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Impact of effect-site concentration of propofol on cardiac systolic function assessed by tissue Doppler imaging

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Abstract

Objective: To evaluate the relationship between effect-site concentration (C_E) of propofol during total intravenous anaesthesia (TIVA) and cardiac systolic function using tissue Doppler imaging (TDI) in patients undergoing cardiovascular procedures.

Methods: Stepwise increments of C_E of propofol of 1.0, 2.0, 3.0 and 4.0 μg/ml (modified Marsh model) were achieved using a target-controlled infusion device. Transthoracic echocardiographic assessments using TDI were performed for each C_E of propofol and corresponding systolic myocardial velocity (s′), mean arterial blood pressure (MAP), heart rate (HR) and bispectral index (BIS) were evaluated.

Results: Data from 31 patients were analysed in this prospective study. The s′ velocity decreased with increasing propofol C_E and values recorded at propofol C_E 3.0 and 4.0 μg/ml were near or below 8 cm/s indicating abnormal cardiac systolic function. MAP, HR and BIS also decreased with each propofol C_E increment.

Conclusion: Although the recommended dosage for propofol is up to 4.0 μg/ml, caution should be taken when using propofol concentrations above 2.0 μg/ml during TIVA in patients with underlying cardiovascular diseases.

Keywords

Propofol, cardiac systolic function, tissue Doppler imaging, target-controlled infusion

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Introduction

Propofol is a commonly used intravenous agent for induction and maintenance of anaesthesia because it has a rapid onset and a short duration of action.[1] However, induction of anaesthesia with 2 mg/kg propofol frequently causes a drop in blood pressure (BP) secondary to decreased systemic vascular resistance and cardiac contractility, which may occasionally lead to transient adverse events, especially in patients with cardiovascular diseases.[2] Furthermore, in patients with a low cardiac output status, continuous infusion of a relatively low-dose of propofol may result in hypotension during induction of anaesthesia.[3] The concentration of propofol required for anaesthesia during surgery ranges from 2.5 – 4.5 μg/ml[1] and a concentration of 2.0 – 4.0 μg/ml is usually recommended during cardiovascular procedures.[4] However, the effects of different concentrations of propofol on cardiac systolic function have not been clarified, especially in patients undergoing cardiovascular procedures who are expected to be at risk for complications.[3]

Echocardiography is widely used for the evaluation of cardiac systolic function. In particular, tissue Doppler imaging (TDI) is a relatively novel technique that measures myocardial tissue velocities during systole and diastole and reduces dependency on left ventricular (LV) preload change.[5–7]

It was hypothesized that determining the optimal concentration of propofol for anaesthesia that would not affect cardiac systolic function may be beneficial in total intravenous anaesthesia (TIVA) where a safe induction and maintenance of anaesthesia is required. Therefore, this present study evaluated the relationship between effect-site concentration (C_E) of propofol and cardiac systolic function using TDI, in patients undergoing cardiovascular procedures.

Patients and methods

Study population

This was a single-centre, prospective study that took place between January 2013 and May 2014 at Konkuk University Medical Centre, Seoul, Korea. Patients undergoing general anaesthesia under TIVA for cardiovascular procedures were eligible for inclusion. Exclusion criteria were: (i) age <18 years; (ii) urgent or emergency cases; (iii) allergy to egg or soybean oil; (iv) left ventricular ejection fraction (LVEF) <40%; (v) regional wall motion abnormality; (vi) atrial fibrillation.

The study was approved by the Institutional Review Board of Konkuk University Medical Centre, Seoul, Korea (approval no. KUH1160049) and registered at http://cris.nih.go.kr (KCT0000635). Written informed consent was obtained from all patients.

Anaesthetic regimen and TDI

According to our institutional protocol, anaesthesia was performed after all vasoactive agents including dopamine and phenylephrine had been prepared. The anaesthetic technique was standardized. In brief, the patient arrived at the operation room without premedication. After establishing routine patient monitoring (i.e. pulse oximetry, electrocardiography, non-invasive BP monitoring and bispectral index [BIS; a measure of the depth of anaesthesia]), a radial artery was cannulated for continuous invasive systemic BP monitoring. Pre-oxygenation and de-nitrogenation were achieved following eight breaths of maximal inhalation and exhalation with 100% oxygen. During induction of anaesthesia, each patient was supplied with 100% oxygen via a tightly fitted mask. Target end-tidal carbon dioxide (CO_2) concentration was maintained, and respiration parameters (i.e. tidal volume and respiration rate) were checked. Intravenous lidocaine (0.5 mg/kg) was used to prevent the pain induced by the propofol injection.

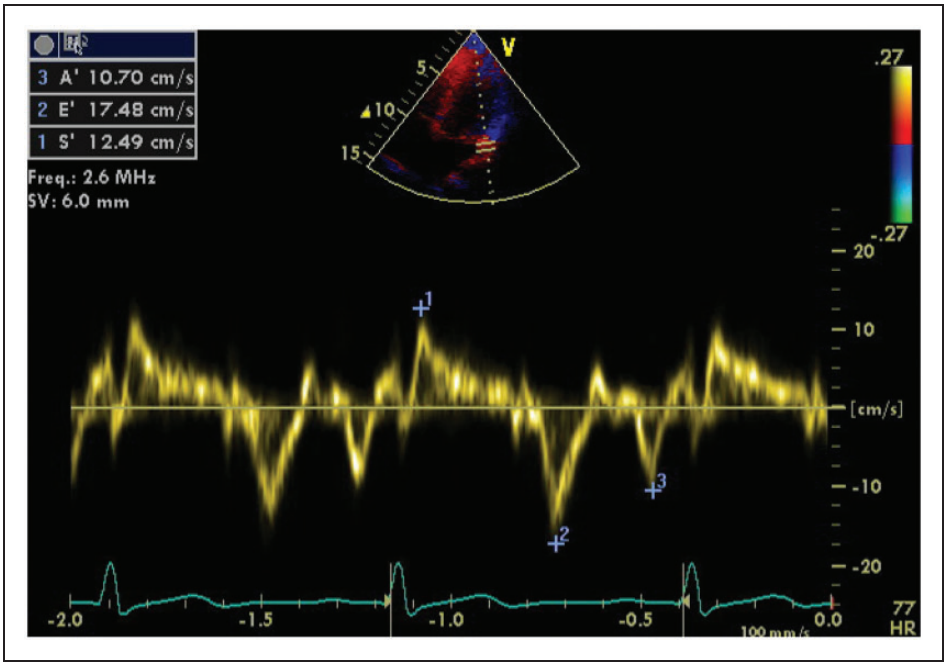

Figure 1. An example of transthoracic echocardiographic assessment using tissue Doppler imaging in the evaluation of effect-site concentration of propofol and cardiac systolic function in patients undergoing cardiovascular procedures. s′ velocity, upward deflection during systole (systolic myocardial velocity); e′ velocity, downward deflection corresponding to early diastolic phase (early diastolic myocardial relaxation velocity); a′ velocity, downward deflection corresponding to late diastolic phase (late myocardial relaxation velocity with atrial contraction); Freq, frequency; SV, stroke volume; HR, heart rate. The colour version of this figure is available at: http://imr.sagepub.com

Transthoracic echocardiographic assessments using TDI were performed using a 5 MHz transducer (GE Healthcare, Wauwatosa, WI, USA) as recommended in guidelines.[8] Pulsed wave TDI was evaluated after obtaining an apical four-chamber view with optimal gain and the best signal-to-noise ratio. The sample volume was positioned at the left lateral ventricular wall with the mitral valve annulus. Three distinctive velocities were recorded; upward deflection during systole (systolic myocardial velocity, s′) and two downward deflections corresponding to the early diastolic phase (early diastolic myocardial relaxation velocity, e′) and late diastolic phase (late myocardial relaxation velocity with atrial contraction, a′) (Figure 1). The s′ velocity was measured for assessment of LV systolic function.

All TDI assessments were performed by the cardiac anaesthesiologist (S-H Kim) at the end of the expiratory period to exclude respiratory effects. A TDI assessment was performed at baseline (i.e. C_E 0.0 μg/ml) after the lidocaine injection. Anaesthesia was induced by administration of propofol at an initial effect-site target concentration of 1.0 μg/ml using a target-controlled infusion device with a built-in modified Marsh model (Orchestra® Base Primea; Fresenius Vial, Brézins. France).[9] A second TDI assessment was performed 5 min after the plasma concentration (C_P) and C_E of

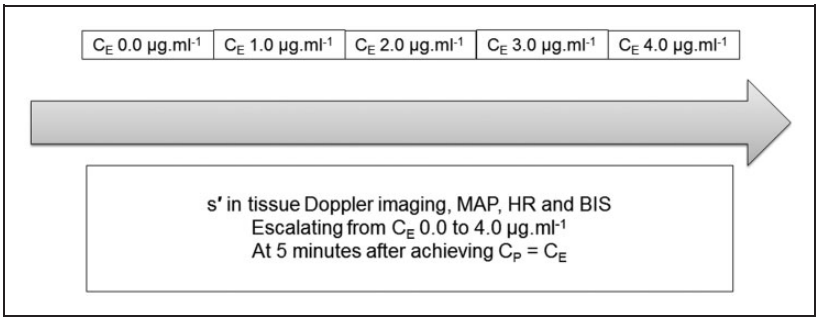

Figure 2. Study protocol for the evaluation of effect-site concentration (C_E) of propofol and cardiac systolic function in patients undergoing cardiovascular procedures. Stepwise increments of propofol C_E (0.0, 1.0, 2.0, 3.0 and 4.0 μg/ml) were achieved using a target-controlled infusion device. Assessments of s′ velocity (using tissue Doppler imaging), mean arterial blood pressure (MAP), heart rate (HR) and bispectral index (BIS) were evaluated 5 min after achieving the same plasma concentration (C_P) and C_E of propofol.

propofol were equivalent. Further TDI assessments were made 5 min after the C_P and C_E of propofol were equivalent for all dose increases of propofol up to 4.0 μg/ml (Figure 2). At the same time-points, mean arterial blood pressure (MAP), heart rate (HR) and BIS were also measured.

During the dose escalation of propofol, assisted or controlled ventilation using a face mask with 100% oxygen was used if pulse oximetry fell below 95%. The tidal volume, respiration rate and concentration of end-tidal CO_2 were maintained at the same values as for spontaneous ventilation. Crystalloid fluid was infused at 2 × ideal body weight (kg) ml/h throughout the entire anaesthesia.[10] In the event that MAP decreased to <60 mmHg or HR fell to <40 beats per min (bpm), a vasoactive agent (i.e. phenylephrine 30 μg or ephedrine 4 mg [MAP <60 mmHg and HR <40 bpm], or atropine [HR <40 bpm]) was administered and the study was terminated to ensure patient safety.

After all TDI assessments had been completed, anaesthesia care was continued by the attending anaesthesiologists until the end of surgery.

Statistical Analyses

The C_E of propofol and the corresponding TDI (s′ velocity), MAP, HR and BIS were evaluated. The TDIs were evaluated by three assessors, two were blinded observers and one (S-H Kim) had also performed the TDI assessments. To assess inter-observer variability, the values of s′ according to C_E of propofol were analysed using the intra-class correlation coefficient (ICC). The ICC is an established statistic for assessing measurement 'reliability' and is defined using variance components.[11] The better the agreement among assessors, the closer the denominator is to the numerator and the closer the ICC is to 1.0.

The primary outcome variable was s′ velocity. In a pilot study at our centre that involved 10 patients undergoing general anaesthesia under TIVA for cardiovascular procedures, s′ velocity was 9.61 ± 1.89 cm/sec. Another study of non-anaesthetized patients found that a cut-off limit for s′ velocity of 8 cm/sec differentiated between normal (≥50%) and below normal (<50%) LVEF.[12] As it was determined that a minimum difference of 20% in the values of s′ velocity between 0.0 and 4.0 μg/ml C_E of propofol was clinically

significant, a sample size of 31 was estimated to achieve a power of 0.9 and α value of 0.05.

Normality of the data was assessed by the Kolmogorov–Smirnov test and if normally distributed the data were expressed as the mean ± SD or medians (interquartile range) as appropriate. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

All statistical analyses were performed using the SPSS® statistical package, version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows®. The changes in TDI (s′ velocity), MAP, HR and BIS according to C_E of propofol were analysed by analysis of variance on ranks for repeated measurements and Bonferroni's correction was performed if values were statistically significant.

Results

Thirty-eight patients were enrolled in the study. Seven patients could not be evaluated up to C_E 4.0 μg/ml and did not complete the study. Therefore, the final analysis was performed on 31 patients (Table 1).

The ICC values for inter-observer reliability of s′ velocity assessments were 0.93 (95% confidence interval [CI] 0.88, 0.96), 0.84 (95% CI 0.73, 0.91), 0.94 (95% CI 0.89, 0.97), 0.93 (95% CI 0.88, 0.96) and 0.94 (95% CI 0.89, 0.97) for propofol C_E 0.0, 1.0, 2.0, 3.0 and 4.0 μg/ml, respectively.

The s′ velocity decreased with increasing propofol C_E (Table 2). With the exception of the s′ velocity between 0.0 and 1.0 μg/ml and between 3.0 and 4.0 μg/ml propofol C_E, all comparisons between doses were statistically significantly different ($P < 0.05$ for all comparisons). During the study period, no new-onset regional wall motion abnormalities were detected. MAP and HR showed no significant differences between 0.0 and 1.0 μg/ml propofol C_E, but decreased significantly with each propofol C_E increment from 2.0 to 4.0 μg/ml ($P < 0.05$ for all comparisons). The BIS decreased significantly

Table 1. Demographic baseline characteristics for patients undergoing cardiovascular procedures during total intravenous anaesthesia with propofol.

Characteristic		Study population $n = 31$
Sex, male/female		23/8
Age, years		61 (54, 68)
Height, cm		164 ± 8
Weight, kg		67 (61, 72)
Smoking history, pack-years		0 (0, 20)
Current medications		
	α-blocker	1 (3)
	Angiotensin receptor blocker	10 (32)
	β-blocker	5 (16)
	ACE inhibitor	3 (10)
	Calcium channel blocker	11 (36)
	Vasodilator	3 (10)
	Diuretics	6 (19)
	Digoxin	1 (3)
	Dyslipidaemia medication	5 (16)
	Diabetes medication or insulin	6 (19)
Diagnosis		
	Cardiac valve disease	15 (48)
	Coronary artery disease	7 (23)
	Pericardium disease	1 (3)
	Aorta or vascular disease	7 (23)
	Intracardiac shunt disease	1 (3)
Operation		
	Aortic valve repair	8 (26)
	Mitral valve repair	7 (23)
	Off-pump CABG	7 (23)
	Pericardiectomy	1 (3)
	Graft interposition	4 (12)
	Vascular bypass surgery	3 (10)
	Intracardiac shunt closure	1 (3)
LVEF, %		67.2 (62.3, 71.7)

Values are shown as mean ± SD, median (interquartile range), *n* or *n* (%).
ACE inhibitor, angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass grafting surgery; LVEF, left ventricular ejection fraction.

with each propofol C_E increment ($P < 0.05$ for all comparisons).

Discussion

This present study evaluated cardiac systolic function by assessing the s′ velocity of TDI parameters at the left lateral ventricular wall. The s′ velocity is less dependent on preload, closely related to LVEF,[13,14] and is better correlated with ventricular contractility compared with LVEF.[13,15] The LV wall is composed of three myocardial layers with non-homogenous deformation creating multiple directed movements including circumferential and longitudinal contractions.[16] The subendocardial layer of the left ventricle is mainly composed of longitudinal fibres and has greater oxygen consumption with less collateral blood flow than the other layers.[17] Therefore, the subendocardial layer of the left ventricle is vulnerable to ischaemia.[18] Even in patients with normal LVEF, s′ velocity values are often low,[19] but they provide early information regarding abnormal longitudinal systolic function well before any deterioration in LVEF.[6] The s′ velocity has been reported to be a predictor of myocardial perfusion defect[20] and has been shown to be useful in the detection of early abnormalities in LV in patients with coronary artery disease.[21] Therefore, in our opinion measuring the longitudinal contraction with s′ velocity is a valid parameter for assessing early cardiac systolic dysfunction in patients undergoing cardiovascular procedures. Furthermore, the ICC statistic showed that there was substantial inter-observer reliability of the s′ velocity assessments.

A previous study indicated that an s′ velocity below 8 cm/s suggests LV systolic dysfunction.[12] In the present study, at propofol concentrations of 3.0 and 4.0 μg/ml, the s′ velocity was near or below 8 cm/s during cardiovascular procedures. These observations indicate that propofol at concentrations >2.0 μg/ml during TIVA could induce deterioration of subendocardial function in patients with underlying cardiovascular diseases even in those with normal LVEF. Therefore, because patients undergoing cardiovascular procedures are usually susceptible to low BP and have a right-shift in the autoregulation of coronary blood flow, these current findings suggest that patients showing an s′ velocity near or below 8 cm/s with decreased MAP will require adequate and timely treatment. The combination of propofol as a hypnotic agent with remifentanil as an analgesic agent is the most commonly used regimen for achieving haemodynamic stability during TIVA.[22] However, remifentanil has a limited effect on myocardial contractility[23,24] and may induce hypotension with vasodilatation.[1] Therefore, a combination of remifentanil with propofol >2.0 μg/ml during TIVA may cause significant haemodynamic deterioration partly based on propofol-related longitudinal cardiac systolic dysfunction as observed in this present study.

Although there were no statistically significant decreases in MAP, HR or s′ velocity as propofol C_E increased from 0.0 to 1.0 μg/ml, BIS decreased with statistical significance. This finding is in agreement with another study where the effect of propofol on BIS was shown to be more rapid than its effect on systolic BP.[25] Therefore, it appears that at the onset of the effects of propofol on s′ velocity, its effects on MAP, HR and BIS could differ at the same C_E.

The study was conducted at induction of anaesthesia rather than under maintenance of anaesthesia to confirm the true effects of the different incremental increases of propofol C_E on the s′ velocity of the LV. If the study had been conducted under maintenance of anaesthesia, assessing the true effects of propofol C_E would have been difficult because of various confounding factors such as remifentanil, vasoactive medications and ventilation-related

Table 2. Effect-site concentration of propofol (C_E) and haemodynamic parameters in the evaluation of C_E of propofol and cardiac systolic function in patients undergoing cardiovascular procedures.

Propofol C_E, μg/ml	s′ velocity, cm/sec	MAP, mmHg	HR, bpm	BIS
0.0	9.81 ± 1.87	101 ± 14	78 ± 13	97 (96, 98)
1.0	9.65 ± 1.74	98 ± 14	79 ± 13	89 ± 4*
2.0	8.50 ± 1.71†	91 ± 12†	76 ± 12*	77 ± 8†
3.0	8.09 ± 1.63‡	82 ± 12‡	72 ± 10‡	61 ± 7‡
4.0	7.69 ± 1.71‡	74 ± 14§	68 ± 9§	43 (42, 45)§

Data are expressed as mean ± SD or median (interquartile range).
*$P < 0.05$ compared with C_E 0.0 μg/ml.
†$P < 0.05$ compared with C_E 0.0 and 1.0 μg/ml.
‡$P < 0.05$ compared with C_E 0.0, 1.0 and 2.0 μg/ml.
§$P < 0.05$ compared with C_E 0.0, 1.0, 2.0 and 3.0 μg/ml.
Data were analysed by analysis of variance on ranks for repeated measurements and Bonferroni's correction was performed if values were statistically significant.
s′ velocity, upward deflection (systolic myocardial velocity) during systole in tissue Doppler imaging; MAP, mean arterial blood pressure; HR, heart rate; BIS, bispectral index; bpm, beats per min.

preload changes. Moreover, the incremental increases of propofol C_E during maintenance of anaesthesia may have decreased the values of BIS to below the appropriate anaesthetic depth with accompanying hypotension, which would have required the addition of vasoactive agents.[3]

The Marsh and Schnider models are widely used as pharmacokinetic models for propofol.[9,26] In the present study, the modified Marsh model was used and it has a central compartment volume of 0.228 ml/kg, greater than the 4.271 of the Schnider model.[9,26] Therefore, compared with the Schnider model, the modified Marsh model requires more propofol during induction and maintenance of anaesthesia to sustain the same C_E.[9,26] The lower requirement of propofol with the Schnider model may have translated into a smaller decrement of s′ velocity. Therefore, the decline in s′ velocity may differ according to the adopted pharmacokinetic model for propofol.

The present study had several limitations. First, patients with regional wall motion abnormalities were not enrolled because it was essential to include all segments of the LV wall for precise evaluation of s′ velocity. Further studies are required to access LV contractility after propofol infusion in more diverse segments of LV. Secondly, the measurement of LVEF would have been helpful to confirm the effect of propofol on cardiac systolic function. Previous research has reported good correlation between s′ velocity and LVEF.[27,28] However, LVEF was not measured in the present study because of the risk of displacement of the echocardiographic transducer induced by frequent transducer moving in the simultaneous measurement of s′ velocity. Research has shown that transducer displacement can result in the misalignment of the angle for measuring TDI, which results in incorrect values.[29]

In conclusion, the s′ velocity decreased as propofol C_E increased from 0.0 to 4.0 μg/ml. Importantly, propofol C_E 3.0 and 4.0 μg/ml were associated with s′ velocity near or below 8 cm/s, which indicated cardiac systolic dysfunction. Therefore, although the recommended dosage for propofol is up to 4.0 μg/ml, caution should be taken when using propofol concentrations above 2.0 μg/ml during TIVA in patients with underlying cardiovascular disease.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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