CLINICAL STUDY

Risk Factors for Intraoperative Instability in Sedated Patients Undergoing Pulmonary Vein Isolation Ablation

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Summary

Persistent or paroxysmal atrial fibrillation is typically treated with pulmonary vein isolation (PVI) ablation under deep sedation with propofol. Intraoperative hemodynamic or respiratory instability often interferes with the surgical procedure. We retrospectively investigated risk factors in 80 patients who underwent their first PVI ablation for atrial fibrillation at our hospital. Background and echocardiography findings were collected from their electronic charts and the questionnaires they completed during hospitalization. Total intraoperative propofol dose and bolus injections (total number and volume) were defined as surrogate measures of patient instability. Single and stepwise multiple regression were performed using each measure as the dependent variable. When total propofol dose was employed as the dependent variable, significant associations were observed with drinking status ($P < 0.05$) and body mass index (BMI) ($P < 0.05$). When total number or volume of intravenous propofol boluses were each used as the dependent variable, significant associations were noted with age ($P < 0.05$) and BMI ($P < 0.05$). Separately, statistical analyses were conducted using total propofol dose or total number of bolus injections as the dependent variable and echocardiography parameters as independent variables. A significant association was detected between total dose and left atrial dimension ($P < 0.05$). These results suggested that younger age, higher BMI (obesity), and current drinking status adversely affect patient stability under deep sedation. To ensure safe ablation, physicians should pay attention to these risk factors when administering deep sedation for PVI.

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Key words: Atrial fibrillation, Catheter ablation, Sedation, Alcohol drinking, Obesity

Pulmonary vein isolation (PVI) ablation is an established method of atrial fibrillation (AF) treatment that has been greatly facilitated by the development of 3-dimensional electroanatomical mapping technology. To prevent complications, operative time should be reduced to the greatest extent possible by minimizing the patient's intraoperative body movements with effective anesthesia or sedation.[1,2] In a Japanese survey of 165 cardiovascular centers published in 2014,[3] general anesthesia was used for 0.5% of all AF ablation surgeries performed (n = 3,373). Conscious sedation and deep sedation were used for 50% and 46%, respectively, which were mostly performed by cardiovascular internists. The sedative agents widely used for PVI include 1% propofol and dexmedetomidine. Common analgesics include pentazocine and fentanyl. The dosing regimens of these medications vary across institutions.

At our hospital, 1% propofol and pentazocine are administered for sedation and analgesia, respectively. To prevent propofol-induced respiratory suppression during PVI, a supraglottic airway device (i-gel®; Japan Medicalnext Co., Ltd., Osaka, Japan) is inserted. Sedation is performed using a weight-adjusted propofol bolus and continuous infusion. The level of sedation is managed based on the clinically proven Bispectral Index (BIS) monitoring system (A-3100C, Covidien Japan, Tokyo), which measures the patient's level of consciousness based on electroencephalographic signals.[4-6] Doses of propofol are modified based on the BIS score. In our clinical experience, we encountered cases where BIS scores changed rapidly, leading to more propofol bolus injections or a larger total propofol dose than planned before surgery. We retrospectively investigated the risk factors for hemodynamic or respiratory instability in deeply sedated patients undergoing PVI.

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Table I. Patient Demographic and Background Characteristics

Characteristic	Value
Age (years), mean ± SD	65 ± 13
Sex (male/female), *n*	60/20
Body mass index (kg/m^2), mean ± SD	25 ± 3
Type of atrial fibrillation (paroxysmal/persistent), *n*	48/32
Current drinker, *n* (%)	47 (59%)
Current smoker, *n* (%)	19 (24%)
Hypertension, *n* (%)	42 (53%)
Diabetes mellitus, *n* (%)	20 (25%)
Cardiac failure, *n* (%)	29 (36%)
Stroke, *n* (%)	3 (4%)
CHADS2 score	1.7 ± 1.4

SD indicates standard deviation.

Methods

Study population: The study population consisted of 80 patients who underwent their first PVI AF ablation at our hospital between April 2021 and April 2022.

Patient demographics and background: Patient demographic and background data were collected from electronic charts, nursing records, and questionnaire surveys that they completed during hospitalization. Specifically, data on the following variables were taken from electronic charts: age; sex; height; weight; body mass index (BMI); drinking status (current or former/never drinker); smoking status (current or former/never smoker); history of diabetes, cardiac failure, or stroke (yes or no); and echocardiography findings (left atrial dimension [LAD], left atrial volume index [LAVI], left ventricular ejection fraction [LVEF]). These data were used to determine the CHADS2 (congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke) score for each patient. The Ethics Committee approved all procedures used in this research of Tokushima University Hospital.

Induction and maintenance of propofol sedation: In all patients, sedation was induced using intravenous propofol, taking note of biological monitoring indicators, electrocardiography findings, percutaneous oxygen saturation, blood pressure, and BIS parameters. The induction bolus dose was between 1.5 and 2.0 mg/kg; attention was paid to keep BIS scores below 50. A supraglottic airway device (i-gel®) was inserted to keep the upper airway open. A ventilation device (Monnal™ T60, Air Liquide Medical Systems, Antony, France) was used for respiratory management. The ventilation device was set to the assisted pressure-controlled ventilation mode. End-tidal carbon dioxide levels were monitored using the mainstream capnometer (Nihon Kohden, Tokyo, Japan).

For the maintenance of sedation during PVI, propofol was infused at a rate between 4 and 6 mg/kg/h; attention was paid to keep BIS scores below 60. Additional bolus propofol doses were administered as appropriate when there was involuntary patient movement, unstable respiration, unexpected fluctuations in blood pressure, or the BIS score reached the threshold. After completion of the surgery, the patient's electronic charts and nursing records were reviewed to collect data on the total dose of propofol (sum of induction and maintenance doses), total bolus doses of propofol, and number of bolus doses.

Propofol sedation and outcomes: We evaluated the relationship between propofol sedation and procedural outcomes including the first-pass PVI and atrial tachyarrhythmia recurrence. First-pass PVI was defined as successful bilateral PVI at or before completion of the encircling lesion set. Atrial tachyarrhythmia recurrence was defined as any sustained AF or atrial tachycardia lasting for > 30 seconds, which appeared after the blanking period (> 90 days after the catheter ablation).

Statistical analysis: The total propofol dose adjusted by body weight, total bolus dose adjusted by body weight, and number of bolus injections were defined as surrogate measures of patient instability. Single and stepwise multiple regression analyses were conducted using each measure as the dependent variable.

Results

Patient demographics and background: Table I outlines the demographic and background profile of the study population. The mean age was 65.5 years, 75.0% were male, and the mean (SD) BMI was 25 (3) kg/m^2. The proportion of current drinkers and current smokers was 59% and 24%, respectively. The proportion of patients with hypertension and diabetes mellitus was 53% and 25%, respectively. History of cardiac failure and stroke was present in 36% and 4% of study participants, respectively. The mean (SD) echocardiographic parameters were as follows: LAD, 44 (9) mm; LAVI, 39 (12) mL/m^2, and LVEF, 60 (7) %. The mean CHADS2 score was 1.7 (1.4).

Risk factor analysis: The total dose of propofol during PVI was 19.5 (11.6-36.5) mg/kg. The mean (range) total bolus dose was 4.3 (1.9-8.8) mg/kg. The mean (range) induction dose was 1.5 (0.4-3.9) mg/kg. The mean (range) number of bolus injections was 3.7 (0-9).

Significant associations between total propofol dose and drinking status ($P < 0.05$) or BMI ($P < 0.05$) were observed (Table II). Significant associations between total number or dose of intravenous propofol boluses and age ($P < 0.05$) or BMI ($P < 0.05$) were noted (Table III). Separately, statistical analyses were conducted using total dose or number of bolus injections as the dependent variable and echocardiography parameters as independent variables (Table IV). A significant association was ob-

Table II. Associations Between Patient Factors and Total Propofol Dose

Independent Variable	Univariate Regression Standardized Regression Coefficient	*P* value	Stepwise Multiple Regression Standardized Regression Coefficient
Age	-0.087	0.445	-
Sex	0.215	0.056	-
Body mass index	0.411	0.002	0.373
Drinking status	0.297	0.008	0.236
Smoking status	0.053	0.640	-
Cardiac failure	-0.002	0.986	-

Table III. Associations Between Patient Factors and Propofol Bolus Injections

Independent Variable	Univariate Regression Standardized Regression Coefficient	*P* value	Stepwise Multiple Regression Standardized Regression Coefficient
Associations with Number of Propofol Bolus Injections			
Age	-0.230	0.040	-0.262
Sex	-0.120	0.290	-
Body mass index	0.318	0.004	0.342
Drinking status	0.165	0.144	-
Smoking status	-0.053	0.640	-
Cardiac failure	0.075	0.506	-
Associations with Total Propofol Bolus Dose			
Age	-0.338	0.022	-0.372
Sex	-0.006	0.961	-
Body mass index	0.205	0.003	0.252
Drinking status	0.165	0.684	-
Smoking status	-0.025	0.530	-
Cardiac failure	-0.071	0.824	-

Table IV. Associations Between Echocardiography Parameters and Propofol

Independent Variable	Univariate Regression Standardized Regression Coefficient	*P* value	Stepwise Multiple Regression Standardized Regression Coefficient
Associations with Total Propofol Dose			
LAD	0.289	0.009	0.299
LAVI	0.202	0.422	-
LVEF	0.880	0.442	-
Associations with Total Number of Bolus Injections			
LAD	0.196	0.820	-
LAVI	0.131	0.250	-
LVEF	0.134	0.240	-
Associations with Total Bolus Injection Dose			
LAD	0.011	0.912	-
LAVI	0.910	0.527	-
LVEF	0.125	0.535	-

LAD indicates left atrial dimension; LAVI, left atrial volume index; and LVEF, left ventricular ejection fraction.

served between total dose and LAD ($P < 0.05$).

Sedation and outcomes: Total propofol dose and number of propofol bolus injections were significantly lower in patients with first-pass PVI compared to those without first-pass PVI (Figure 1). There was no significant difference in total propofol bolus dose between patients with and without first-pass PVI (Figure 1). On the other hand, there were no significant differences in total propofol dose, number of propofol bolus injections, and total propofol dose between patients with and without atrial arrhythmia recurrence (Figure 2).

Discussion

General anesthesia is associated with better outcomes of catheter AF ablation than conscious sedation.[7,8] Surgical complications of PVI frequently develop as a result of failure in intraoperative respiratory management for which deep sedation is a viable solution as it decreases the incidence of complications and shortens operative time.[6,9] In this study, AF ablation was conducted under deep sedation using weight-adjusted propofol doses. Based on the institutional dosing algorithm, propofol boluses were adminis-

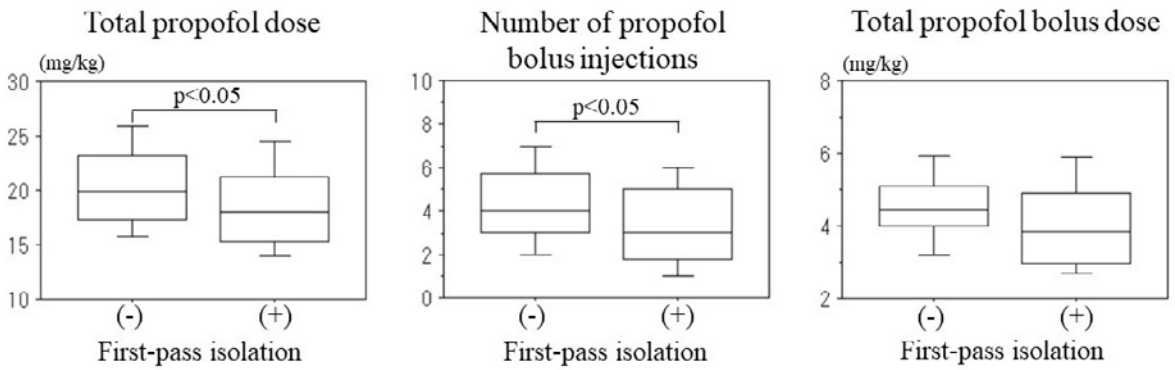

Figure 1. Surrogate markers of sedation instability between patients with and without first-pass pulmonary vein isolation.

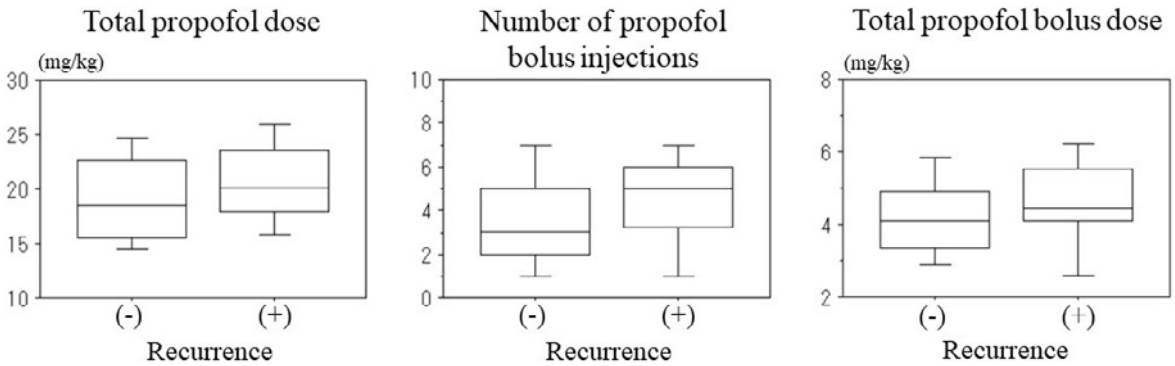

Figure 2. Surrogate markers of sedation instability between patients with and without atrial tachyarrhythmia recurrence.

tered as appropriate when involuntary body movements or spontaneous breathing was observed.

In this study, the regression analyses showed that younger age and higher BMI (including obesity) were identified as risk factors for patient instability based on total number and dose of propofol bolus injections. Because propofol dosage was calculated based on weight, administration of a linear propofol dose might not be sufficient for obese patients. The impact of obesity on intraoperative patient instability might be explained using the 3-compartment pharmacokinetic model of plasma, fast-redistributing tissue, and fat (central, second, and third compartments, respectively). Obesity increases adipose tissue volume and provides a larger reservoir for lipophilic propofol, allowing for a faster decrease of propofol concentrations in the central compartment.[10] Thus, plasma propofol concentrations start to decrease at a faster rate in obese patients than in nonobese patients, increasing the likelihood of more frequent bolus injections in obese patients. The impact of obesity on intraoperative patient instability might also be explained based on the hepatic clearance of propofol. Obese patients often have hepatomegaly and elevated cardiac output. These conditions enhance hepatic blood flow and thereby accelerate the hepatic clearance of propofol, an agent metabolized extensively in the liver.[11]

In this study, younger patients were more likely to have a larger total number of propofol bolus injections and higher total bolus dose of propofol than elderly patients. Age increases the minimum alveolar concentration of volatile analgesics and influences the pharmacokinetics and pharmacodynamics of propofol and other intravenous analgesics. In an electroencephalographic study of volunteers who received a bolus propofol dose, the time to 50% depression from peak effect was prolonged with age.[12] In a pharmacokinetic-pharmacodynamic study of propofol, the lag time between propofol administration and appearance in the arterial circulation increased with age.[13] Moreover, age decreases the target-controlled infusion dose and effect-site concentration of propofol.[12,14] Schnider, *et al* proposed the following formula to describe the probability of the volunteer being unconscious at the end of the infusion (Punc) as a function of age:[12]

$$Punc = C4.29 / [C4.29 + (2.9 - 0.022 \times age)\ 4.29],$$

where C represents the propofol concentration at the end of the infusion. This equation indicates that younger patients need higher propofol concentrations than elderly patients to attain the same level of sedation. These considerations suggest that propofol doses should be adjusted based on patient age as well as weight.

Our study also discovered that current drinking status is a significant risk factor for patient instability during PVI ablation under deep sedation. Similar to ethanol, propofol induces sedative and hypnotic effects by potentiating γ-aminobutyric acid type A receptors in the central nervous system.[15] Their similar mechanisms of action suggest that current drinkers are less responsive to propofol sedation because of greater hepatic metabolism and resistance.

Our results were in line with the finding that the dose that produced loss of consciousness in surgery with general anesthesia is higher in alcohol abusers than in social drinkers.[16)]

Regarding possible relationships between echocardiography parameters and propofol use, a significant association was detected between total dose and LAD. Given that bolus injections were not significantly correlated with any of the echocardiography parameters, there is little convincing evidence for the observed association. The most likely explanation would be that a greater total propofol dose is necessary for longer operative time resulting from a larger left atrium.

In the present study, we also evaluated the influence of destabilization of deep sedation on procedural outcomes. We found that a higher total dose of propofol or a higher number of propofol bolus injection, surrogate markers of sedation instability, were associated with the lower first-pass PVI. Because the absence of first-pass PVI was reported to be associated with poor PVI durability and AF ablation outcomes,[17)] the sedation instability might result in the poor outcomes. In addition, these surrogate markers tended to be higher in patients with atrial tachyarrhythmia recurrence compared with those without recurrence, but it did not reach statistical significance. These results suggest that sedation instability may influence the outcome of a procedure.

Overall, our study showed that younger age, higher BMI (obesity), and current drinking status adversely affect patient stability under deep sedation. To ensure safe and reliable PVI ablation, physicians should pay attention to these factors when administering deep sedation.

This study should be interpreted in light of its limitations. First, we used the amount or bolus numbers of propofol as the surrogate marker of sedation instability instead of BIS value. This was because rapid injection of propofol was often administered before the BIS changes since patient involuntary movement or unstable respiration often occurs before the BIS changes. Second, we used only propofol as the sedative and only pentazocine as the analgesic that we, as non-anesthesiologists, are familiar with. This may have influenced the results of the present study. Third, small sample size may affect the influence of sedation instability on hard endpoints including atria tachyarrhythmia recurrence or procedural complications. The impact on complications could not be assessed because there were no patients with major complications.

Conclusion

Younger age, higher BMI (obesity), and current drinking status are significant independent risk factors for hemodynamic or respiratory instability under deep sedation. These factors should be duly noted to ensure safe and reliable PVI under deep sedation.

Disclosure

Conflicts of interest: None.

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