博士学位論文

論　文　目　録

近畿大学大学院医学研究科

医学系麻酔・疼痛制御・集中治療学

松島　麻由佳

論　文　目　録

受付番号	医　第　　号	氏　名	松島　麻由佳

学位論文

題　目

Propofol suppresses the His-ventricular conduction in paediatric patients
（プロポフォールは小児患者においてHis-心室伝導を抑制する）
Journal of Clinical Pharmacy and Therapeutics
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副　論　文

題　名

1.Sevoflurane prolonged the QTc interval and increased transmural dispersion of repolarization in a patient with long QT syndrome 3: a case report
（症例報告：セボフルランはQTc間隔を延長し、3型QT延長症候群の患者における再分極の経壁的分散を増加させた）
北浦淳寛、中尾慎一、濱﨑真一、法里慧、辻本宜敏、木村誠志、松島麻由佳
JA Clinical Reports
2017年 5月 online掲載
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2.Sevoflurane causes greater QTc interval prolongation in chronically hyperglycemic patients than in normoglycemic patients
（セボフルランは、慢性的高血糖患者において、正常血糖患者よりもQTc間隔の延長を引き起こす）
木村誠志、中尾慎一、北浦淳寛、岩元辰篤、法里慧、松島麻由佳、濱﨑真一
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博士学位論文

論　文　要　旨

プロポフォールは小児患者において

His-心室伝導を抑制する

令和３年２月

近畿大学大学院医学研究科

医学系麻酔・疼痛制御・集中治療医学

松島　麻由佳

論　文　内　容　の　要　旨

【背景、目的】
プロポフォールは世界中で最も一般的に使用されている静脈麻酔薬であり、すべての年齢層で安全に使用できると考えられている。しかし、様々な年齢層のヒトで、プロポフォールにより重度の房室ブロックが引き起こされたという報告が散見される。基礎研究では心臓の房室結節機能やヒス束ープルキンエ機能を抑制するとの報告があるが、ヒトでは房室ブロックが誘発される正確なメカニズムはまだ解明されていない。本研究では、小児の心臓刺激伝導系と心臓自律神経系に対するプロポフォールの効果を調べた。

【方法】近畿大学医学部倫理委員会の許可を得た後文書で親権者の同意を得、UMIN (University Hospital Medical Information Network) に登録した。全身麻酔下で高周波カテーテルアブレーション(RFCA)を受ける予定の 23 人の小児患者（年齢：6〜15 歳、男性：16、女性：7）を対象とした。プロポフォール 2 mg/kg と 0.5 μg/kg /min のレミフェンタニルで麻酔導入し、ロクロニウム 1 mg/kg を投与後に気管挿管を行った。 RFCA の間、麻酔はプロポフォール 5〜7 mg/kg/h とレミフェンタニル 0.2 μg/kg/min で維持した。 RFCA 終了後、プロポフォール 5 mg/kg/h とレミフェンタニル 0.2 μg/kg/min で少なくとも 10 分間麻酔を維持し、低濃度プロポフォール群（LC）とした。続いてレミフェンタニル濃度は一定のまま、プロポフォール 2 mg/kg を単回投与後 10 mg/kg/h で 10 分間維持し、高濃度プロポフォール群(HC) とした。両群とも、使用量は臨床使用範囲であり、プロポフォール血中濃度が定常状態になっていることをコンピューターシミュレーションにより確認している。
それぞれの群で電気生理学検査を行い、心臓刺激伝導系の評価として洞結節回復時間（SNRT）、洞房伝導時間（SACT）、心房-ヒス（A-H 時間）、ヒス-心室（H-V）時間を計測した。同時に得られた体表心電図データから心臓自律神経系の評価として RR 間隔変動を用いて心拍変動解析を行った。また同時に Q-T 時間、QTc 時間も計測した。

【結果】測定中に重篤な不整脈や低血圧は見られず、術中覚醒は一人もなかった。高濃度プロポフォール群で H-V 時間が有意に延長したが洞結節回復時間、洞房伝導時間、A-H 時間は低濃度群と高濃度群で有意差は見られなかった。心拍変動解析では HF（高周波数帯域）が有意に低下したが、LF/HF（低周波数帯域と高周波数帯域の比)には変化がなかった。
また Q-T 時間、QTc 時間は両群で有意差は見られなかった。

【考察】ヒス束の下で発生する HV ブロックは生命を脅かすことが多いため、HV 伝導遅延は、プロポフォールによって誘発される重度の AV ブロックの原因となる可能性がある。

自律神経系への影響としてプロポフォールは副交感神経活動を直接抑制し、交感神経活動も抑制された可能性がある。

【結論】小児患者において高濃度のプロポフォールは HV 伝導を抑制した。プロポフォールが重度の房室ブロックを引き起こすメカニズムの解明に役立つ可能性がある。

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Doctoral Dissertation

Propofol suppresses the His-ventricular conduction in paediatric patients

February　2021

Department of Anesthesiology, pain control and intensive care,
Kindai University Graduate School of Medical Sciences

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課博 ・ 論博

同　意　書

2021 年 2 月 12 日

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論文題目

Propofol suppresses the His-ventricular conduction in paediatric patients

下記の学位論文提出者が、標記論文を貴学医学博士の学位論文（主論文）として使用することに同意いたします。

また、標記論文を再び学位論文として使用しないことを誓約いたします。

記

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ORIGINAL ARTICLE

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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 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,[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 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 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]

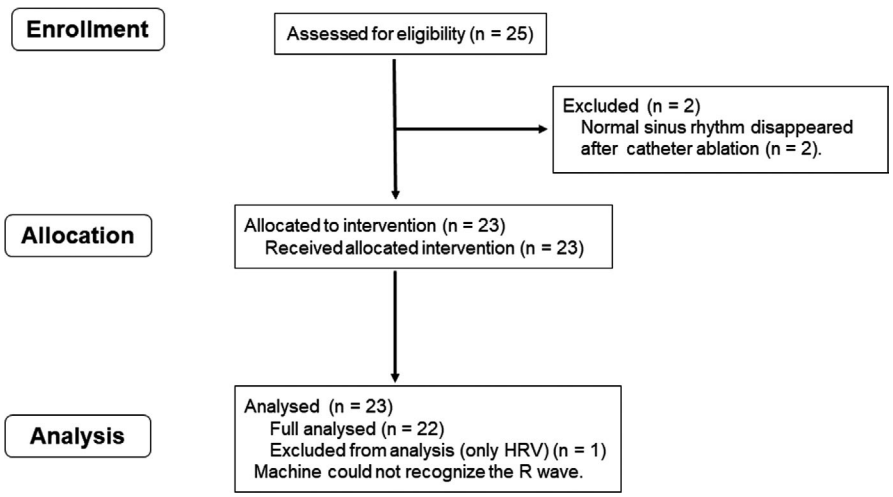

FIGURE 1 The structured patient flow chart for this study. HRV: heart rate variability

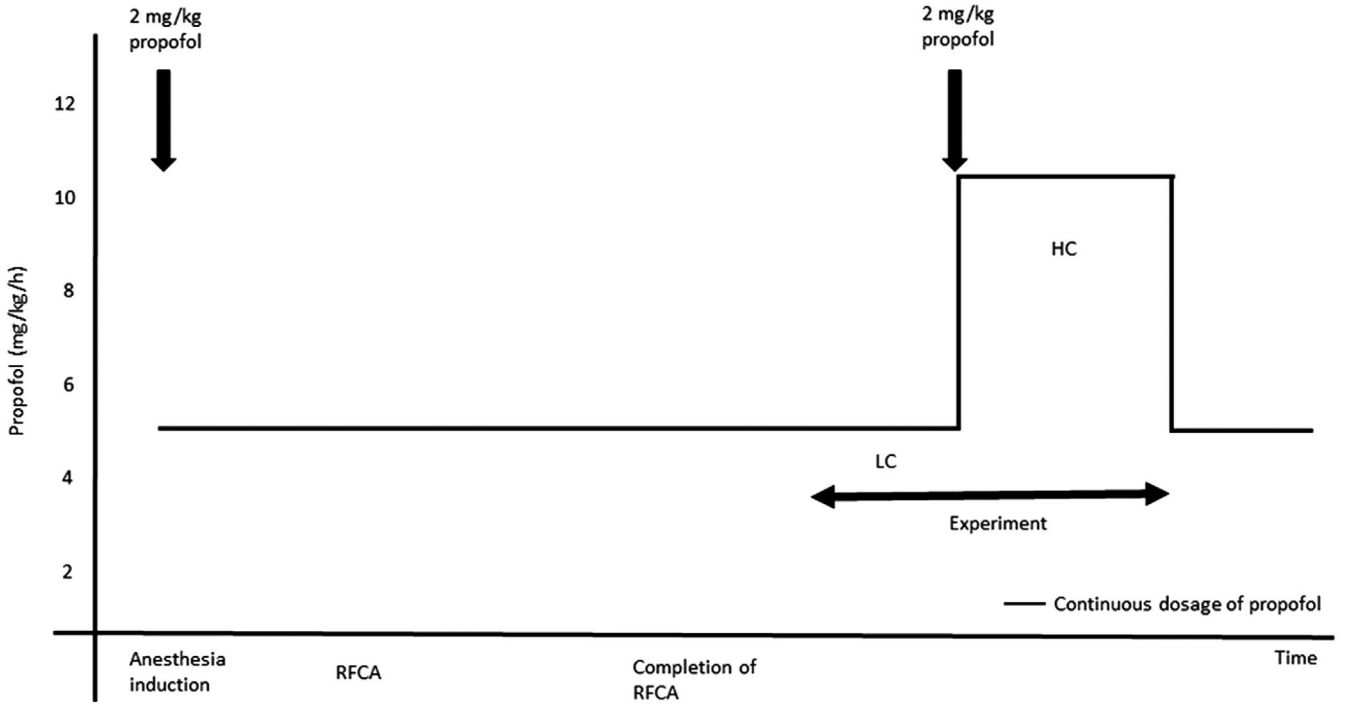

FIGURE 2 Timing of each measurement and propofol administration for the radiofrequency catheter ablation (RFCA) anaesthesia. The vertical line denotes the administered dose of propofol, and the horizontal line denotes the time and the procedures performed. Anaesthesia was induced with 2 mg/kg propofol and 0.5 μg/kg/min remifentanil and maintained with 5-7 mg/kg/h propofol 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)

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%; $\alpha = 0.05$, $\beta = 0.20$).[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, $EtCO_2$ 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 deference 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.

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

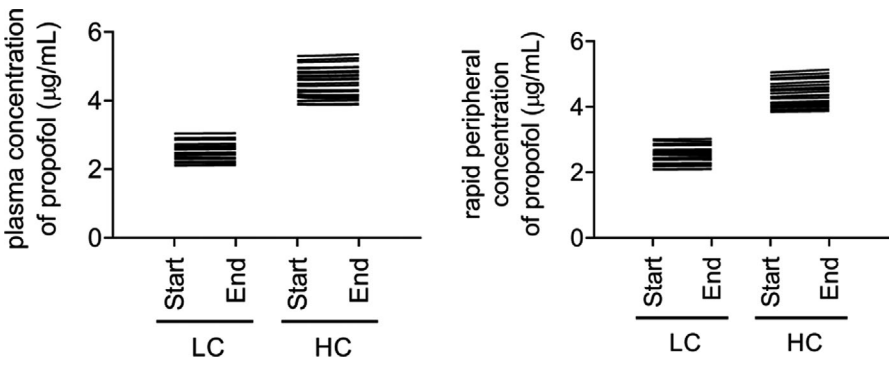

FIGURE 3 The mean of the individual predicted plasma and rapid peripheral concentrations of propofol during the study measurement on the low concentration state (LC) and the high concentration state (HC)

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: $EtCO_2$, 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*	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 al[25]

and Scheffer et al[26] 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[27] and Kanaya et al[28] 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 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,[28] in depth of anaesthesia, in analgesia, and in surgical stimulation.[31] 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.[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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