of $0.17 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) on HRV using a fast Fourier transform. Although they observed a single time point for comparison with the awake state, total spectral power decreased (-53%) after anesthesia induction with propofol, while individual component periodicities were affected differently. The reduction in LF power (-33% , $P = 0.053$) was significantly less than that of midfrequency (-65%) and HF (-62%) power. Therefore, the ratio of spectral power showed a shift toward LF in the HRV spectrum, suggesting sympathetic dominance. Schefter *et al.*¹⁸ investigated the effects of thiopentone, etomidate, and propofol on beat-to-beat HR and blood pressure fluctuations in 35 unpremedicated female patients. They observed changes in HRV after a bolus injection of 4 mg/kg thiopentone, 2.5 mg/kg propofol, or 0.3 mg/kg etomidate. Propofol decreased HF (-62%) without significant change in LF, suggesting sympathetic dominance. In contrast, thiopentone decreased both LF (-46%) and HF (-59%), and

etomidate had no effect. Their results clearly indicate that propofol, thiopentone, and etomidate show differences in their effects on HRV. These findings concerning the effects of propofol on HRV are in reasonably good agreement with our present results.

Anesthesia with propofol is sometimes associated with bradycardia; however, the mechanism underlying this is not known. Because the autonomic nervous system plays an important role in regulating HR, propofol might induce bradycardia by altering the relative activities of the sympathetic and parasympathetic components. Deutchman *et al.*¹⁶ examined the effects of propofol anesthesia on HRV in female patients scheduled for laparoscopic surgery. They observed that induction of anesthesia with propofol was associated with a significant reduction in total, LF, and HF power. Maintenance of anesthesia with propofol resulted in further reductions in total and LF, but not HF, power. They speculate that propofol anesthesia reduces parasympathetic tone to a lesser degree than sympathetic tone, developing to bradycardia. However, several points should be discussed to resolve the question. First, induction and maintenance of anesthesia with propofol did not cause a reduction in HR in their study, indicating a discrepancy between HR and autonomic tone. Similarly, in our present results, propofol anesthesia caused a reduction in HF, but not in LF, without significant change in HR. HRV is a measure of an end-organ response to peripheral and central neural centers that both produce and respond to HR and blood pressure oscillations. Anesthetics that may disrupt integrative processes of the central nervous system or communication between the central nervous system and the end organ or the direct effects of anesthetics on the end organ itself will obviously affect changes in how the end organ responds and the measurement of it. Therefore, interpretation of HRV data must consider (1) the ability of the end organ to respond appropriately to neural regulation, (2) the ability of the two respective neural rhythms (sympathetic and vagal) to arrive at the heart, and (3) the ability of the neural regulatory centers to receive and integrate information from peripheral receptors. Such multifactors might be associated with lack of correlation between HR and autonomic tone. In addition, the fact that induction of anesthesia with propofol caused larger decreases in muscle sympathetic nerve activity and blood pressure, indicating a decrease in peripheral sympathetic nerve activity, with a small increase in HR, indicating a decrease in cardiac parasympathetic nerve activity, in humans^{7,8} support our HRV data. However, the direct negative chronotropic effect of propofol³³ may offset an increase in HR response to HRV in the present study.

Second, a lack of information about the depth of anesthesia might cause misinterpretation of the results because they observed HRV at just after and after 5 min of propofol administration. Because they administered a

2.5-mg/kg intravenous bolus of propofol followed by an infusion at a rate of $150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the depth of anesthesia should be lightening during the anesthesia. In fact, HF and entropy decreased in a BIS-dependent manner in our results. Third, propofol may decrease HR *via* its direct effect on heart. In animal experiments, propofol exerts a negative inotropic and chronotropic effect.^{9,33} Recently, the negative chronotropic effect of propofol is reported to be mediated in part by M₂-acetylcholine receptor activation, which involves the enhancement of nitric oxide production in cultured rat ventricular myocytes.³³ Although the differences in species may exist, the ineffectiveness of prophylactic anticholinergics and inadequate response to atropine on propofol-induced bradycardia support this idea.^{3,10,11} Therefore, it is unlikely that changes in autonomic tone are the sole reason for modulation of HRV resulting in bradycardia during propofol anesthesia.

Effects of Sevoflurane on Heart Rate Variability

Although sevoflurane is widely used for its favorable property of low blood-gas solubility that permits more rapid induction and emergence from anesthesia and more rapid control of anesthetic depth,²⁵ little is known about the effects of sevoflurane on HRV. However, it can be speculated that sevoflurane has little or no effect on HRV because of its mild cardiovascular depression. Several studies have examined the effects of sevoflurane on the autonomic nervous system by means of measuring sympathetic nerve activity or baroreflex sensitivity as an alternative to measuring HRV.^{28,34} In humans, sevoflurane attenuates baroreflex control of HR.³⁴ Because sevoflurane attenuated both pressor and depressor baroreflex sensitivities, both sympathetic- and vagal nerve-mediated reflex would be attenuated. In the present study, sevoflurane attenuated the LF without any significant effects in HF and entropy, indicating sevoflurane may inhibit sympathetic nerve activity without any significant changes in parasympathetic nerve activity. Differences in autonomic nervous tone during the study period would explain the differences in the effect of sevoflurane on sympathetic or parasympathetic nerve activities. Our results showed the direct effects of anesthetics on HRV, *i.e.*, static side of the autonomic nervous system. In contrast, the effects of anesthetics on the baroreflex showed the dynamic side of autonomic nervous system-mediated responses. Therefore, it is not surprising that sevoflurane showed different effects between HRV and baroreflex. In fact, sevoflurane has been reported to have different effects on spontaneous efferent renal sympathetic nerve activity and the baroreceptor-sympathetic reflex in rabbits.²⁶ Although differences in species should be considered to interpret the findings to humans, the idea supports our findings and helps us to understand the differences.

Limitations

We recognize several limitations of our study. First, we did not measure sympathetic and parasympathetic nerve activity *per se*. Although HRV is a widely used, noninvasive technique to assess autonomic indexes of neural cardiac control, the changes in HRV might not reflect the effects of anesthetics on the autonomic nervous system but on the reflex arc. In fact, baroreflex function and the autonomic nervous system are influenced by various physiologic and pathophysiologic factors,¹⁵ including sex,³⁵ age,³⁶ hypothermia,³⁷ and preexisting cardiopulmonary diseases.^{36,38} However, there is no alternative method to assess the effects of the autonomic nervous system on the cardiovascular system *in vivo*. Second, anesthesia-induced changes in respiratory rate and tidal volume should influence HRV. The HF component of HRV has been known to result from respiratory-related vagal modulation of HR, and the amplitude has been demonstrated to correlate with cardiac vagal tone.¹⁵ However, it has also been recognized that the amplitude decreases with respiratory frequency and increases with tidal volume.³⁹⁻⁴¹ The respiratory influence on RRI fluctuations in the 0.01- to 0.05-Hz range has been associated with tidal volume changes and is considered to be a sign of instability of the ventilatory chemoreceptor feedback mechanisms.^{15,42} Because the intrathoracic pressure changes are relatively low, the direct mechanical transfer of tidal volume oscillations to the heart rate fluctuations was not taken into consideration.^{39,41} Therefore, we might underestimate the effects of anesthetics on HRV if the induction of anesthesia resulted in decreases in respiratory rate and tidal volume. In the present study, we tried to maintain steady state respiration to minimize the influences on HRV. Third, it was uncertain whether the equal depth of anesthesia was achieved at the same BIS value between propofol and sevoflurane anesthesia. Although BIS has been found to be an effective measure of depth of sedation with propofol, midazolam, isoflurane, and sevoflurane,^{19,20,43} the BIS demonstrates significant variability among the anesthetics. To date, the precise mechanism underlying these variations in BIS is not known. Moreover, there is no convincing evidence that the BIS value was independent of the depth of anesthesia in our present study. Therefore, we believe that the gradual decreases in the BIS values correlated with the depth of anesthesia during propofol and sevoflurane anesthesia.

In summary, propofol decreased HF and entropy rather than LF in the BIS-dependent manner, indicating that cardiac parasympathetic nerve would be inhibited to a greater degree than sympathetic nerve during induction of anesthesia with propofol. Therefore, it is unlikely that propofol-mediated bradycardia is due to cardiac parasympathetic nerve stimulation. Conversely, sevoflurane maintains hemodynamics, HF, and entropy, indicat-

ing that sevoflurane has little or no effect on cardiac parasympathetic tone.

References

- Smith I, White PF, Nathanson M, Gouldson R: Propofol: An update on its clinical use. *ANESTHESIOLOGY* 1994; 81:1005-43
- Hug CCJ, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, Walawander CA, White PF, Apfelbaum JL, Grasela TH: Hemodynamic effects of propofol: Data from over 25000 patients. *Anesth Analg* 1993; 77(suppl 4):S21-9
- Tramer MR, Moore RA, McQuay HJ: Propofol and bradycardia: causation, frequency and severity. *Br J Anaesth* 1997; 78:642-51
- Clayes MA, Gepts E, Camu F: Haemodynamic changes during anaesthesia induced and maintained with propofol. *Br J Anaesth* 1988; 60:3-9
- Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K: Haemodynamic effects of prolonged propofol infusions supplementing nitrous oxide anaesthesia for peripheral vascular surgery. *Br J Anaesth* 1987; 59:954-60
- Robinson BJ, Ebert TJ, O'Brien TJ, Colincio MD, Muzi M: Mechanisms whereby propofol mediates peripheral vasodilation in humans: Sympathoinhibition or direct vascular relaxation? *ANESTHESIOLOGY* 1997; 86: 64-72
- Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP: Sympathetic responses to induction of anaesthesia in humans with propofol or etomidate. *ANESTHESIOLOGY* 1992; 76:725-33
- Ebert TJ, Muzi M: Propofol and autonomic reflex function in humans. *Anesth Analg* 1994; 78:369-75
- Kanaya N, Murray PA, Damron DS: Propofol and ketamine only inhibit intracellular Ca^{2+} transients and contraction in rat ventricular myocytes at supraclinical concentrations. *ANESTHESIOLOGY* 1998; 88:781-91
- Thomson SJ, Yate PM: Bradycardia after propofol infusion (letter). *Anaesthesia* 1987; 42:430
- Marsch SC, Schaefer HG: Pronounced bradycardia after application of POR-8 (ornipressin) under total intravenous anaesthesia with propofol (letter). *Acta Anaesthesiol Scand* 1990; 34:514
- Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ: Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; 213:220-2
- Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A: Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dogs. *Circ Res* 1986; 59:178-93
- Palazzolo JA, Estafanous FG, Murray PA: Entropy measures of heart rate variation in conscious dogs. *Am J Physiol* 1998; 274:H1099-105
- Yodkowski EH, Introna RPS, Montano N, Crumrine RS: Heart rate variability and neural control of the circulation: Implications for anesthesiologists. *Advances in Anesthesia* 1998; 15:33-74
- Deutschman CS, Harris AP, Fleisher LA: Changes in heart rate variability under propofol anesthesia: A possible explanation for propofol-induced bradycardia. *Anesth Analg* 1994; 79:373-7
- Galletly DC, Buckley DHF, Robinson BJ, Corfiatis T: Heart rate variability during propofol anesthesia. *Br J Anaesth* 1994; 72:219-20
- Scheffer GJ, Ten-Voorde BJ, Karemaker JM, Ros HH, de Lange JJ: Effects of thiopentone, etomidate and propofol on beat-to-beat cardiovascular signals in man. *Anaesthesia* 1993; 48:849-55
- Kearse LA, Jr, Manberg P, Chamoun N, deBros F, Zaslavsky A: Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. *ANESTHESIOLOGY* 1994; 81:1365-70
- Ibrahim AE, Taraday JK, Kharasch ED: Bispectral Index monitoring during sedation with sevoflurane, midazolam, and propofol. *ANESTHESIOLOGY* 2001; 95: 1151-9
- Ohtomo N, Tanaka Y: New method of time series analysis and "MemCalc," A Recent Advance in Time Series Analysis by Maximum Entropy Method. Sapporo, Hokkaido University, 1994, pp 11-29
- Sawada Y, Ohtomo N, Tanaka Y, Tanaka G, Yamakoshi N, Terachi S, Shimamoto K, Nakagawa M, Satoh S, Kuroda S, Iimura O: New technique for time series analysis combining the maximum entropy method and non-linear least squares method: Its value in heart rate variability analysis. *Med Biol Eng Comput* 1997; 35:318-22
- Murasato Y, Hirakawa H, Harada Y, Nakamura T, Hayashida Y: Effects of systemic hypoxia on R-R interval and blood pressure variabilities in conscious rats. *Am J Physiol* 1998; 275:H797-804
- Takusagawa M, Komori S, Umetani K, Ishihara T, Sawanobori T, Kohno I, Sano S, Yin D, Ijiri H, Tamura K: Alterations of autonomic nervous activity in recurrence of variant angina. *Heart* 1999; 82:75-81
- Ebert TJ, Harkin CP, Muzi M: Cardiovascular responses to sevoflurane: A review. *Anesth Analg* 1995; 81:S11-22
- Saeki Y, Hasegawa Y, Shibamoto T, Yamaguchi Y, Hayashi T, Tanaka S, Wang HG, Koyama S: The effects of sevoflurane, enflurane, and isoflurane on baroreceptor-sympathetic reflex in rabbits. *Anesth Analg* 1996; 82:342-8
- Kanaya N, Kawana S, Tsuchida H, Miyamoto A, Ohshika H, Namiki A: Comparative myocardial depression of sevoflurane, isoflurane and halothane in cultured neonatal rat ventricular myocytes. *Anesth Analg* 1998; 87:1041-7
- Ebert TJ, Muzi M, Lopatka CW: Neurocirculatory responses to sevoflurane in humans: A comparison to desflurane. *ANESTHESIOLOGY* 1995; 83:88-95
- Kanaya N, Sato H, Seki S, Nakayama M, Namiki A: Propofol anesthesia enhances the pressor response to intravenous ephedrine. *Anesth Analg* 2002; 94:1207-11
- Ohtomo N, Terachi S, Tanaka Y, Tokiwano K, Kaneko N: New method of time series analysis and its application to Wolf's sunspot number data. *Jpn J Appl Phys* 1994; 33:2821-31
- Pincus SM: Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci U S A* 1991; 88:2297-301
- Kamijo Y, Goto H, Nakazawa K, Benson KT, Arakawa K: Arterial baroreflex attenuation during and after continuous propofol infusion. *Can J Anaesth* 1992; 39:987-91
- Yamamoto S, Kawana S, Miyamoto A, Ohshika H, Namiki A: Propofol-induced depression of cultured rat ventricular myocytes is related to the M_2 -acetylcholine receptor-NO-cGMP signaling pathway. *ANESTHESIOLOGY* 1999; 91: 1712-9
- Nagasaki G, Tanaka M, Nishikawa T: The recovery profile of baroreflex control of heart rate after isoflurane or sevoflurane anesthesia in humans. *Anesth Analg* 2001; 93:1127-31
- Mohamed MK, El-Mas MM, Abdel-Rahman AA: Estrogen enhancement of baroreflex sensitivity is centrally mediated. *Am J Physiol* 1999; 276:R1030-7
- Gribbin B, Pickering TG, Sleight P, Peto R: Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res* 1971; 29:424-31
- Tanaka M, Nagasaki G, Nishikawa T: Moderate hypothermia depresses arterial baroreflex control of heart rate during, and delays its recovery after, general anesthesia in humans. *ANESTHESIOLOGY* 2001; 95:51-5
- Patakas D, Louridas G, Kakavelas E: Reduced baroreceptor sensitivity in patients with chronic obstructive pulmonary disease. *Thorax* 1982; 37:292-5
- Novak V, Novak P, De Champlain J, Le Blanc AR, Martin R, Nadeau R: Influence of respiration on heart rate and blood pressure fluctuations. *J Appl Physiol* 1993; 74:617-26
- Brown TE, Beightol LA, Koh J, Eckberg DL: Important influence of respiration on human R-R interval power spectra is largely ignored. *J Appl Physiol* 1993; 75:2310-7
- Hayano J, Mukai S, Sakakibara M, Okada A, Tanaka K, Fujinami T: Effects of respiratory interval on vagal modulation of heart rate. *Am J Physiol* 1994; 267:H33-40
- Lange RL, Hecht HH: The mechanisms of Cheyne-Stokes respiration. *J Clin Invest* 1962; 41:41-52
- Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *ANESTHESIOLOGY* 1997; 86:836-47