Propofol suppresses the His-ventricular conduction in paediatric patients

Mayuka Matsushima MD\(^1\) | Seishi Kimura MD, PhD\(^1\) | Atsuhiro Kitaura MD\(^1\) | Shinichi Hamasaki MD, PhD\(^1\) | Tatsushige Iwamoto MD, PhD\(^1\) | Takashi Mino RN, MSN\(^1\) | Kenichi Masui MD, PhD\(^2\) | Shinichi Nakao MD, PhD\(^1\) \(^\circ\)

\(^1\)Department of Anesthesiology, Faculty of Medicine, Kindai University, OsakaSayama, Osaka, Japan
\(^2\)Department of Anesthesiology, Showa University School of Medicine, Shinagawa, Tokyo, Japan

Correspondence
Shinichi Nakao, Department of Anesthesiology, Kindai University Faculty of Medicine, Osaka, OsakaSayama, Japan.
Email: nakaos@med.kindai.ac.jp

Abstract

What is known and objective: Propofol is the most commonly used intravenous anaesthetic worldwide and is considered to be safe for all ages. However, there have been some reports that propofol induces severe atrioventricular (AV) blocks in humans and some studies demonstrated that propofol suppressed the cardiac conduction system in animals. A precise mechanism by which the block is induced has not been elucidated yet in humans. The objective of this study was to investigate the effects of propofol on the cardiac conduction system and the cardiac autonomic nervous balance in children.

Methods: We enrolled 23 paediatric patients (age: 6-15 years; males: 16, females: 7) who were scheduled to undergo radiofrequency catheter ablation (RFCA) under general anaesthesia. Anaesthesia was induced with 2 mg/kg propofol and 0.5 µg/kg/min remifentanil, and tracheal intubation was performed with the aid of 1 mg/kg rocuronium. Anaesthesia was maintained with 5-7 mg/kg/h propofol and 0.2 µg/kg/min remifentanil during the RFCA. After the completion of the RFCA, anaesthesia was further maintained with 5 mg/kg/h propofol and 0.2 µg/kg/min remifentanil for at least 10 min (LC: low propofol concentration state), followed by the injection of 2 mg/kg propofol and the infusion of 10 mg/kg/h propofol for 10 min (HC: high propofol concentration state). The sinus node recovery time (SNRT), sinoatrial conduction time (SACT), atrial-His (AH) interval and the His-ventricular (HV) interval were measured at the end of both the LC and HC. Cardiac autonomic regulation was simultaneously assessed based on heart rate variability.

Results and discussion: Propofol significantly suppressed intrinsic cardiac HV conduction, but did not affect the SNRT, SACT or the AH interval. As HV blocks, which occur below the His bundle, are often life-threatening, the HV conduction delay may be a cause of severe AV blocks induced by propofol. Propofol directly suppressed parasympathetic nerve activity, and sympathetic nerve activity was also suppressed.
What is new and conclusion: These results indicate that propofol suppresses the HV conduction and might help to elucidate the mechanism by which propofol causes lethal AV blocks.

1 | INTRODUCTION

Propofol is the most commonly used intravenous anaesthetic worldwide and has advantages over inhalation anaesthesia such as less postoperative nausea and emergence delirium especially in children, widely used for anaesthesia to radiofrequency catheter ablation (RFCA) in paediatric patients, and favoured over volatile anaesthetics. Propofol is a safe intravenous anaesthetic, but can rarely cause severe atrioventricular (AV) blocks in humans. In fact, propofol was found to suppress the cardiac conduction system, especially AV node and/or His-Purkinje conduction, in isolated perfused hearts and animals. Curiously, almost all researches in humans have demonstrated that propofol has no effect on the cardiac conduction system. The aim of this study was to investigate the simultaneous effects of propofol on the cardiac conduction system, such as sinus node function, the atrial-His (AH) interval, and the His-ventricular (HV) interval, and the autonomic nerve balance in pediatric patients because the autonomic nervous system affects the cardiac conduction system.

2 | METHODS

The study was carried out after obtaining institutional approval from the Kindai University Faculty of Medicine Human Subjects Review Committee (No. 26 - 101) and written informed consent from the parents of the patients. The study was registered in UMIN (University Hospital Medical Information Network), which is accepted by the ICMJE (International Committee of Medical Journal Editors), and the registered number was UMIN000016448.

Twenty-three patients (age: 6-15 years; males: 16, females: 7) who were scheduled to undergo radiofrequency catheter ablation (RFCA) were prospectively enrolled in this study. Twelve patients suffered from Wolff-Parkinson-White syndrome, 8 patients suffered from paroxysmal supraventricular tachycardia, and 3 patients suffered from premature ventricular contractions with transient ventricular tachycardia. All of the patients had physical statuses of I or II according to the American Society of Anesthesiologists classification and apart from their cardiac arrhythmias were otherwise healthy (Figure 1).

The administration of all anti-arrhythmia drugs was stopped 2 days before the RFCA. The patients did not receive any premedication. During the procedure, all patients were monitored using electrocardiography, non-invasive and invasive arterial blood pressure monitors, pulse oximetry and capnography. In addition, pharyngeal temperature and bispectral index (BIS) measurements were also obtained in each case. In the RFCA procedure, anaesthesia was induced with 2 mg/kg propofol and 0.5 µg/kg/min remifentanil, and tracheal intubation was performed with the aid of 1 mg/kg rocuronium. Anaesthesia was maintained with 5-7 mg/kg/h propofol to maintain BIS value less than 60, and 0.2 µg/kg/min remifentanil. After the completion of the RFCA, anaesthesia was further maintained with 5 mg/kg/h propofol and 0.2 µg/kg/min remifentanil for at least 10 min (LC: low propofol concentration state), followed by the injection of 2 mg/kg propofol and the infusion of 10 mg/kg/h propofol for 10 min (HC: high propofol concentration state) (Figure 2). We estimated the plasma and rapid peripheral concentrations of propofol using the Elevedel model for broad population including patients aged 3 months or older to adults. These propofol doses and concentrations were completely within normal clinical ranges.
The sinus node recovery time (SNRT), sinoatrial conduction time (SACT), AH interval and HV interval were measured at the end of both the LC and the HC. Cardiac autonomic regulation was simultaneously assessed using power spectral analysis of the beat-to-beat variations in the patient’s heart rate (heart rate variability) using MemCalc/Q-Tch® (GMS Co., Ltd., Tokyo). The HF (high frequency: 0.15-0.4 Hz) peak and the ratio of the LF (low frequency: 0.04-0.15 Hz) peak to the HF (LF/HF) peak were also evaluated. All data are presented as mean ± standard deviation (SD) values. The required sample size was calculated using previously reported data regarding the AH interval change by salbutamol (from 87 ± 17 ms to 70 ± 20 ms, mean ± SD) for the paired t test (target power: 80%; \( \alpha = 0.05, \beta = 0.20 \)). The estimated required sample size was 12 patients. Normal distributions of all sample data were analysed and confirmed with the Kolmogorov-Smirnov test. Comparisons of the electrophysiological and heart rate variability data obtained before (LC) and after (HC) the increase in the propofol concentration were performed using the paired t test. Physiological variables (heart rate, mean arterial pressure, EtCO\(_2\) and SpO\(_2\), body temperature), and QT and QTc intervals among groups (pre-ablation, LC, and HC) were analysed by one-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test. p-values of <0.05 were considered to be statistically significant.

3 | RESULTS

Table 1 shows the baseline characteristics of the patients. No abnormal arrhythmias or hypotension occurred during the experiment. None of the patients complained of memory during the anaesthesia. Figure 3 shows the mean of the predicted plasma and rapid peripheral concentrations of propofol during the study measurement on the low concentration state, 2.5 [2.1-3.0] μg/mL and 2.5 [2.1-3.0] μg/mL, respectively, and that on the high concentration state, 4.5 [3.9-5.3] μg/mL and 4.4 [3.9-5.1] μg/mL, respectively. Table 2 shows changes in physiological variables during the procedures, at pre-ablation, at the LC, and at the HC. There was a significant difference between pre-ablation state and the HC in EtCO\(_2\). When the propofol concentration was increased, only the HV interval was significantly prolonged (from 40.1 ± 7.0 ms to 42.0 ± 7.1 ms; \( p = 0.0172 \)), and there were no significant changes in the SNRT, SACT, or the AH interval. Although the HF peak decreased significantly when the propofol concentration was increased (\( p = 0.0015 \)), the LF/HF ratio did not change (Table 3). Table 4 shows heart rate, QT interval and QTc interval (Fredericia's formula) changes in electrocardiogram at pre-ablation, at the LC, and at the HC. There were no significant differences of these variables among the procedures.
We have demonstrated that an increased blood propofol concentration significantly suppresses the HV conduction, and significantly reduces the HF peak, but does not affect the LF/HF ratio. As the HF peak is considered to reflect cardiac parasympathetic nerve activity, the LF peak is assumed to be a representative of sympathetic or of mixed sympathetic and vagal modulation activities\textsuperscript{19,20} and the LF/HF is recognized as a tool to assess cardiovascular autonomic regulation where increase in the LF/HF is assumed to reflect a shift to ‘sympathetic dominance’ and decrease in the LF/HF corresponds to a ‘parasympathetic dominance’,\textsuperscript{20,21} our results indicated that

### TABLE 1  baseline characteristics of the patients

| No. | Age | M: male, F: female | Diagnosis                                      | BW (kg)  | Height (cm) |
|-----|-----|---------------------|------------------------------------------------|----------|-------------|
| 1   | 12  | F                   | Premature ventricular contraction              | 34       | 144.5       |
| 2   | 14  | M                   | Premature ventricular contraction              | 49       | 163.2       |
| 3   | 14  | F                   | Atrioventricular reentrant tachycardia         | 41.5     | 164         |
| 4   | 14  | M                   | Atrioventricular nodal reentrant tachycardia   | 50       | 165         |
| 5   | 10  | M                   | Wolff-Parkinson-White syndrome                 | 47.9     | 141.1       |
| 6   | 7   | M                   | Wolff-Parkinson-White syndrome                 | 23.1     | 122.7       |
| 7   | 14  | F                   | Atrioventricular nodal reentrant tachycardia   | 46       | 163         |
| 8   | 15  | M                   | Atrioventricular nodal reentrant tachycardia   | 67       | 175         |
| 9   | 11  | F                   | Wolff-Parkinson-White syndrome                 | 34.6     | 143.7       |
| 10  | 10  | M                   | Wolff-Parkinson-White syndrome                 | 33.2     | 146.5       |
| 11  | 7   | M                   | Supraventricular tachycardia                  | 19.3     | 117.7       |
| 12  | 14  | F                   | Atrioventricular nodal reentrant tachycardia   | 57.9     | 158.2       |
| 13  | 13  | M                   | Wolff-Parkinson-White syndrome                 | 38.4     | 154.3       |
| 14  | 14  | M                   | Wolff-Parkinson-White syndrome                 | 63.6     | 169.5       |
| 15  | 12  | M                   | Supraventricular tachycardia                  | 61.5     | 165.5       |
| 16  | 12  | M                   | Wolff-Parkinson-White syndrome                 | 44.8     | 156.2       |
| 17  | 13  | M                   | Wolff-Parkinson-White syndrome                 | 48       | 163.4       |
| 18  | 7   | M                   | Wolff-Parkinson-White syndrome                 | 25.1     | 120.3       |
| 19  | 14  | M                   | Wolff-Parkinson-White syndrome                 | 61.2     | 176.8       |
| 20  | 12  | M                   | Supraventricular tachycardia                  | 48       | 162         |
| 21  | 11  | F                   | Wolff-Parkinson-White syndrome                 | 42.1     | 150.6       |
| 22  | 6   | M                   | Wolff-Parkinson-White syndrome                 | 24.8     | 123         |
| 23  | 7   | F                   | Premature ventricular contraction              | 25       | 124         |
| Mean & SD | 11.4 ± 2.8 | | 42.9 ± 13.9 | 150.9 ± 18.9 |
propofol directly suppressed parasympathetic nerve activity and that sympathetic nerve activity was also suppressed. Moreover, since the HV conduction is not affected by autonomic nerve activity, our findings indicate that propofol suppressed intrinsic the HV conduction. In fact, the patients who suffered propofol-induced lethal AV blocks had various risk factors, such as central hypoventilation syndrome which is characterized by ageing, or diabetes mellitus (DM) with a right bundle branch block. However, it should be noted that there have been several reports about propofol inducing severe AV blocks in patients of various ages. AV blocks are evaluated in terms of the block site; that is, whether it is above or below the His bundle. AH blocks, which occur above the His bundle, are generally benign, while HV blocks, which occur below the His bundle, are often life-threatening.

The cardiac conduction system is influenced by the balance of autonomic activity, and propofol affects autonomic activity. Based on examinations of heart rate variability, Galletly et al.

### TABLE 2 Physiological variables

|                  | Pre-ablation | Low propofol concentration state (LC) | High propofol concentration state (HC) | \( p \) value |
|------------------|--------------|----------------------------------------|----------------------------------------|--------------|
| HR (bpm)         | 71.9 ± 11.9  | 73.4 ± 8.9                             | 69.1 ± 8.3                             | 0.3426       |
| MAP (mmHg)       | 64.9 ± 9.9   | 69.4 ± 10.2                            | 70.7 ± 8.9                             | 0.1138       |
| EtCO\(_2\) (mmHg)| 36.0 ± 2.3   | 35.5 ± 2.1                             | 34.3 ± 1.9\(^7\)                       | 0.0321       |
| SpO\(_2\) (%)    | 99.8 ± 0.3   | 99.8 ± 0.4                             | 99.9 ± 0.4                             | 0.4068       |
| Temp (°C)        | 36.4 ± 0.6   | 36.4 ± 0.6                             | 36.5 ± 0.2                             | 0.5008       |

Data are shown as mean ± SD values. Abbreviations: EtCO\(_2\), end tidal CO\(_2\); HR, heart rate; MA, mean arterial pressure; SpO\(_2\), oxygen saturation of peripheral artery; Temp, temperature. \(^*\)\( p < 0.05 \) vs pre-ablation.

### TABLE 3 Electrophysiological and heart rate variability data

|                  | n  | Low propofol concentration state (LC) | High propofol concentration state (HC) | \( p \) value |
|------------------|----|----------------------------------------|----------------------------------------|--------------|
| SNRT (ms)        | 23 | 1185.26 ± 233.99                       | 1207.43 ± 245.25                       | 0.8791       |
| SACT (ms)        | 23 | 186.56 ± 65.90                         | 177.26 ± 62.76                         | 0.5057       |
| AH (ms)          | 23 | 83.95 ± 20.14                          | 87.39 ± 20.13                          | 0.0643       |
| HV (ms)          | 23 | 40.08 ± 7.03                           | 42.00 ± 7.07\(^7\)                     | 0.0172       |
| HF (msec)        | 22 | 1938.70 ± 1875.01                      | 713.60 ± 506.57\(^7\)                 | 0.0015       |
| LF/HF            | 22 | 3.26 ± 1.51                            | 2.66 ± 1.85                            | 0.0742       |

Values are mean ± SD. Abbreviations: AH, atrial-His interval; HF, Hi frequency component; HV, His-ventricular interval; LF, low frequency component; SACT, sinoatrial conduction time; SNRT, sinus node recovery time. \(^*\)\( p < 0.05 \) vs LC.

### TABLE 4 Heart rates, QT intervals and QTc intervals in the electrocardiogram

|                  | n  | Pre-ablation | Low propofol concentration state (LC) | High propofol concentration state (HC) | \( p \) value |
|------------------|----|--------------|----------------------------------------|----------------------------------------|--------------|
| HR (heart rate)  | 23 | 71.9 ± 11.9  | 73.4 ± 8.9                             | 69.1 ± 8.3                             | 0.3426       |
| QT (ms)          | 23 | 380.3 ± 39.5 | 374.5 ± 33.7                           | 375.7 ± 29.0                           | 0.8419       |
| QTc (ms)         | 23 | 401.7 ± 43.2 | 390.7 ± 30.1                           | 390.3 ± 29.5                           | 0.4832       |
and Scheffer et al reported that induction of anaesthesia with propofol resulted in a greater reduction in the HF power than the LF power, indicating that parasympathetic nerve was suppressed more than sympathetic nerve. More recent studies by Riznyk et al and Kanaya et al also showed that propofol caused reductions in the HF power, which agrees with our results, and preserved the power of the LF peak, and concluded that propofol reduced cardiac parasympathetic activity more than sympathetic activity in young or middle-aged patients. In contrast, some studies showed that propofol reduces parasympathetic tone to a lesser degree than sympathetic tone, resulting in a dominant parasympathetic milieu. Unfortunately, as we did not measure the LF power, we could not clarify a direct effect of propofol on sympathetic nerve activity, but our results that parasympathetic nerve was directly suppressed and sympathetic nerve activity was also suppressed directly or indirectly by propofol quite agree with a majority of other results. However, the discrepancy between our result and some other studies might be attributed to various factors, such as differences in methods for analysing heart rate variability, in depth of anaesthesia, in analgesia, and in surgical stimulation. In fact, unlike other reports, since we used remifentanil, which is a short-acting and strong mu-opioid receptor antagonist, sympathetic tone would have been already suppressed considerably.

We set two different propofol concentration conditions, that is, the LC and the HC, using bolus injections followed by continuous infusions, and measured all of the parameters at the end of the continuous infusions (Figure 3). In contrast, the plasma concentration of propofol might transiently reach an unexpectedly high level after a bolus injection. Indeed, some lethal AV blocks occurred after the bolus administration of propofol. In particular, Olson et al reported that 180 mg of propofol caused an intranodal heart block, which required cardiopulmonary resuscitation (including the administration of adrenalin) and temporary transvenous ventricular pacing in a patient with type II DM and a right bundle branch block. Interestingly, in isolated heart studies, which are not influenced by the autonomic nervous system, propofol suppressed AV conduction in adult hearts, but not in neonatal hearts, at a clinically relevant concentration.

Several potential limitations of our study should be considered. First, this study involved paediatric patients who underwent RFCA because evaluations of the cardiac conduction system, such as the SNRT, SACT, AH interval, and HV interval, can only be performed under general anaesthesia in such patients. Second, all of the patients exhibited abnormal cardiac conduction before the RFCA, and the influence of the RFCA might not have been completely excluded. Third, we did not measure the patients’ blood propofol concentrations.

5 | CONCLUSIONS

Propofol significantly prolonged the HV interval in paediatric patients who underwent RFCA. This result might help to elucidate the mechanism by which lethal AV blocks are induced by propofol.

CONFLICT OF INTEREST
There is no conflict of interest.

ORCID
Shinichi Nakao https://orcid.org/0000-0001-9475-9963

REFERENCES
1. Chidambaran V, Costandi A, D’Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. CNS Drugs. 2015;29:543-563.
2. Lai LP, Lin JL, Wu MH, et al. Usefulness of intravenous propofol anesthesia for radiofrequency catheter ablation in patients with tachyarrhythmias: infeasibility for pediatric patients with ectopic atrial tachycardia. Pacing Clin Electrophysiol. 1999;22:1358-1364.
3. Hino H, Oda Y, Yoshida Y, Suzuki T, Shimada M, Nishikawa K. Electrophysiological effects of desflurane in children with Wolff-Parkinson-White syndrome: a randomized crossover study. Acta Anaesthesiol Scand. 2018;62:159-166.
4. Ganansia MF, Francois TP, Ormezzano X, Pinaud ML, Lepage JY. Atrioventricular Mobitz I block during propofol anesthesia for laparoscopic tubal ligation. Anesth Analg. 1989;69:524-525.
5. Sochala C, Deenen D, Ville A, Govaerts MJ. Heart block following propofol in a child. Paediatr Anaesth. 1999;9:349-351.
6. Takase H, Kudoh A, Takazawa T. A case of severe bradycardia and AV block during administration of propofol. Masui. 2003;52:1000-1002.
7. Morozowich ST, Saslow SB. Progression of asymptomatic bifascicular block to complete heart block during upper gastrointestinal endoscopy with propofol sedation. Can J Anesth. 2009;56:83-84.
8. Noh JI, Lee JH, Woo SY, et al. Complete atrioventricular nodal block after propofol administration in an elderly patient undergoing total knee replacement arthroplasty - A case report. Korean J Anesthesiol. 2013;64:363-366.
9. Olson N, Lim MJ, Ferreira SW, Mehrdad AA. Potential for intra-nodal heart block and cardiogenic shock with propofol administration. Cardiology Res. 2013;4:35-40.
10. Alphin RS, Martens JR, Dennis DM. Frequency-dependent effects of propofol on atrioventricular nodal conduction in guinea pig isolated heart. Mechanism and potential antidysrhythmic properties. Anesthesiology. 1995;83:382-394.
11. Wu MH, Su MJ, Sun SS. Age-related propofol effects on electrophysiological properties of isolated hearts. Anesth Analg. 1997;84:964-971.
12. Pires LA, Huang SK, Wagshal AB, Kulkarni RS. Electrophysiological effects of propofol on the normal cardiac conduction system. Cardiology. 1996;87:319-324.
13. Sharpe MD, Dobkowski WB, Murkin JM, Klein G, Yee R. Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction in Wolff-Parkinson-White syndrome during alfentanil/midazolam anesthesia. Anaesthesiology. 1995;82:888-895.
14. Lavoie J, Walsh EP, Burrows FA, Laussen P, Lulu JA, Hansen DD. Effects of propofol or isoflurane anesthesia on cardiac conduction in children undergoing radiofrequency catheter ablation for tachyarrhythmias. Anesthesiology. 1995;82:888-895.
15. Warpechowski P, Lima GG, Medeiros CM, et al. Randomized study of propofol effect on electrophysiological properties of the atrioventricular node in patients with nodal reentrant tachycardia. Pacing Clin Electrophysiol. 2006;29:1375-1382.
16. Elevedj DJ, Colin P, Absalom AR, Struys MRF. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anesthesia and sedation. Br J Anaesth. 2018;120:942-959.
17. Reves JG, Glass PSA, Lubarsky DA, McEvoy MD, Martinez-Ruiz R. Intravenous anesthetics. In: Miller RD, Eriksson LI, Fleischer
LA, Wiener-Kronish JP, Young WL, eds. Miller’s Anesthesia. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:719-768.

18. Insulander P, Juhlin-Dannfelt A, Freyschuss U, Vallin H. Electrophysiologic effects of salbutamol, a β2-selective agonist. J Cardiovasc Electrophysiol. 2004;15:316-322.

19. Berntson GG, Bigger JT, Eckberg D, Grossman P, Kaufmann PG, Malik M. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology. 1997;34:623-648.

20. Billman GE. Heart rate variability – a historical perspective. Front Physiol. 2011;2:86.

21. Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol. 2013;4:26.

22. Lauer M, Sung R. Anatomy and physiology of the conduction system. In: Podrid PJ, Kowey PR, eds. Cardiac Arrhythmia: Mechanism, Diagnosis, and Management, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:3-36.

23. Gillette PC, Garson A. Pediatric Arrhythmias Electrophysiology and Pacing. St. Louis, MI: Saunders; 1990:216-248.

24. Denes P. His purkinje disease. In: Podrid PJ, Kowey PR, eds. Cardiac Arrhythmia: Mechanism, Diagnosis, and Management, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:693-719.

25. Galletly DC, Buckley DH, Robinson BJ, Corfiatis T. Heart rate variability during propofol anesthesia. Brit J Anaesth. 1994;72:219-220.

26. Scheffer GJ, Ten Voorde BJ, Karember JM, Ros HH, De Lange JJ. Effects of thiopentone, etomidate and propofol on beat-to-beat cardiovascular signals in man. Anaesthesia. 1993;48:849-855.

27. Riznyk L, Fijałkowska M, Przesmycki K. Effects of thiopental and propofol on heart rate variability during fentanyl-based induction of general anesthesia. Pharmacol Rep. 2005;57:128-134.

28. Kanaya N, Hirata N, Kurosawa S, Nakayama M, Namiki A. Differential effects of propofol and sevoflurane on heart rate variability. Anesthesiology. 2003;98:34-40.

29. Deutschman CS, Harris AP, Fleisher LA. Changes in heart rate variability under propofol anesthesia; a possible explanation for propofol-induced bradycardia. Anesth Analg. 1994;79:373-377.

30. Win NN, Fukayama H, Kohase H, Umino M. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. Anesth Analg. 2005;101:97-102.

31. Jeanne M, Logier R, De Jonckheere J, Tavernier B. Heart rate variability during total intravenous anesthesia: Effects of nociception and analgesia. Auton Neurosci. 2009;147:91-96.

32. Shinohara K, Aono H, Unruh GK, Kindscher JD. Suppressive effects of remifentanil on hemodynamics in barodenervated rabbits. Canadian J Anaesth. 2000;47:361-366.