Dexmedetomidine Versus Propofol Sedation Improves Sublingual Microcirculation After Cardiac Surgery: A Randomized Controlled Trial

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Objectives: **To compare the effects of dexmedetomidine and propofol on sublingual microcirculation in patients after cardiac surgery.**

Design: **A prospective, randomized, single-blind study.**

Setting: **University hospital.**

Participants: **Adult patients undergoing elective valve surgery with cardiopulmonary bypass.**

Interventions: **On arrival in the intensive care unit (ICU), patients were assigned randomly to receive either dexmedetomidine (0.2-1.5 μg/kg/h) or propofol (5-50 μg/kg/min) with open-label titration to a target Richmond Agitation-Sedation Scale of 0 to −3.**

Measurements and Main Results: **Sublingual microcirculation was recorded using sidestream dark-field imaging at ICU admission (baseline [T1]) and 4 hours (T2) and 24 hours after ICU admission (T3). At T2, median changes in perfused small-vessel density and the De Backer score from baseline were significantly greater in the dexmedetomidine group (n = 29) than in the propofol group (n = 32) (1.3 *v* 0 mm/mm^2, p = 0.025; 0.9 *v* −0.1/mm, p = 0.005, respectively); median changes in small-vessel density and the proportion of perfused small vessels from baseline also tended to be higher in the dexmedetomidine group compared with the propofol group (1.0 *v* −0.1 mm/mm^2, p = 0.050; 2.1% *v* 0.5%, p = 0.062, respectively). At T3, there still was a trend toward greater improvements in the small vessel density, proportion of perfused small-vessels, perfused small-vessel density, and De Backer score from baseline in the dexmedetomidine group than in the propofol group.**

Conclusions: **This trial demonstrated that dexmedetomidine sedation may be better able to improve microcirculation in cardiac surgery patients during the early postoperative period compared with propofol.**

KEY WORDS: dexmedetomidine, propofol, sedation, cardiac surgery, microcirculation

MICROCIRCULATION PLAYS an important role in tissue perfusion, fluid homeostasis, and the delivery of oxygen and other nutrients.[1] Impairment of sublingual microcirculation, such as a decreased proportion and density of perfused small vessels, has been observed in cardiac surgery patients, especially in cardiopulmonary bypass (CPB) patients.[2-5] Impaired microcirculation persists for at least 24 hours after cardiac surgery.[2] Increased microcirculatory flow is associated with reduced organ failure in the early stage of critical illness.[6] Therefore, perioperative therapeutic strategies to improve microcirculation may be preferred for patients undergoing cardiac surgery with CPB.

Sedatives and analgesic medications are administered routinely to most cardiac surgery patients to reduce pain and anxiety.[7,8] Current guidelines suggest propofol and dexmedetomidine as first-line sedatives in the intensive care unit (ICU).[9] Dexmedetomidine is a highly selective alpha-$_2$ agonist that has been shown to downregulate inflammatory responses,[10-12] restore perfused small-vessel density (PSVD) in a rat model of surgical stress and pain,[13] and increase functional capillary density in an endotoxemia rodent model.[12] However, the effects of dexmedetomidine on microcirculation remain unclear in patients after cardiac surgery.

Thus, the authors designed and conducted a randomized controlled trial to test the hypothesis that dexmedetomidine attenuated sublingual microcirculatory alterations while effectively sedating mechanically ventilated patients after cardiac valve surgery with CPB compared with propofol.

METHODS

This randomized, controlled clinical trial was approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University and performed in the ICU between June and August 2015. Written informed consent was obtained from the patient or next of kin before enrollment. The study inclusion criteria were age 18 years or older, elective cardiac valve surgery with CPB, and admission to the ICU intubated and ventilated. Patients were excluded when they had at least 1 of the following characteristics on arrival in the ICU: acute severe neurologic disorder, mean arterial pressure less than 55 mmHg (despite administration of appropriate intravenous volume replacement and vasopressors), heart rate less than 50 beats per minute, grade II or III atrioventricular conduction block (unless pacemaker installed), propofol or dexmedetomidine allergy or other contraindications, insulin-dependent diabetes, or body mass index $\geq$30 kg/m^2. In addition, patients who underwent reoperation, received 2 or more sedatives after randomization, and had a sedation time $<$4 hours or $\geq$24 hours also were excluded.

All patients were administered anesthesia using similar strategies. Induction was performed with midazolam and sufentanil, and paralysis was achieved with cisatracurium. The anesthetic maintenance regimen was sevoflurane (1%-2%) and doses of propofol and sufentanil adjusted according to a desired target-controlled infusion. CPB was managed according to a standard protocol. During CPB, propofol was used for

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This trial was registered at chictr.org.cn (ChiCTR-IPR-15006611).

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sedation. After being transferred to the ICU, patients were enrolled in the study if they were expected to require sedation for more than 4 hours. Then, they were randomly assigned at a 1:1 ratio to receive sedation with either propofol or dexmedetomidine according to the random number table. The patients and the researchers who analyzed sublingual microcirculatory images were blinded to the group allocation.

During the study period, the mechanical ventilation parameters consisted of a 35% inspiratory oxygen concentration and a positive end-expiratory pressure of 3 cmH_2O. The tidal volume was adjusted to maintain partial pressure of arterial carbon dioxide at 35-to-45 mmHg; epinephrine and dobutamine were used to maintain cardiovascular stability. Sufentanil was infused continuously (usually at a rate of 0.06 μg/kg/h) for intravenous analgesia up to 48 hours postoperatively. Pain was assessed using the Critical-Care Pain Observation Tool (range 0 [no pain] to 8 [maximal pain]) or the Visual Analog Scale (range 0 [no pain] to 10 [worst pain imaginable]) before and after extubation, respectively. If the Critical-Care Pain Observation Tool score was greater than 2,[9] or if the Visual Analog Scale score was greater than 3,[14] an intravenous bolus of extra analgesic (morphine or tramadol) was given.

Dexmedetomidine or propofol was infused continuously without a loading dose. The sedation level was assessed using the Richmond Agitation-Sedation Scale (RASS), which ranged from –5 (unarousable) to 4 (combative). The assessment of the RASS score was performed every 2 hours or more often if required (eg, patient's condition changed). The sedative was titrated to maintain the RASS score between 0 and –3.[15] The maximum intravenous infusion speed of dexmedetomidine was not greater than 1.5 μg/kg/h, whereas that of propofol was not greater than 50 μg/kg/min.[9] The infusion of sedative was stopped before extubation at the discretion of the attending physicians.

Microvascular blood flow was visualized using sidestream dark-field (SDF) imaging with a 5-fold magnification lens.[16] SDF images were recorded as soon as possible after ICU admission and before the infusion of sedatives (baseline [T1]) and 4 (T2) and 24 hours after ICU admission (T3). The optical probe was applied to the sublingual mucosa after gently removing saliva with cotton swabs. Images of approximately 15-second duration were acquired from at least 5 different fields at each time point. SDF images were analyzed off-line using dedicated software (Automated Vascular Analysis 3.2; Academic Medical Center, Amsterdam, The Netherlands) by 2 investigators unaware of the origin of the video clips.

Only parameters for the small vessels (less than 20-μm diameter) were calculated.[17,18] The De Backer score was calculated as the number of small vessels crossing the lines (3 equidistant horizontal and 3 equidistant vertical lines drawn on the screen) divided by the total length of the lines.[16,17] Small-vessel density (SVD) was calculated using the software as the total small vessel length divided by the total area of the image.[16,17] The proportion of perfused small vessels (PPV) was calculated as 100 multiplied by the number of small vessels with continuous flow (normal and sluggish) divided by the total number of small vessels.[16,17] PSVD was calculated by multiplying the SVD by the PPV.[16,17] For each patient, the values obtained from 5 sites were averaged.[17] Improvement in microcirculation was represented by changes in the PSVD greater than 10% from baseline.[2]

Clinical parameters, such as temperature, heart rate, and arterial pressure, also were obtained at T1, T2, and T3. Arterial blood samples were withdrawn simultaneously, and blood gases, hemoglobin, and lactate concentrations were measured (GEM Premier 3000; Instrumentation Laboratory, Bedford, MA). The Acute Physiology and Chronic Health Evaluation II score[19] and the Sequential Organ Failure Assessment score[20] were obtained on ICU admission.

Clinical adverse events were recorded during the ICU stay, which were defined as follows: hypotension (a systolic blood pressure less than 90 mmHg or mean arterial pressure less than 65 mmHg), bradycardia (heart rate less than 60 beats/min), postoperative nausea and vomiting, and atrial fibrillation and delirium (confusion assessment method for the ICU). Intubation time (from ICU admission to the time of extubation) also was recorded.

Given that PSVD is a major parameter that reflects microcirculation,[2,3,5,12,13] PSVD at T2 was the primary endpoint in this study. Based on the preliminary study, for a power of 0.8 and a 2-sided α level of 0.05, a sample of 28 patients in each group was considered to be appropriate to detect a 10% difference of PSVD between the 2 groups at T2. Considering a compliance rate of 80%, 68 patients were enrolled in the study. Patient data were described using descriptive statistics and presented as medians (interquartile range), unless indicated otherwise. All continuous variables were assessed for normality using the Shapiro-Wilk test. Differences between groups were tested using parametric student's t test or the Mann-Whitney U test for nonparametric data. Microcirculatory and hemodynamic data over time were analyzed using repeated-measures analysis of variance. Categorical variables were compared using the Fisher exact test. SPSS, Version 16.0 for Windows (SPSS, Chicago, IL), was used for statistical analysis. A p value less than 0.05 (2-sided) was considered statistically significant.

RESULTS

A total of 174 patients who underwent cardiac surgery were assessed for eligibility (Fig 1). After 106 patients were excluded, including 38 patients who refused to participate, 68 patients were assigned randomly to the following: 34 patients received propofol and 34 patients received dexmedetomidine. In the propofol group, 2 patients were infused with sedative for more than 24 hours. In the dexmedetomidine group, 3 patients were switched to propofol due to the request of the attending physicians, 1 patient withdrew consent, and 1 patient was infused with sedative for more than 24 hours. Ultimately, 32 patients were analyzed in the propofol group and 29 patients were analyzed in the dexmedetomidine group. There were no significant differences in demographic data and baseline characteristics between the groups (Table 1).

The SVD, PPV, PSVD, and De Backer score improved over time in both groups (Table 2). However, PSVD and the De Backer score changed differently over time in the 2 groups in favor of the dexmedetomidine group (for time × group; $p = 0.048$, $p = 0.014$, respectively; Table 2). Furthermore, at T2,

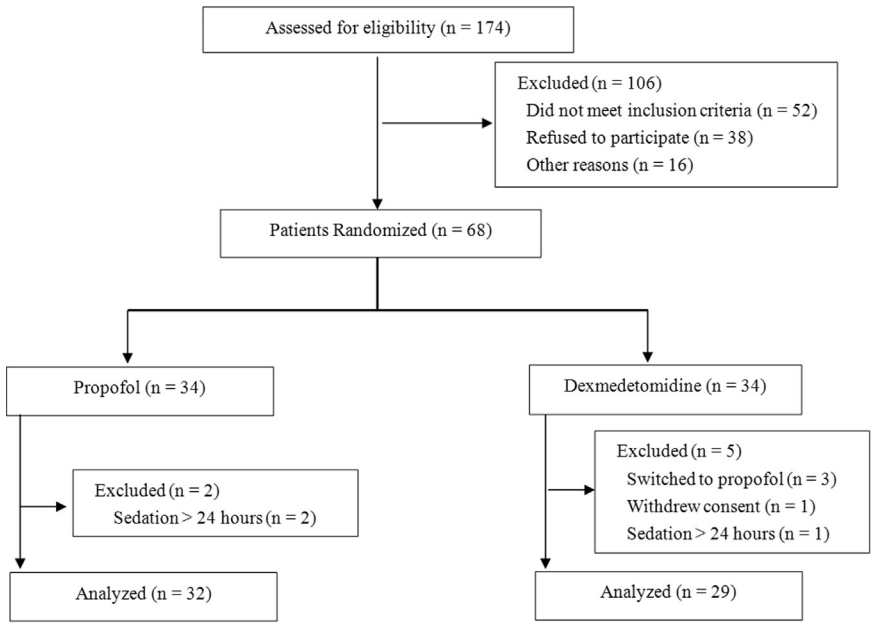

Fig 1. Flow diagram of participant selection.

changes in the PSVD and De Backer score from baseline were significantly greater in the dexmedetomidine group than in the propofol group (1.3 [–0.2 to 2.8] *v* 0 [–1.1 to 0.9] mm/mm^2, p = 0.025; 0.9 [0.2 to 2.3] *v* –0.1 [–1.3 to 1.1] /mm, p = 0.005, respectively; Fig 2); changes in SVD and PPV from baseline also tended to be higher in the dexmedetomidine group compared with the propofol group (1.0 [–0.6 to 2.6] *v* –0.1 [–1.2 to 0.9] mm/mm^2, p = 0.050; 2.1% [0.2% to 4.1%] *v* 0.5% [–1.2% to 3.3%], p = 0.062, respectively; Fig 2). In addition, at T2, an improvement in microcirculation was present in 13 (44.8%) and 5 (15.6%) patients in the dexmedetomidine and propofol groups, respectively (p = 0.023).

At T3, an improvement in microcirculation was present in 18 (62.1%) and 19 (59.4%) patients in the dexmedetomidine and propofol groups, respectively. However, at T3, there still was a trend toward greater improvements in the SVD, PPV, PSVD and De Backer score from baseline in the dexmedetomidine group than in the propofol group (2.8 [–0.4 to 4.6] *v* 2.3 [0.1 to 3.1] mm/mm^2, p = 0.213; 2.5% [1.6% to 4.7%] *v* 2.2% [0% to 3.9%], p = 0.289; 2.8 [0.1 to 5.3] *v* 2.3 [0.3 to 3.3] mm/mm^2, p = 0.187; 2.0 [0 to 3.2] *v* 1.5 [0 to 2.4] /mm, p = 0.193, respectively; Fig 2).

There were no significant differences between the 2 groups regarding clinical parameters, including the temperature, mean arterial pressure, heart rate, and hemoglobin and arterial blood lactate levels at each time point (see Table 2). Changes in the temperature, mean arterial pressure, heart rate, and hemoglobin and arterial blood lactate levels over time were similar in both groups (Table 2). Moreover, no significant difference was found in the use of epinephrine and dobutamine between the 2 groups at each time point (Table S1).

The scores for sedation and analgesia were similar in the 2 groups at each time point (Table S2). The median (interquartile range) dexmedetomidine infusion rate was 0.67 (0.38-0.76) μg/kg/h, and the median (interquartile range) propofol infusion rate was 0.90 (0.73-1.19) mg/kg/h throughout their duration (864 [681-1,072] *v* 851 [708-984] min; p = 0.355). For 24 hours postoperatively, more patients were given morphine or tramadol in the dexmedetomidine group than in the propofol group (1 [3.1%] *v* 7 [24.1%]; p = 0.022). In addition, the intubation time was similar between the dexmedetomidine group and propofol group (18.9 [17.7-22.0] *v* 21.0 [17.5-

Table 1. Baseline Data for All Patients at Enrollment

Characteristics	Propofol (n = 32)	Dexmedetomidine (n = 29)	p Value
Age, y	55 (48-62)	53 (48-63)	0.737
Female, n (%)	17 (53)	19 (66)	0.435
BMI, kg/m^2	21.2 (19.6-25.3)	23.2 (20.9-24.1)	0.237
Hypertension, n (%)	8 (25)	8 (28)	>0.999
Diabetes, n (%)	2 (6)	3 (10)	0.662
Smoking history, n (%)	10 (31)	6 (21)	0.395
Preoperative LVEF, %	62 (57-69)	62 (56-70)	0.556
NYHA class	2 (2-3)	3 (2-3)	0.380
Type of surgery, n (%)			0.348
Valve repair	3 (9)	3 (10)	
MVR	6 (19)	6 (21)	
AVR	4 (13)	6 (21)	
MVR+AVR	9 (28)	3 (10)	
MVR+TV Repair	5 (16)	9 (31)	
MVR+AVR+TV Repair	5 (16)	2 (7)	
CPB time, min	68 (54-80)	73 (60-88)	0.194
Cross-clamp time, min	46 (34-59)	51 (35-64)	0.649
APACHE II score	15 (12-18)	16 (14-18)	0.275
SOFA score	5 (5-6)	5 (5-6)	0.905

NOTE. Data presented as median (interquartile range) unless otherwise stated.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AVR, aortic valve replacement; BMI, body mass index; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; MVR, mitral valve replacement; NYHA, New York Heart Association; SOFA, Sequential Organ Failure Assessment; TV, tricuspid valve.

Table 2. Microcirculatory Variables and Clinical Parameters at Each Time Point

	T1	T2	T3
SVD, mm/mm^2			
Propofol*	14.1 (12.4-16.4)	13.8 (11.4-16.9)	15.6 (13.5-17.9)
Dexmedetomidine*	13.9 (11.1-15.7)	15.4 (12.1-17.7)	16.1 (14.3-18.9)
PSVD, mm/mm^2†			
Propofol*	13.4 (11.2-15.4)	13.4 (10.8-15.9)	15.2 (13.2-16.8)
Dexmedetomidine*	12.8 (10.4-15.0)	14.9 (11.5-17.1)	15.3 (13.8-17.9)
PPV, %			
Propofol*	95.5 (92.8-96.9)	95.4 (94.0-97.2)	96.8 (95.5-98.2)
Dexmedetomidine*	93.6 (92.3-95.4)	96.2 (94.2-97.3)	96.2 (95.1-97.9)
De Backer score, n/mm†			
Propofol*	8.9 (8.1-10.2)	8.6 (6.9-10.5)	9.8 (8.8-11.8)
Dexmedetomidine*	8.7 (7.0-9.9)	9.6 (8.1-11.5)	10.5 (9.0-11.7)
Temperature, °C			
Propofol*	36.4 (36.0-36.8)	37.5 (37.1-38.0)	37.8 (37.2-38.2)
Dexmedetomidine*	36.2 (35.7-36.4)	37.3 (36.8-37.5)	37.8 (37.3-38.0)
MAP, mmHg			
Propofol	79 (72-85)	78 (72-82)	78 (72-83)
Dexmedetomidine	76 (74-85)	79 (76-88)	81 (74-88)
Heart rate, bpm			
Propofol	94 (75-110)	95 (84-103)	95 (85-112)
Dexmedetomidine	92 (81-110)	87 (79-100)	100 (90-110)
Hemoglobin, g/dL			
Propofol	9.0 (8.2-10.4)	9.2 (8.4-10.7)	8.0 (7.5-9.2)
Dexmedetomidine	9.6 (8.4-10.7)	9.0 (8.1-10.4)	8.4 (7.5-9.8)
Serum lactate, mmol/L			
Propofol	5.1 (3.5-6.3)	3.8 (2.8-5.5)	2.1 (1.5-3.0)
Dexmedetomidine	5.5 (3.7-6.4)	4.2 (3.0-6.4)	2.3 (1.3-3.0)

NOTE. Data presented as median (interquartile range).

Abbreviations: ICU, intensive care unit; MAP, mean arterial pressure; PPV, proportion of perfused small-vessels; PSVD, perfused small-vessel density; SVD, small-vessel density; T1, ICU admission; T2, 4 hours after ICU admission; T3, 24 hours after ICU admission.

*$p < 0.05$ values over time (repeated measures analysis of variance).

†$p < 0.05$ between groups over time (repeated measures analysis of variance).

22.5] h; $p = 0.784$). The incidences of adverse events were comparable in the 2 groups (Table 3).

DISCUSSION

This was the first study to compare the effects of the first-line sedatives dexmedetomidine and propofol on changes of microcirculation in patients after cardiac surgery. This study showed that dexmedetomidine sedation contributed to an earlier and greater improvement in sublingual microcirculation in patients after valve surgery with CPB compared with propofol. Recent studies have shown that the use of dexmedetomidine during the perioperative period decreased the incidence of postoperative complications, including delirium, in patients undergoing cardiac surgery,[21-23] which was supported by the findings in the study presented here.

As a selective and potent alpha$_2$-receptor agonist, dexmedetomidine has the following dual vasomotor effects: the activation of alpha-$_2$-adrenoceptors on vascular smooth muscle cells results in vasoconstriction, whereas the activation of alpha-2-adrenoceptors on endothelial cells and inhibition of sympathetic nervous activity cause vasodilation.[12,13,24,25] The net effect of alpha-$_2$-adrenergic stimulation is usually vasodilation.[13,25,26] However, propofol administration also induces generalized vasodilation throughout the arteriolar tree.[27] In the study presented here, hypotension occurred with similar prevalence in the 2 groups, and there were no differences in the macrodynamics and use of epinephrine and dobutamine between the 2 groups. Furthermore, Miranda et al found that dexmedetomidine did not alter the mean internal arteriolar and venular diameters in the lipopolysaccharide model.[12] Therefore, the authors of this study speculated that an earlier and greater improvement in microvascular perfusion induced by dexmedetomidine might not be due to a direct vasoactive effect.

Recent studies have demonstrated that dexmedetomidine could attenuate inflammatory responses, decrease leukocyte-endothelial interactions, and produce mild hypocoagulation, which could assist in the recruitment of microcirculation.[11-13] In a surgical stress and pain rat model, PSVD of the intestinal mucosa and muscle were significantly higher in a dexmedetomidine-treated group than in the control group.[13] The benefit of dexmedetomidine on microcirculation was confirmed in an endotoxemia rodent model, and the investigators reported that dexmedetomidine decreased leukocyte-endothelial interactions and was associated with the significant attenuation of capillary perfusion deficits.[12] These results were in accordance with those of the study presented here, which demonstrated an increase of small vessels with continuous flow during dexmedetomidine infusion. In addition, studies have shown that propofol infusion for anesthesia reduced capillary blood flow in young patients who underwent transvaginal oocyte retrieval,[27] and changing the sedative infusion from

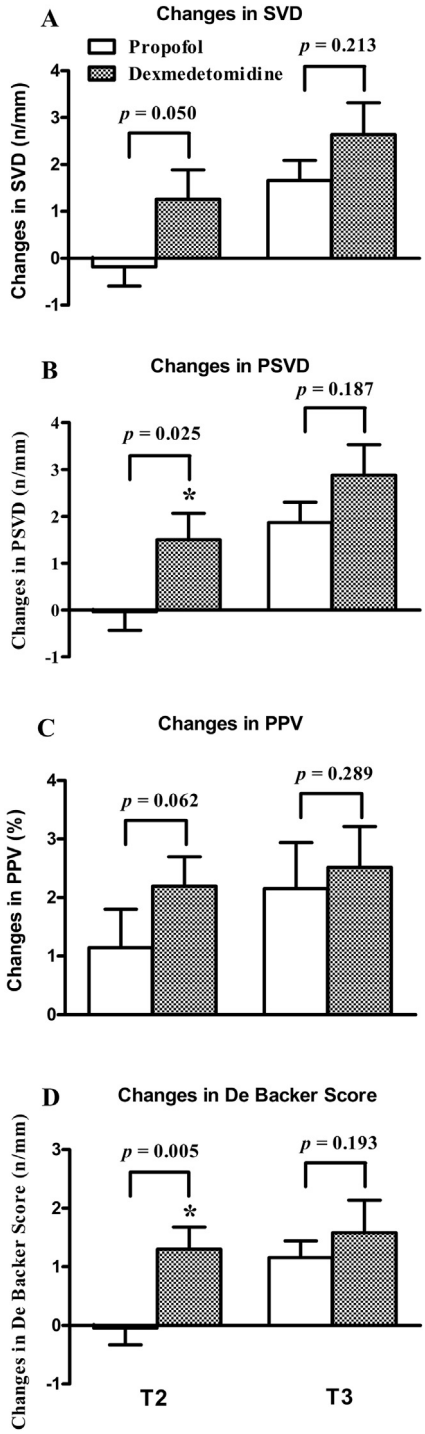

Fig 2. Changes in microcirculatory perfusion parameters from baseline to T2 and T3. The microcirculatory perfusion parameters included (A) SVD; (B) PSVD; (C) PPV; and (D) De Backer score. Propofol, sedation with propofol (n = 32); dexmedetomidine, sedation with dexmedetomidine (n = 29). *p < 0.05 compared with the propofol group. *Bar charts* demonstrate the mean; *error bars* indicate the standard error of the mean (above the mean). PPV, proportion of perfused small vessels; PSVD, perfused small-vessel density; SVD, small-vessel density; T2, 4 hours after ICU admission; T3, 24 hours after ICU admission.

Table 3. Adverse Events During ICU Stay

	Propofol (n = 32)	Dexmedetomidine (n = 29)	p Value
Hypotension	11 (34)	9 (31)	0.793
Bradycardia	1 (3)	5 (17)	0.093
Nausea/vomiting	7 (22)	3 (10)	0.307
Delirium	2 (6)	0 (0)	0.493
Atrial fibrillation	19 (59)	17 (59)	>0.999
New-onset AF	5/18 (28)	1/11 (9)	0.362

NOTE. Data presented as n (%).
Abbreviations: AF, atrial fibrillation; ICU, intensive care unit.

propofol to midazolam resulted in an improvement of the sublingual microcirculation in patients with septic shock.[28] Although propofol, which acts by potentiating gamma aminobutyric acid type-A receptors,[29] also attenuates inflammatory responses,[30,31] a clinical study showed that the levels of tumor necrosis factor-alpha, interleukin-1, and interleukin-6 were significantly higher in the propofol group than in the dexmedetomidine group during sedation for patients after abdominal surgery.[32] Proinflammatory cytokines induced endothelial-leukocyte cell interactions,[33] resulting in the obstruction of small vessels by leukocyte plugs[21] and the activation of the coagulation system, which may lead to microvascular thrombosis.[34] Cardiac surgery with CPB induced a systemic inflammatory response.[8] Dexmedetomidine lacked clinically significant anticholinergic effects and attenuated the inflammatory response of CPB.[11,23] In the study presented here, C-reactive protein and the neutrophil-lymphocyte ratio (NLR) tended to be lower in the dexmedetomidine group than that in the propofol group on the morning of the first postoperative day (Table S3). In addition, the change in NLR from ICU admission to the morning of the first postoperative day was significantly lower in the dexmedetomidine group than in the propofol group (Fig S1). The NLR is an emerging biomarker of inflammation, and elevated NLR predicts a poorer outcome in cardiovascular surgery.[35,36] Therefore, dexmedetomidine showed stronger inhibitory effects on the inflammatory response than propofol, which may have been one possible reason why changes in the PSVD and De Backer score were significantly greater in the dexmedetomidine group than in the propofol group at T2.

This study had several limitations. First, only valve surgery patients were included; thus, further studies are required to confirm whether dexmedetomidine also induces earlier improvements of microcirculation than propofol for sedation in patients after other types of major surgery. Second, the effects of the sedatives should be interpreted with the target of light-to-moderate sedation and the concomitant use of sufentanil and dobutamine. There may be interactions between the concomitant use of drugs and dexmedetomidine/propofol, and the results might have been different if different analgesics and pressors had been chosen. Third, a spontaneous improvement of the microcirculatory parameters over time after surgery in both groups may have interfered with the microcirculatory effects of dexmedetomidine and propofol. However, it may not be appropriate that the intubated and ventilated patients were not given sedatives in the early postoperative period. Finally, the sublingual area may not be representative of other vascular

beds, although some studies have shown that sublingual microcirculation could reflect intestinal microcirculation.[37,38] However, the sublingual mucosa currently is the most commonly used site for SDF measurements in humans.[39]

In summary, this was the first prospective, randomized clinical study to investigate the effects of dexmedetomidine and propofol on sublingual microcirculation in patients who underwent valve surgery. These results demonstrated that dexmedetomidine may accelerate the recovery of sublingual microcirculatory perfusion in patients after valve surgery compared with propofol. Larger randomized controlled trials should be performed to confirm the improvements in microcirculation induced by dexmedetomidine.

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APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jvca.2016.05.038.

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