


ORIGINAL ARTICLE

Propofol suppresses the His-ventricular conduction in paediatric patients

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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 remifentanyl, 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 remifentanyl 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 remifentanyl 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.

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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,¹ widely used for anaesthesia to radiofrequency catheter ablation (RFCA) in paediatric patients,² and favoured over volatile anaesthetics.³ Propofol is a safe intravenous anaesthetic, but can rarely cause severe atrioventricular (AV) blocks in humans.⁴⁻⁹ 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.¹⁰⁻¹² Curiously, almost all researches in humans have demonstrated that propofol has no effect on the cardiac conduction system.¹³⁻¹⁵ 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 paediatric 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 remifentanyl, 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 remifentanyl. After the completion of the RFCA, anaesthesia was further maintained with 5 mg/kg/h propofol and 0.2 µg/kg/min remifentanyl 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 Eleveld model for broad population including patients aged 3 months or older to adults.¹⁶ These propofol doses and concentrations were completely within normal clinical ranges.¹⁷

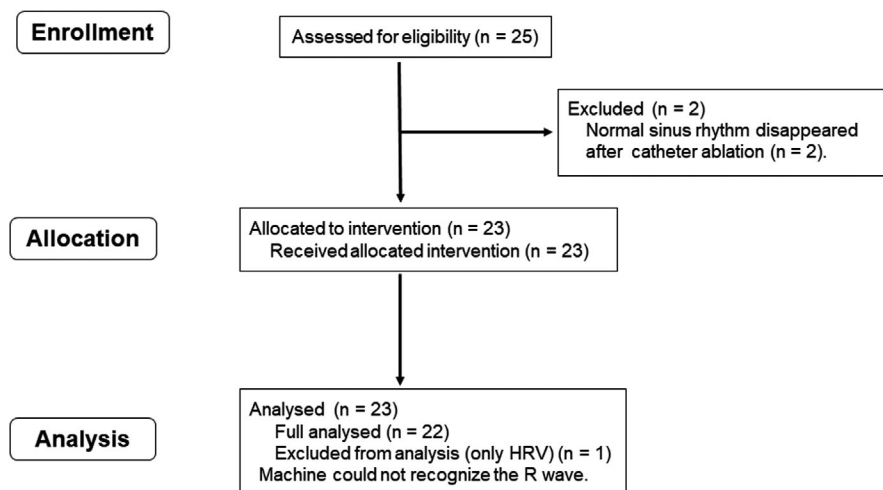


FIGURE 1 The structured patient flow chart for this study. HRV: heart rate variability

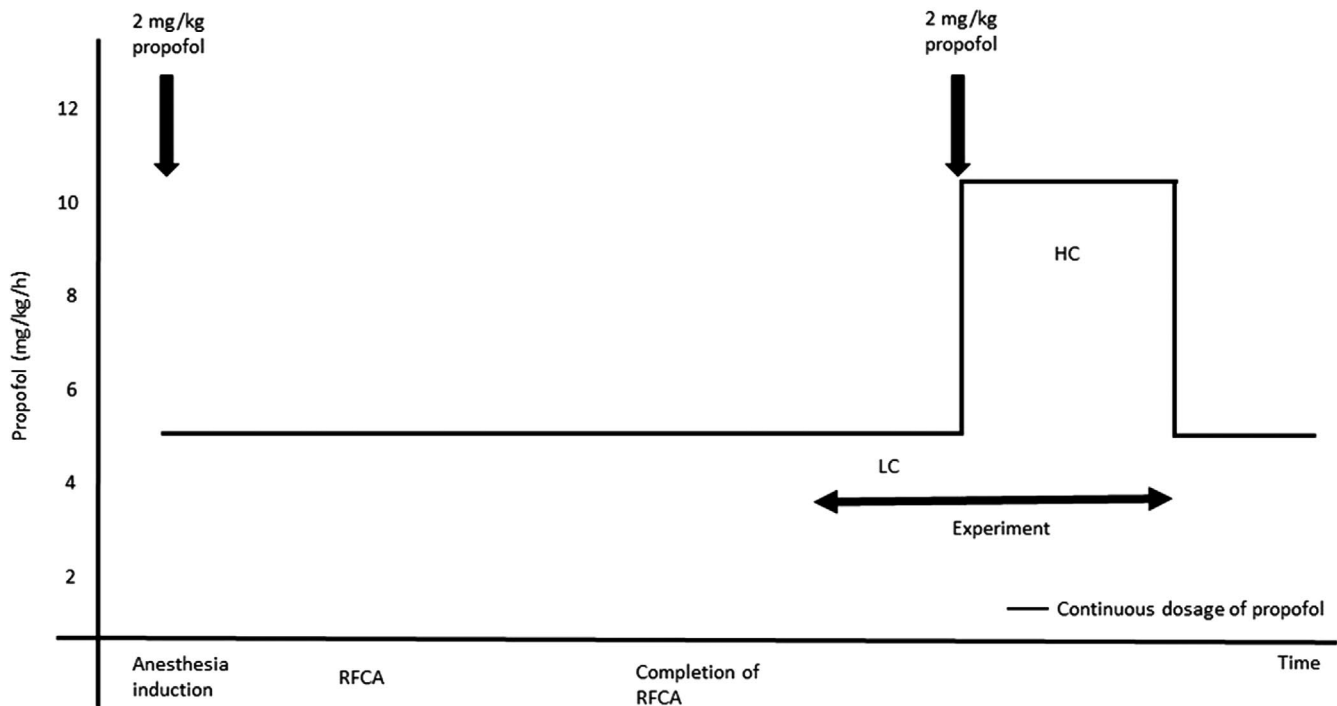


FIGURE 2 Timing of each measurement and propofol administration for the radiofrequency catheter ablation (RFCA) anaesthesia. The vertical line denotes the administered dose of propofol, and the horizontal line denotes the time and the procedures performed. Anaesthesia was induced with 2 mg/kg propofol and 0.5 $\mu\text{g}/\text{kg}/\text{min}$ remifentanyl and maintained with 5–7 mg/kg/h propofol and 0.2 $\mu\text{g}/\text{kg}/\text{min}$ remifentanyl. After the completion of the RFCA, anaesthesia was further maintained with 5 mg/kg/h propofol and 0.2 $\mu\text{g}/\text{kg}/\text{min}$ remifentanyl 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), 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 \pm 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 \pm SD) for the paired *t* test (target power: 80%; $\alpha = 0.05$, $\beta = 0.20$).¹⁸ 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, EtCO₂ and SpO₂, 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] $\mu\text{g}/\text{mL}$ and 2.5 [2.1–3.0] $\mu\text{g}/\text{mL}$, respectively, and that on the high concentration state, 4.5 [3.9–5.3] $\mu\text{g}/\text{mL}$ and 4.4 [3.9–5.1] $\mu\text{g}/\text{mL}$, 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 EtCO₂. 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.

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

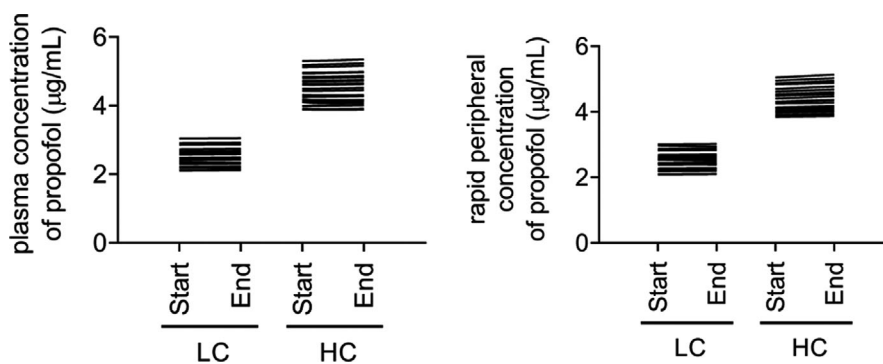


FIGURE 3 The mean of the individual predicted plasma and rapid peripheral concentrations of propofol during the study measurement on the low concentration state (LC) and the high concentration state (HC)

4 | DISCUSSION

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^{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',^{20,21} our results indicated that

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*	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: EtCO₂, end tidal CO₂; HR, heart rate; MA, mean arterial pressure; SpO₂, 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*	0.0172
HF (msec)	22	1938.70 ± 1875.01	713.60 ± 506.57*	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

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,²² our findings indicate that propofol suppressed intrinsic the HV conduction. To the best of our knowledge, this is the first study to simultaneously investigate the effects of propofol on the cardiac conduction system and autonomic activity.

We cannot clarify the reason for the discrepancy in the HV interval between our results and those of other human studies that demonstrated that propofol did not affect the HV interval.¹³⁻¹⁵ Curiously, however, one study showed that propofol induced marked HV prolongation, but the effect was not significant.¹⁴ In contrast, most animal studies showed that clinically relevant concentrations of propofol suppressed AV node and/or His-Purkinje conduction.¹⁰⁻¹² Although the HV interval in the HC was significantly longer than that in the LC in the present study, it is still within a normal range (30-55 ms).²³ However, it should be noted that there have been several

reports about propofol inducing severe AV blocks in patients of various ages.⁴⁻⁹ 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.²⁴ Propofol might carry a risk of excessive suppression of cardiac conduction (specifically HV block) in patients with pre-existing risk factors related to the cardiac conduction system. In fact, the patients who suffered propofol-induced lethal AV blocks had various risk factors, such as central hypoventilation syndrome which is characterized by a generalized disorder of autonomic function,⁵ ageing,⁶⁻⁸ endotoxic shock,⁶ bifascicular block (right bundle branch block and left anterior fascicular block),⁷ or diabetes mellitus (DM) with a right bundle branch block.⁹

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 al²⁵

and Scheffer et al²⁶ 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 al²⁷ and Kanaya et al²⁸ 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.^{29,30} 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 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,²⁸ in depth of anaesthesia, in analgesia, and in surgical stimulation.³¹ In fact, unlike other reports, since we used remifentanyl, which is a short-acting and strong mu-opioid receptor antagonist, sympathetic tone would have been already suppressed considerably.³²

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.^{5,8,9} In particular, Olson et al reported that 180 mg of propofol caused an infranodal 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.⁹ 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.¹¹

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.

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