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Pharmacodynamic Analysis of the Influence of Propofol on Left Ventricular Long-Axis Systolic Performance in Cardiac Surgical Patients

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ABSTRACT

Background: Propofol induced a decline in the left ventricular (LV) systolic performance in non-cardiac surgery. We tested the hypothesis that propofol decreased the LV contractile function by dose dependent manner in cardiac surgery patients.

Methods: Anesthesia was maintained with target-controlled infusions of propofol and remifentanyl in cardiac surgery patients. With a fixed effect-site concentration (C_e) of remifentanyl (20 ng/mL) after sternotomy, the C_e of propofol was adjusted to maintain a Bispectral index of 40–60 (C_e1). Mitral annular Doppler tissue image tracings and other echocardiographic variables, including end-diastolic and end-systolic volumes, stroke volume, and mitral inflow pulse wave Doppler profile at C_e1 , were recorded using transesophageal echocardiography. Echocardiographic recordings were repeated after the C_e -values of propofol were doubled and tripled at 10-minute intervals (defined as C_e2 and C_e3 , respectively). Serial changes in echocardiographic variables for each C_e of propofol were assessed using generalized linear mixed effect modeling. The pharmacodynamic relationship between the C_e of propofol and peak systolic mitral annular velocity (S_m) was analyzed by logistic regression using non-linear mixed effect modeling (NONMEM).

Results: Means of C_e1 , C_e2 , and C_e3 were 0.8, 1.6, and 2.4 $\mu\text{g/mL}$, respectively, and their means of S_m (95% confidence interval) were 9.7 (9.3–10.2), 8.7 (8.2–9.1), and 7.5 cm/sec (7.0–8.0), respectively ($P < 0.01$). C_e values of propofol and S_m showed a significant inter-correlation and predictability (intercept, 10.8; slope–1.0 in generalized mixed linear modeling; $P < 0.01$). C_e values producing 10% and 20% decline of S_m with 50%-probability were 1.4 and 2.1 $\mu\text{g/mL}$, respectively.

Conclusion: Propofol reduces LV systolic long-axis performance in a dose-dependent manner.

Trial Registration: ClinicalTrials.gov Identifier: NCT01826149

Keywords: Doppler Tissue Imaging; Propofol; Pharmacodynamics; Systolic Long-Axis Performance

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Bang JY, Kim TY. Data curation: Bang JY, Kim S. Formal analysis: Bang JY, Choi BM. Investigation: Bang JY, Kim S. Supervision: Choi BM, Kim TY. Writing - original draft: Bang JY, Choi BM. Writing - review & editing: Choi BM, Kim TY.

INTRODUCTION

Propofol has been known to induce decreases in cardiac output by vasodilation and suppressive effects on myocardial contractility through an animal study¹ and low-risk patients group.^{2,3} In our previous study, propofol induced a transient decline of peak systolic mitral annular velocity (Sm) in Doppler tissue imaging (DTI) in transthoracic echocardiography during anesthesia induction in patients undergoing non-cardiac surgery.³ Patients undergoing cardiac surgery have reduced cardiac reserve compared to the patients who underwent non-cardiac surgery. Therefore, further reduction of intraoperative cardiac performance may exert deleterious effects on patient outcome. However, it is difficult to find previous studies which investigated the dose-response effects of propofol on left ventricular (LV) systolic performance during total intravenous anesthesia employing propofol and remifentanyl in patients for cardiac surgery.

Mitral annular motion in DTI is used to evaluate global LV performance in the clinical setting and has several merits, including relatively easier, less operator- and load-dependent application.⁴⁻⁶ The Sm in DTI depicts systolic long-axis LV performance and its value showed a close relation to the degree of a systolic increase in LV pressure (dp/dt) in animal studies.^{7,8} It also showed superiority in detecting small- or minor-changes in LV systolic performance that were not noted in LV ejection fraction (LVEF) monitoring in various clinical settings.^{9,10}

Therefore, we hypothesized that intraoperative increments in propofol concentration would suppress LV systolic performance by dose dependent manner in cardiac surgery patients. In this study, we tested Sm changes during increments of propofol dosage with a fixed dose of remifentanyl during cardiac surgery in patients.

METHODS**Patients**

This study was conducted prospectively in patients who underwent elective cardiac surgery. The patients were excluded according to the following preoperative criteria: contraindications for transesophageal echocardiography (TEE), atrial fibrillation, pacemaker implantation, pericardial and infiltrative myocardial disease, infective endocarditis, ischemic heart disease, mitral annular pathology limiting its motion, regional wall motion abnormality, and LVEF < 50%. The patients who had a history of allergic reaction to anesthetic agents, including propofol and its component, remifentanyl or rocuronium, were also excluded.

Anesthetic monitoring and maintenance

Routine monitoring, including electrocardiogram, pulse oximetry, Bispectral index (BIS; Aspect Medical System Inc., Norwood, MA, USA), and infrared regional cerebral O₂ saturation, was started upon each patient's arrival at the operating room. After establishing invasive arterial pressure monitoring, anesthesia was induced and maintained with target-controlled infusion (TCI) of 2% propofol (Fresofol™; Fresenius-Kabi AG, Bad Homburg, Germany) and remifentanyl (Ultiva™; GSK Korea, Seoul, Korea). To induce anesthesia, propofol-TCI was started to achieve an effect-site concentration (C_e) of propofol of 2.0–3.0 µg/mL, bolus rocuronium 0.9 mg/kg was administered, and remifentanyl-TCI was started to achieve its plasma concentration (C_p) of 20 ng/mL for 7 minutes. Propofol and remifentanyl were administered by using a TCI pump (Orchestra™; Fresenius Kabi, Bad

Homburg vor der Höhe, Germany) using the Schnider and Minto models, respectively.^{11,12} During the increase in the C_p of remifentanyl, the C_e of propofol was gradually reduced to 0.7–1.5 $\mu\text{g}/\text{mL}$ to maintain stable hemodynamics and BIS of 40–60. With the completion of tracheal intubation, central venous and pulmonary arterial catheter were placed to monitor central venous pressure (CVP), pulmonary arterial pressure (PAP), cardiac index, and mixed venous O_2 saturation (SvO_2). A TEE probe (X7-2t™ with iE33™ echo-console; Philips, San Jose, CA, USA) was inserted and routine TEE examination was performed in accordance with the guidelines of the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists. When systolic blood pressure (BP) decreased below 80 mmHg, intravascular volume loading with hydroxyethyl starch or phenylephrine bolus with or without its infusion was applied, considering the changes in stroke volume (SV) and systemic vascular resistance. If bolus phenylephrine was required repetitively, continuous infusion of phenylephrine was started. Urine output was replaced by balanced crystalloid infusion.

Increments in the C_e of propofol and TEE image recording

After achieving a BIS of 40–60 and stable hemodynamics during the pre-bypass period, the C_e of propofol was recorded as C_{e1} . Then, three consecutive DTI tracings of the lateral mitral annular motion in the midesophageal 4-chamber view were recorded as digital images with a sweep speed of 6.67 cm/sec. The Doppler beam was properly aligned with the target tissue less than 30 degrees of angle. Pulsed-wave Doppler tracings of mitral inflow and 2-dimensional images for LVEF were also recorded in the midesophageal 4-chamber or 2-chamber view for future offline analyses. These recordings were repeated after increasing C_e to the double and triple of C_{e1} (C_{e2} and C_{e3} , respectively). All echocardiographic recordings were digitally stored during a short interruption of positive pressure ventilation by a single investigator (TK). None of the digital images of DTI tracings included patient information or recording times.

During the doubling and tripling of C_{e1} , phenylephrine infusion rate was increased to maintain a mean BP within 80%–120% of the pre-induction level. The degrees of mitral regurgitation (MR), heart rate (HR), BP, PAP, CVP, cardiac index, SvO_2 , and BIS were recorded at C_{e1} , C_{e2} , and C_{e3} .

Off-line analyses of recorded TEE images

An echocardiographer, who was not involved in the current study, exported the digitally recorded TEE images to software (QLAB™; Philips Healthcare, Bothell, WA, USA) and processed their off-line analyses of following data: S_m , peak velocity of mitral annular at relaxation (e'), and late atrial contraction (a') of DTI; transmitral peak flow velocity at early filling (E), transmitral peak flow velocity at atrial contraction (A), E/A ratio and deceleration time (DT) of the early diastolic transmitral inflow Doppler; and LV end-diastolic and end-systolic volumes (LV-EDV and LV-ESV) for calculating LVEF with modified Simpson method. The values of S_m , e' , and a' at each C_e value were measured twice, and the mean values of two measurements were referred for statistical analyses. Changes in LV-EDV were analyzed to determine the changes in LV preload.¹³ To assess the LV afterload change, changes in the effective arterial elastance were estimated by using LV end-systolic BP and SV.¹⁴

Pharmacodynamic modelling for predicting the C_e of propofol producing an S_m decline

The C_e values for reducing S_m from that at C_{e1} were determined using a pharmacodynamic modelling technique. With observation of S_m at C_{e1} , C_{e2} , and C_{e3} , “non-responses” and

“responses” were joined to 0 or 1. The occurrence of Sm decline by $\geq 10\%$ and $\geq 20\%$ from its values at C_e was considered a “response,” whereas the occurrence of a decline $< 10\%$ and $< 20\%$ was considered a “non-response.”

The pharmacodynamic relationship between C_e and Sm were analysed using logistic regression. $C_{e_{50-10\%}}$ and $C_{e_{50-20\%}}$ were defined as C_e values producing 10% and 20%

$$\text{Prob} = \frac{C_e^\gamma}{C_{e_{50}}^\gamma + C_e^\gamma}$$

decrease in Sm, respectively, with 50% probability. The relationship between the probability of response (Prob) and the C_e of propofol was analyzed using a sigmoid *E_{max}* model:

where $C_{e_{50}}$ is C_e value associated with the occurrence of the “response” with 50% probability and γ is the steepness of the C_e -vs.-response relation.

$C_{e_{95-10\%}}$, $C_{e_{95-20\%}}$ were defined as C_e values producing “response” with 95% probability.

The likelihood (L) of the observed response (R) was described by the following equation with Prob.

$$L = R \times \text{Prob} + (1 - R) \times (1 - \text{Prob})$$

The logistic regression model was fitted using NONMEM® 7 level 3 (ICON Development Solutions, Dublin, Ireland). Inter-individual random variabilities of pharmacodynamic parameters were estimated by assuming a log-normal distribution. Diagonal matrices were estimated for the various distributions of η , where η represented inter-individual random variability with a mean of zero and a variance of ω^2 . Model parameters were estimated using the option “LIKELIHOOD LAPLACE METHOD = conditional” of NONMEM.

Statistical analyses

The statistical significance of the changes in dependent variables according to an increase in the propofol concentration was assessed using generalized mixed linear modelling to handle the dependencies in repeated measurements within the same person.^{15,16} All of the dependent variables at each level of the propofol concentration were estimated using the least square means and standard error. Statistical analysis was performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). A *P* value less than 0.05 was considered statistically significant.

Ethics statement

The study protocol was reviewed and approved by Konkuk University Medical Center Institutional Review Board (KUH1160053). It was registered at the registry of Clinical Trials (ClinicalTrials.gov: NCT01826149). All subject submitted informed consent when they were recruited.

RESULTS

Thirty-eight patients undergoing elective mitral valve surgery were initially interviewed and recruited. Two were excluded due to atrial fibrillation and ischemic heart disease and 3 were

Table 1. Demographic and preoperative echocardiographic indexes (n = 33)

Variables	Value
Age, yr	50.3 ± 13.2
Men/women	26/7 (78.8/21.2)
Weight, kg	65.6 ± 9.6
BSA, kg/m ²	1.7 ± 0.2
Coexisting disease	
Hypertension	10 (30.3)
Diabetes mellitus	8 (24.2)
Chronic renal failure	5 (15.2)
Concurrent medications	
CCB	13 (39.4)
ARB	8 (24.2)
ACEI	5 (15.2)
β-blocker	10 (30.3)
Warfarin	7 (21.2)
Aspirin	4 (12.1)
Insulin	6 (18.2)
Sulfonylurea	2 (6.1)
Preoperative diagnosis for operation	
Mitral regurgitation	21 (63.6)
Mitral and tricuspid regurgitation	12 (36.4)
Preoperative transthoracic echocardiography	
LVEF, %	61.7 ± 8.9
E, cm/sec	69.5 ± 22.8
A, cm/sec	56.8 ± 26.1
E/A	1.5 ± 0.9
Diastolic performance profile	
Normal	15 (45.5)
Diastolic dysfunction grade 1	12 (36.4)
Diastolic dysfunction grade 2	6 (18.2)

Values are presented as number of patients (%) or mean ± standard deviation.

BSA = bovine serum albumin, CCB = calcium channel blocker, ARB = angiotensin receptor blocker, ACEI = angiotensin converting enzyme inhibitor, LVEF = left ventricular ejection fraction, E = peak velocity during early diastolic filling, A = peak velocity during atrial contraction.

excluded due to improper DTI alignment. Finally, recorded TEE data of 33 patients were analysed (**Table 1**).

The mean values of *Ce1*, *Ce2* and *Ce3* were 0.8 µg/mL, 1.6 µg/mL and 2.4 µg/mL, respectively (**Table 2**). During these increments, the proportion of grading in diastolic performance and the degree of MR did not show significant changes. The mean values of BIS at *Ce1*, *Ce2*, and *Ce3* were 50, 43 and 37, respectively, and their mean differences at *Ce2* vs. *Ce1* and *Ce3* vs. *Ce1* were 7.7 (95% confidence interval [CI], 5.3–10.1) and 13.2 (95% CI, 10.9–15.6), respectively. Phenylephrine infusion rates were significantly increased at *Ce2* vs. *Ce1* and *Ce3* vs. *Ce1*: mean differences were 0.03 (95% CI, 0.00–0.05) µg/kg/min and 0.07 (95% CI, 0.04–0.09) µg/kg/min, respectively.

HR, cardiac index and systemic vascular resistance index values at *Ce1*, *Ce2* and *Ce3* did not show significant changes during the increments. Although blood pressures were significantly reduced at *Ce2* vs. *Ce1* and *Ce3* vs. *Ce1*, respectively, those were well maintained within 80%–120% of the pre-induction level.

TEE data

Serial hemodynamic and echocardiographic data during the increments in the *Ce* of propofol was summarized in **Table 2**. The mean (95% CI) values of Sm were 9.7 (9.3–10.2), 8.2 (7.5–9.1) and 7.5 (7.1–8.0) at *Ce1*, *Ce2*, and *Ce3*. Sm was significantly reduced in all comparisons of *Ce2*

Table 2. Serial hemodynamic and transesophageal echocardiographic data during the increments in Ce of propofol

Variables	Ce1 ^a	Ce2 ^b	Ce3 ^c	P value
Ce, µg/mL	0.8 ± 0.1	1.6 ± 0.2	2.4 ± 0.3	< 0.01
BIS	50 (49–52)	43 (41–44)	37 (36–39)	< 0.01
HR, bpm	66 (62–70)	68 (64–72)	67 (64–71)	0.02
BP, mmHg	77 (73–81)	74 (71–78)	73 (69–77)	< 0.01
PAP	18 (17–20)	19 (17–20)	19 (18–21)	0.09
Phenylephrine infusion rate, µg/kg/min	0.04 (0.03–0.06)	0.07 (0.06–0.09)	0.11 (0.09–0.13)	< 0.01
CVP	8 (7–9)	8 (7–9)	8 (7–9)	0.09
SvO ₂ , %	81 (79–83)	82 (80–84)	81 (79–83)	0.14
Cardiac index, L/min/m ²	2.4 (2.2–2.7)	2.4 (2.2–2.7)	2.5 (2.2–2.7)	0.29
LV dimensions in the 2D image				
LV-ESV	49 (43–55)	50 (44–56)	53 (48–59)	0.01
LV-EDV	120 (111–128)	117 (108–125)	119 (110–128)	0.12
LVEF	59.6 (56.9–62.2)	57.9 (55.2–60.5)	55.7 (53.1–58.3)	< 0.01
SV	71 (66–76)	66 (62–72)	66 (61–71)	< 0.01
SVRI, dyn·s·cm ⁻⁵ ·m ²	1,767.1 (1,514.6–2,019.5)	1,753.1 (1,500.6–2,005.5)	1,668.9 (1,416.4–1,921.3)	0.25
Mitral inflow PW Doppler profile				
E, cm/sec	68 (60–76)	72 (64–79)	71 (63–78)	0.12
A, cm/sec	49 (43–56)	50 (44–57)	46 (40–53)	0.02
E/A	1.4 (1.2–1.7)	1.5 (1.3–1.7)	1.7 (1.4–1.9)	< 0.01
DT, ms	169 (149–190)	164 (144–185)	159 (138–179)	0.28
Mitral annular PW tissue Doppler parameters				
Sm, cm/sec	9.7 (9.3–10.2)	8.2 (7.5–9.1)	7.5 (7.1–8.0)	< 0.01
e', cm/sec	11.7 (10.5–12.9)	11.7 (10.5–12.9)	11.1 (9.9–12.3)	0.25
a', cm/sec	10.2 (9.0–11.4)	9.2 (8.0–10.4)	8.4 (7.2–9.6)	< 0.01
E/e'	7.0 (6.0–8.0)	7.0 (6.0–8.0)	7.3 (6.3–8.3)	0.69

Values are presented as mean ± standard deviation or mean (95% confidence interval) as appropriate.

Ce = effect-site concentration, BIS = bispectral index, HR = heart rate, BP = blood pressure, PAP = pulmonary artery pressure, CVP = central venous pressure, SvO₂ = mixed venous oxygen saturation, LV-ESV = left ventricular end-systolic volume, LV-EDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, SV = stroke volume, SVRI = systemic vascular resistance index, PW = pulsed-wave, E = peak mitral inflow velocity during early diastolic filling, A = peak mitral inflow velocity during atrial contraction, DT = deceleration time, Sm = peak systolic velocity of the mitral annulus descending toward the apex, e' = peak velocity of the mitral annulus ascending away from the apex during early relaxation, a' = peak velocity of the mitral annulus ascending away from the apex during atrial contraction.

^aCe maintaining a BIS of 40–60 with a remifentanyl concentration of 20 ng/mL; ^bCe as two-times large as Ce1; ^cCe three-times large as Ce1.

vs. Ce1, and Ce3 vs. Ce1, as shown in **Fig. 1**; the mean differences were 1.08 cm/sec (95% CI, 0.43–1.73) and 2.22 cm/sec (95% CI, 1.57–2.87). The intra-observer intra-class correlation coefficient for Sm measurements was 0.82 (95% CI, 0.74–0.88). The mean values of a' were significantly reduced in comparisons of Ce2 vs. Ce1 and Ce3 vs. Ce1: The mean changes were 1.02 cm/sec (95% CI, 0.68–2.73), and 1.80 cm/sec (95% CI, 0.1–3.51), respectively.

LVEF was significantly reduced in Ce2 vs. Ce1 and Ce3 vs. Ce1: the mean changes were 1.70% (95% CI, -2.01–5.41) and 3.85% (95% CI, 0.14–7.56) (**Fig. 1**). LV-ESV was significantly increased in Ce3 vs. Ce1 and Ce3 vs. Ce2; the mean changes were -4.2 mL (95% CI, -12.4–3.9) and -3.6 mL (95% CI, -11.71–4.62) (**Fig. 2**). SV was significantly decreased in Ce2 vs. Ce1 and Ce3 vs. Ce1: the mean changes were 3.8 mL (95% CI, -3.3–10.9) and 4.6 mL (95% CI, -2.5–11.7). However, LV-EDV, total arterial resistance and systemic vascular resistance index did not show significant changes during the increments.

While the E did not show significant changes, the A velocity was significantly reduced with the increments of propofol's Ce and E/A ratio was resultantly increased. The e', E and E/e' data showed no significant changes during the increments.

As indicated in **Table 3**, the linear regression equation predicting the changes of Sm, a' and LVEF due to an increase of Ce showed a significant correlation between Ce and Sm (intercept, 10.8; slope, -1.0; P < 0.01) as well as Ce and LVEF (intercept, 61.3; slope, -2.2; P < 0.01).

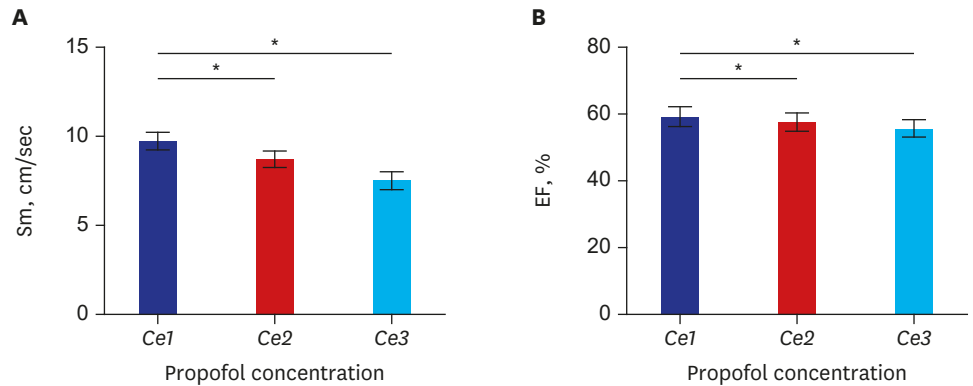


Fig. 1. Serial changes in (A) Sm and (B) EF with increments in Ce of propofol from Ce1 to Ce3. (A) As propofol concentration increases from Ce1 (0.8 ± 0.1) to Ce2 (1.6 ± 0.2) and Ce3 (2.4 ± 0.3), Sm was decreased. (B) As propofol concentration increases from Ce1 (0.8 ± 0.1) to Ce2 (1.6 ± 0.2) and Ce3 (2.4 ± 0.3), EF was decreased. The error bars indicate the standard error at each concentration.

Sm = peak systolic velocity of the mitral annulus descending toward the apex, EF = ejection fraction, Ce = effect-site concentration.

*P < 0.05.

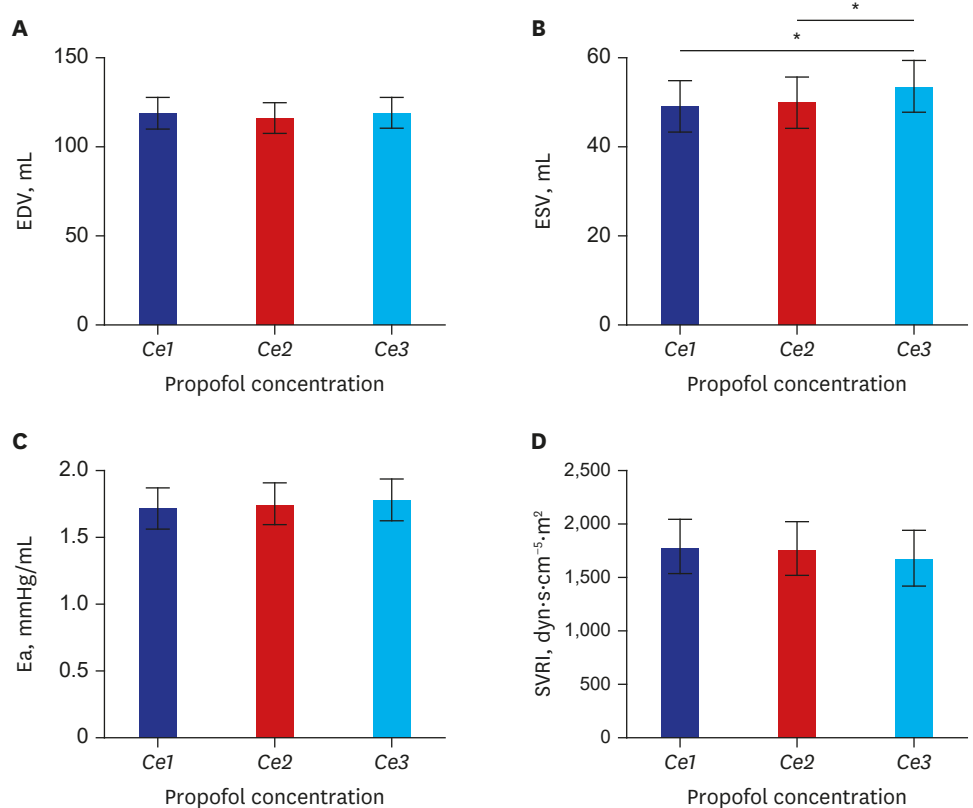


Fig. 2. Serial changes in (A) EDV, (B) ESV, (C) Ea, (D) SVRI with increments in Ce of propofol from Ce1 to Ce3. While (A) EDV and (D) SVRI was decreased as effect site of concentration of propofol increases, (B) ESV was significantly increased. (C) Ea was maintained during the entire range of propofol's effect site concentrations. The changes in EDV, EA, and SVRI according to concentration were not significant. The error bars indicates the standard error.

EDV = end diastolic volume, ESV = end systolic volume, Ea = total arterial elastance, SVRI = systemic vascular resistance index, Ce = effect-site concentration.

*P < 0.05.

Any change in the degree of MR was not observed during the TEE measurement.

Table 3. Regression equation of indicators of left ventricular systolic performance and atrial contractile function according to the changes in the effect-site concentration of propofol

Variables	Intercept (SE)	P value	Slope (SE)	P value
Sm	10.83 (0.75)	< 0.01	-1.01 (0.26)	< 0.01
a'	0.02 (0.01)	0.03	0.04 (0.01)	< 0.01
LVEF	61.34 (1.46)	< 0.01	-2.24 (0.57)	< 0.01

Values are presented as mean (SE).

SE = standard error, Sm = peak systolic velocity of the mitral annulus descending toward the apex, a' = peak velocity of the mitral annulus ascending away from the apex during atrial contraction, LVEF = left ventricular ejection fraction.

Population pharmacodynamic parameter estimates for the Ce producing a reduction in BIS and Sm values

The $C_{e50-10\%}$ and $C_{e50-20\%}$ were 1.4 and 2.1 $\mu\text{g/mL}$, respectively. Further, those values with 95% probability were 3.9 and 4.2 $\mu\text{g/mL}$, respectively (Fig. 3). The estimates of γ (the steepness of the concentration-vs.-response relation) with relative standard error and inter-individual variability presented as the percent coefficient of variation are 2.9 (43.1% and 40.1%) for a 10%-decrease in the Sm and 4.3 (46.8% and 36.1%) for a 20%-decrease in the Sm. Inter-individual random variability was modeled using a log-normal model.

DISCUSSION

We evaluated the long-axis function of LV by monitoring Sm during increments in the Ce values of propofol with a fixed concentration of remifentanyl. Our results demonstrated a propofol-induced dose-dependent decline in LV systolic long-axis function in cardiac surgical patients. While EDV, systemic vascular resistance, and total arterial elastance, which were representative of preload and afterload, were maintained, SV was decreased and ESV was

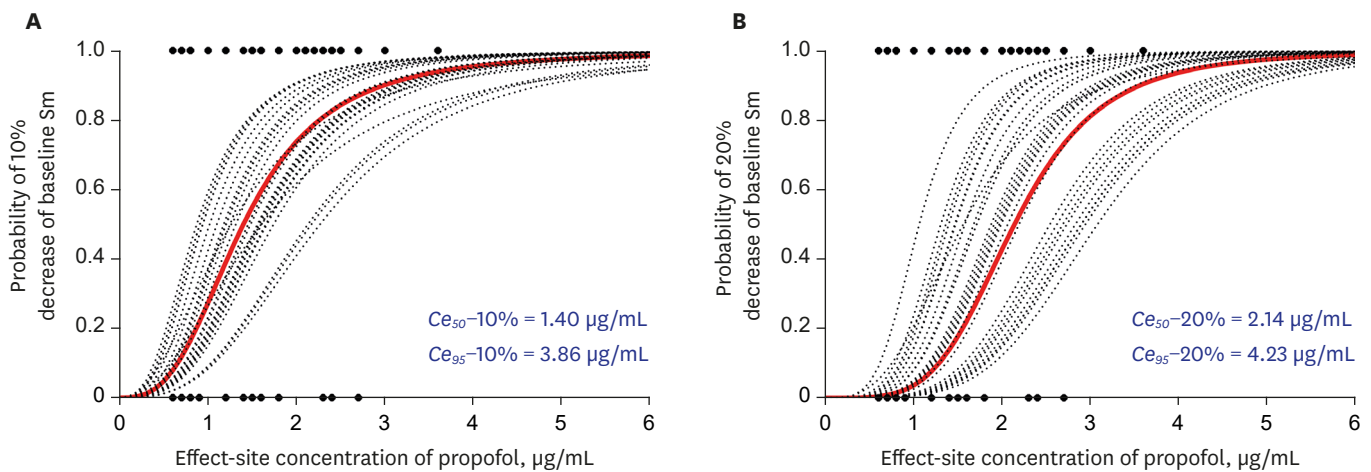


Fig. 3. The relationship between the probability of a 10% (A) and 20% (B) decrease in the Sm from baseline and the Ce of propofol. (A) The estimates of the C_{e50} ($C_{e50-10\%}$, the effect-site concentration of propofol associated with a 50% probability of a decrease in the Sm) with RSE and interindividual variability presented as % coefficient variation were 1.4 $\mu\text{g/mL}$ (13.3, 39.9%). The mean C_{e95} ($C_{e95-10\%}$, the effect-site concentration of propofol associated with a 95% probability of a decrease in the Sm) was 3.86 $\mu\text{g/mL}$ for a 10% decrease in the Sm. The estimate of γ (the steepness of the concentration-vs.-response relation) with RSE and interindividual variability presented as % coefficient variation was 2.9 (43.1, 40.1%) for a 10% decrease in the Sm. Interindividual random variability was modeled using a log-normal model. (B) The estimates of the C_{e50} ($C_{e50-20\%}$ and $C_{e95-20\%}$, the effect-site concentration of propofol associated with a 50% and 95% probability of a decrease in the Sm, each respectively) with RSE and interindividual variability presented as % coefficient variation were 2.14 $\mu\text{g/mL}$ (12.5, 42.7%). The mean C_{e95} ($C_{e95-20\%}$, the effect-site concentration of propofol associated with a 95% probability of a decrease in the Sm) was 4.23 $\mu\text{g/mL}$ for a 20% decrease in the Sm. The estimate of γ with RSE and interindividual variability presented as % coefficient variation was 4.3 (36.8, 12.5%) for a 20% decrease. Interindividual random variability was modeled using a log-normal model. RSE = relative standard error.

increased. This suggested that the decline in LV contractile function might be attributed by decrease in long-axis cardiac performance as represented with the decline with S_m , not by decreased preload or increased afterload.

The previous study showed that propofol bolus of 2 mg/kg decreased S_m measured at 1, 3 and 5 minutes after propofol administration in patients with normal LV function.^{3,17} While it was found S_m measured at the lateral annulus of the mitral valve was decreased by 26%–29% after propofol bolus administration, the dose effect of propofol was not evaluated. In this study, we confirmed propofol decreased S_m by dose dependent manner. The degree of S_m reduction at each 1.0 $\mu\text{g/mL}$ increment of propofol was 1.0 cm/sec and the predicted S_m at $C_e 0 \mu\text{g/mL}$ was 10.8 cm/sec.

S_m by DTI reflects the peak velocity of myocardial fiber shortening oriented in the longitudinal direction and is believed to give an estimation of the global systolic function of the LV with high feasibility and reproducibility.¹⁸ Of note, the predicted value of S_m at $C_e 0 \mu\text{g/mL}$ of 10.8 cm/sec in this study was greater than the S_m measured with TTE in healthy patients.¹⁹ This can be explained by the discrepancy in the measurement method, by which we monitored S_m during the anesthesia with TCI of propofol and remifentanyl. Therefore, LV afterload might be reduced by remifentanyl-induced vasodilation in all patients and systolic regurgitant flow in mitral insufficiency in half of the patients. Furthermore, S_m measured at lateral mitral annulus is higher than another site as a result of a predominance of longitudinal myocardial fibers in the LV free wall.²⁰ Although there is an angle between the direction of motion of the lateral wall and the ultrasound beam, the lateral mitral annulus is regarded as the most appropriate for quick assessment of global LV function.¹⁹

In the meantime, because S_m is not completely independent of the LV loading condition,⁶ a possible bias due to changes in the LV loading condition should be eliminated to evaluate the LV contractile performance analyzing S_m . Vasodilation, which reduces LV-preload, can be coupled with the reduced systolic performance. However, this potential bias due to vasodilation seemed to be attenuated by the appropriate increments in phenylephrine infusion in our study. Phenylephrine is a selective alpha 1 adrenoceptor agonist, which increase in afterload and venous return. In this study, considering that systemic vascular resistance index and EDV, representing afterload and preload respectively, was maintained, the significant decrease in LVEF, increase in LV-ESV and decreased S_m might be due to propofol's direct cardiac effect, rather than its indirect effect through vasodilation and LV loading condition.

S_m has been known as a more sensitive marker of global function¹⁵ and decreased S_m could predict the poor outcome.²¹ Therefore, S_m might be useful as a surrogate measure to avoid a decline in LV contractility by propofol concentration in high risk patients. We estimated C_{e50} -10% and C_{e50} -20%, which predicted a decrease in S_m by 10% and 20% while BIS value was maintained below 40. These values can be referenced in the titration of propofol concentration.

Our results showed significant declines in the a' and A velocity, which results in the increase of E/A ratio, as in a propofol-induced compromise in atrial contractile performance in the previous studies.^{3,22-26} The decline in atrial contraction may be problematic in patients with diastolic dysfunction because the role of atrial contraction is relatively increased to maintain overall diastolic performance, and the decline might contribute for reducing LV systolic

performance through “left atrial-LV coupling.”²⁵⁻²⁷ However, the absence of significant changes in the e' and E/e' might suggest preservation of LV diastolic function (early filling) during propofol increments.

Our study has several limitations. First, because our data lacks clinical outcome, it is still unclear whether the dose-dependent S_m declines from 9.7 cm/sec to 7.5 cm/sec speculated in our study was clinically relevant in terms of increasing perioperative risk and outcome. But it does not seem to be ethical to test whether decreased S_m by increased propofol concentration would lead to a bad outcome. In fact, decreased S_m has known to be associated with poor outcome in patients with heart failure, MR or ischemic heart disease.^{21,28-30} Therefore, we should try to avoid even mild suppression of S_m as far as possible.

Second, S_m is not fully independent of the changes in LV-loading condition.^{31,32} To minimize this bias, we employed DTI velocities in the lateral mitral annulus, which are more TEE compatible and less load-dependent than those in the medial annulus.³³ We also tried to keep the LV loading condition and vascular tone constant by extra-volume infusion and phenylephrine-infusion before and during our study, respectively, as partly supported by the constant degree of MR, CVP, E/e' , LV-EDV, systemic vascular resistance index and arterial elastance during the increments.

Third, associated MR could be a compounding factor for the analyses of our results related to LV loading condition. However, MR and lower LA pressure could accommodate possible changes in LV afterload. Furthermore, the absence of any changes in the degree of MR might support the constant LV loading during the increments.

Fourth, the effect of the high target C_e of remifentanyl and combined use with propofol on the contractility of myocardium should be considered. However, remifentanyl has been known to have no significant negative inotropic effect on even a failing heart.³⁴ Therefore it is less likely for the use of remifentanyl to make an influence on the conclusion.

In conclusion, propofol reduces the intraoperative S_m , indicating LV systolic long-axis performance, in a dose-dependent manner during propofol-remifentanyl anesthesia for cardiac surgery.

REFERENCES

1. Coetzee A, Fourie P, Coetzee J, Badenhorst E, Rebel A, Bolliger C, et al. Effect of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. *Anesth Analg* 1989;69(4):473-83.
[PUBMED](#)
2. Schmidt C, Roosens C, Struys M, Deryck YL, Van Nooten G, Colardyn F, et al. Contractility in humans after coronary artery surgery. *Anesthesiology* 1999;91(1):58-70.
[PUBMED](#) | [CROSSREF](#)
3. Yang HS, Song BG, Kim JY, Kim SN, Kim TY. Impact of propofol anesthesia induction on cardiac function in low-risk patients as measured by intraoperative Doppler tissue imaging. *J Am Soc Echocardiogr* 2013;26(7):727-35.
[PUBMED](#) | [CROSSREF](#)
4. Bergquist BD, Leung JM, Bellows WH. Transesophageal echocardiography in myocardial revascularization: I. Accuracy of intraoperative real-time interpretation. *Anesth Analg* 1996;82(6):1132-8.
[PUBMED](#)

5. Isaaz K, Thompson A, Ethevenot G, Cloez JL, Brembilla B, Pernot C. Doppler echocardiographic measurement of low velocity motion of the left ventricular posterior wall. *Am J Cardiol* 1989;64(1):66-75.
[PUBMED](#) | [CROSSREF](#)
6. Skubas N. Intraoperative Doppler tissue imaging is a valuable addition to cardiac anesthesiologists' armamentarium: a core review. *Anesth Analg* 2009;108(1):48-66.
[PUBMED](#) | [CROSSREF](#)
7. Tabata T, Cardon LA, Armstrong GP, Fukamach K, Takagaki M, Ochiai Y, et al. An evaluation of the use of new Doppler methods for detecting longitudinal function abnormalities in a pacing-induced heart failure model. *J Am Soc Echocardiogr* 2003;16(5):424-31.
[PUBMED](#) | [CROSSREF](#)
8. Kim DH, Kim YJ, Kim HK, Chang SA, Kim MS, Sohn DW, et al. Usefulness of mitral annulus velocity for the early detection of left ventricular dysfunction in a rat model of diabetic cardiomyopathy. *J Cardiovasc Ultrasound* 2010;18(1):6-11.
[PUBMED](#) | [CROSSREF](#)
9. Sanderson JE. Heart failure with a normal ejection fraction. *Heart* 2007;93(2):155-8.
[PUBMED](#) | [CROSSREF](#)
10. Vinereanu D, Nicolaidis E, Tweddel AC, Fraser AG. "Pure" diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. *Eur J Heart Fail* 2005;7(5):820-8.
[PUBMED](#) | [CROSSREF](#)
11. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998;88(5):1170-82.
[PUBMED](#) | [CROSSREF](#)
12. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I. Model development. *Anesthesiology* 1997;86(1):10-23.
[PUBMED](#) | [CROSSREF](#)
13. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2(5):358-67.
[PUBMED](#) | [CROSSREF](#)
14. Reichek N, Wilson J, St John Sutton M, Plappert TA, Goldberg S, Hirshfeld JW. Noninvasive determination of left ventricular end-systolic stress: validation of the method and initial application. *Circulation* 1982;65(1):99-108.
[PUBMED](#) | [CROSSREF](#)
15. Seo JS, Kim DH, Kim WJ, Song JM, Kang DH, Song JK. Peak systolic velocity of mitral annular longitudinal movement measured by pulsed tissue Doppler imaging as an index of global left ventricular contractility. *Am J Physiol Heart Circ Physiol* 2010;298(5):H1608-15.
[PUBMED](#) | [CROSSREF](#)
16. Uemura K, Kawada T, Sunagawa K, Sugimachi M. Peak systolic mitral annulus velocity reflects the status of ventricular-arterial coupling-theoretical and experimental analyses. *J Am Soc Echocardiogr* 2011;24(5):582-91.
[PUBMED](#) | [CROSSREF](#)
17. Yang HS, Kim TY, Bang S, Yu GY, Oh C, Kim SN, et al. Comparison of the impact of the anesthesia induction using thiopental and propofol on cardiac function for non-cardiac surgery. *J Cardiovasc Ultrasound* 2014;22(2):58-64.
[PUBMED](#) | [CROSSREF](#)
18. Bach DS. Quantitative Doppler tissue imaging as a correlate of left ventricular contractility. *Int J Card Imaging* 1996;12(3):191-5.
[PUBMED](#) | [CROSSREF](#)
19. Nikitin NP, Witte KK, Thackray SD, de Silva R, Clark AL, Cleland JG. Longitudinal ventricular function: normal values of atrioventricular annular and myocardial velocities measured with quantitative two-dimensional color Doppler tissue imaging. *J Am Soc Echocardiogr* 2003;16(9):906-21.
[PUBMED](#) | [CROSSREF](#)
20. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981;45(3):248-63.
[PUBMED](#) | [CROSSREF](#)

21. Agricola E, Galderisi M, Oppizzi M, Schinkel AF, Maisano F, De Bonis M, et al. Pulsed tissue Doppler imaging detects early myocardial dysfunction in asymptomatic patients with severe mitral regurgitation. *Heart* 2004;90(4):406-10.
[PUBMED](#) | [CROSSREF](#)
22. Filipovic M, Michaux I, Wang J, Hunziker P, Skarvan K, Seeberger M. Effects of sevoflurane and propofol on left ventricular diastolic function in patients with pre-existing diastolic dysfunction. *Br J Anaesth* 2007;98(1):12-8.
[PUBMED](#) | [CROSSREF](#)
23. Filipovic M, Wang J, Michaux I, Hunziker P, Skarvan K, Seeberger MD. Effects of halothane, sevoflurane and propofol on left ventricular diastolic function in humans during spontaneous and mechanical ventilation. *Br J Anaesth* 2005;94(2):186-92.
[PUBMED](#) | [CROSSREF](#)
24. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997;30(2):474-80.
[PUBMED](#) | [CROSSREF](#)
25. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J* 2008;156(6):1056-64.
[PUBMED](#) | [CROSSREF](#)
26. Khankirawatana B, Khankirawatana S, Peterson B, Mahrous H, Porter TR. Peak atrial systolic mitral annular velocity by Doppler tissue reliably predicts left atrial systolic function. *J Am Soc Echocardiogr* 2004;17(4):353-60.
[PUBMED](#) | [CROSSREF](#)
27. Manning WJ, Silverman DI, Katz SE, Riley MF, Come PC, Doherty RM, et al. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. *J Am Coll Cardiol* 1994;23(7):1535-40.
[PUBMED](#) | [CROSSREF](#)
28. Nikitin NP, Loh PH, Silva R, Ghosh J, Khaleva OY, Goode K, et al. Prognostic value of systolic mitral annular velocity measured with Doppler tissue imaging in patients with chronic heart failure caused by left ventricular systolic dysfunction. *Heart* 2006;92(6):775-9.
[PUBMED](#) | [CROSSREF](#)
29. Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. *J Am Coll Cardiol* 2003;41(5):820-6.
[PUBMED](#) | [CROSSREF](#)
30. Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. *J Hypertens* 2005;23(1):183-91.
[PUBMED](#) | [CROSSREF](#)
31. Amà R, Segers P, Roosens C, Claessens T, Verdonck P, Poelaert J. The effects of load on systolic mitral annular velocity by tissue Doppler imaging. *Anesth Analg* 2004;99(2):332-8.
[PUBMED](#)
32. Andersen NH, Terkelsen CJ, Sloth E, Poulsen SH. Influence of preload alterations on parameters of systolic left ventricular long-axis function: a Doppler tissue study. *J Am Soc Echocardiogr* 2004;17(9):941-7.
[PUBMED](#) | [CROSSREF](#)
33. Drighil A, Madias JE, Mathewson JW, El Mosalami H, El Badaoui N, Ramdani B, et al. Haemodialysis: effects of acute decrease in preload on tissue Doppler imaging indices of systolic and diastolic function of the left and right ventricles. *Eur J Echocardiogr* 2008;9(4):530-5.
[PUBMED](#) | [CROSSREF](#)
34. Ogletree ML, Sprung J, Moravec CS. Effects of remifentanyl on the contractility of failing human heart muscle. *J Cardiothorac Vasc Anesth* 2005;19(6):763-7.
[PUBMED](#) | [CROSSREF](#)