



# Nebulized dexmedetomidine improves pulmonary shunt and lung mechanics during one-lung ventilation: a randomized clinical controlled trial

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## ABSTRACT

**Background.** Dexmedetomidine (Dex), a selective  $\alpha_2$ -adrenergic receptor agonist, has been previously reported to attenuate intrapulmonary shunt during one-lung ventilation (OLV) and to alleviate bronchoconstriction. However, the therapeutic effects of nebulized Dex on pulmonary shunt and lung mechanics during OLV have not been evaluated. Here we determine whether nebulized dexmedetomidine improved pulmonary shunt and lung mechanics in patients undergoing elective thoracic surgery in a prospective randomized controlled clinical trial.

**Methods.** One hundred and twenty-eight patients undergoing elective thoracoscopic surgery were included in this study and randomly divided into four groups: 0.9% saline (Placebo group), 0.5  $\mu\text{g}/\text{kg}$  (Dex<sub>0.5</sub> group), 1  $\mu\text{g}/\text{kg}$  (Dex<sub>1</sub> group) and 2  $\mu\text{g}/\text{kg}$  (Dex<sub>2</sub> group) dexmedetomidine. After bronchial intubation, patients received different nebulized doses of dexmedetomidine (0.5  $\mu\text{g}/\text{kg}$ , 1  $\mu\text{g}/\text{kg}$  and 2  $\mu\text{g}/\text{kg}$ ) or 0.9% saline placebo during two-lung ventilation (TLV). OLV was initiated 15 min after bronchial intubation. Anesthesia was maintained with intravenous infusion of cisatracurium and propofol. Bispectral Index values were maintained within 40–50 by adjusting the infusion of propofol in all groups. Arterial blood gas samples and central venous blood gas samples were taken as follows: 15 min after bronchial intubation during two-lung ventilation (TLV<sub>15</sub>), after 30 and 60 min of OLV (OLV<sub>30</sub> and OLV<sub>60</sub>, respectively) and 15 min after reinstatement of TLV (ReTLV). Dynamic compliance was also calculated at TLV<sub>15</sub>, OLV<sub>30</sub>, OLV<sub>60</sub> and ReTLV.

**Results.** Dex decreased the requirement of propofol in a dose-dependent manner ( $P = 0.000$ ). Heart rate (HR) and mean arterial pressure (MAP) displayed no significant difference among groups ( $P = 0.397$  and  $0.863$ ). Compared with the placebo group, Dex administered between 0.5 and 2  $\mu\text{g}/\text{kg}$  increased partial pressure of oxygen ( $P_{aO_2}$ ) significantly at OLV<sub>30</sub> and OLV<sub>60</sub> ( $P = 0.000$ ); however, Dex administered between 1 and 2  $\mu\text{g}/\text{kg}$  decreased pulmonary shunt fraction ( $Q_s/Q_t$ ) at OLV<sub>30</sub> and OLV<sub>60</sub> ( $P = 0.000$ ). Compared with the placebo group, there were significant increases with dynamic compliance ( $C_{dyn}$ ) after OLV in Dex<sub>0.5</sub>, Dex<sub>1</sub> and Dex<sub>2</sub> group ( $P = 0.000$ ). **Conclusions.** Nebulized dexmedetomidine improved oxygenation not only by decreasing pulmonary shunt but also by improving lung compliance during OLV, which may be effective in managing OLV.

Submitted 3 September 2019

Accepted 7 May 2020

Published 5 June 2020

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Academic editor

Paul Tulkens

Additional Information and  
Declarations can be found on  
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DOI 10.7717/peerj.9247

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**Subjects** Anesthesiology and Pain Management, Clinical Trials, Pharmacology, Respiratory Medicine

**Keywords** Nebulizer, Arterial oxygenation, Intrapulmonary shunt, Lung mechanics, One-lung ventilation, Thoracic surgery, Hypoxic pulmonary vasoconstriction, Anesthesia, Dexmedetomidine

## INTRODUCTION

Thoracic surgical procedure frequently requires one-lung ventilation (OLV) to improve the operational field of vision and access to the operative space. However, OLV is commonly associated with hypoxemia due to intrapulmonary shunt in the nonventilated collapsed lung. Hypoxemia, defined as a drop in arterial hemoglobin oxygen saturation ( $S_aO_2$ ), therefore leads to acute hypoxic pulmonary vasoconstriction (HPV) (*Cheng et al., 2017*). HPV is an important protective mechanism by which blood flow is diverted from the nonventilated lung toward a better-ventilated region, thereby maintaining adequate arterial oxygenation. However, many anesthetics, such as inhalation anesthetics and propofol, have shown positive evidence of inhibiting HPV and increasing hypoxemia (*Lumb & Slinger, 2015*).

Dexmedetomidine (Dex) is an  $\alpha_2$ -adrenoreceptor agonist that has found increasing clinical use—for lung protection, for gentle emergence from anesthesia, as an analgesic, as an adjuvant to local anesthetics during regional anesthesia, and even as a supplemental sedative/anxiolytic (*Barends et al., 2017; Nguyen et al., 2017*). In the last few years, some studies have shown that nebulized Dex administration may allow minimal systemic effects and rapid drug absorption through the respiratory mucosa (*Zanaty & El Metainy, 2015; Abdel-Ghaffar et al., 2018*). Although nebulized drug administration may be preferred through pulmonary delivery, there are currently no data describing the nebulized effects of Dex on arterial oxygenation during OLV. This study was designed to test the hypothesis that nebulized Dex may improve arterial oxygenation during OLV. Additionally, this study was meant to explore the feasibility of the application of nebulized Dex in OLV during elective thoracic surgery.

## MATERIALS & METHODS

### Study design and participants

This study was a prospective, randomized controlled clinical trial, performed in Wuxi People's Hospital in China. These researcher obtained ethical approval for the study protocol from the Medical Ethics Committee of Wuxi People's Hospital (Ethical Application Ref: KYuKS201816). This study was registered at the Chinese Ethics Committee of Registering Clinical Trials (ChiCTR1800020112). One hundred and fifty patients undergoing elective thoracoscopic surgery were approached and 128 of them completed the study (*Fig. 1*). Written informed consent was taken from all participants. The inclusion criteria were as follow: an American Society of Anesthesiologists Physical Status rating of I to II, aged 20–80 years and height 150–180 cm. Patients with the following conditions were excluded from participation: previous allergic reaction to Dex, serious cardiovascular disorders, liver or kidney dysfunction, arrhythmia, hypertensive patients,

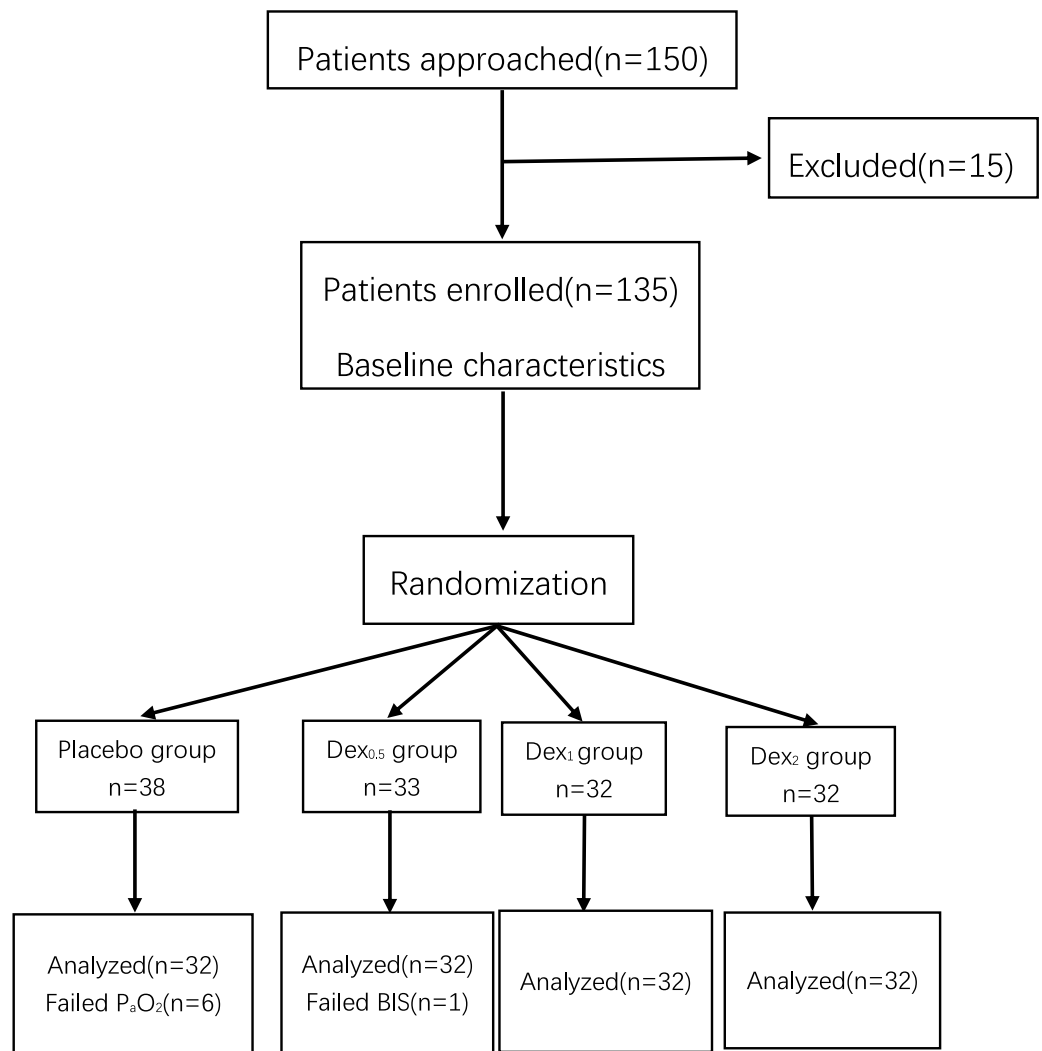
severe neuropsychiatric disease, long-term alcohol dependence, or other drug addiction. Patients were randomly allocated into four study groups: 0.9% saline (placebo group), 0.5  $\mu\text{g}/\text{kg}$  (Dex<sub>0.5</sub> group), 1  $\mu\text{g}/\text{kg}$  (Dex<sub>1</sub> group) or 2  $\mu\text{g}/\text{kg}$  (Dex<sub>2</sub> group). Randomization was performed by a computer-generated randomization table, with group allocation concealed in sealed opaque envelopes. An anesthesia nurse who was not involved in the research study was tasked with opening the envelopes 1 h prior to induction of anesthesia and preparation of dexmedetomidine (Jiangsu Hengrui Medicine Co., Ltd) or placebo in identical nebulizer with matching randomization codes. Dexmedetomidine (0.5  $\mu\text{g}/\text{kg}$ , 1  $\mu\text{g}/\text{kg}$  and 2  $\mu\text{g}/\text{kg}$ ) was diluted with 0.9% saline into 5 ml and an equal volume of 0.9% saline was used as a control in the placebo group. All preoperative and intraoperative management was performed by the same anesthesiologist who was blinded to the study drug. All the data analysis and statistical evaluation was completed by a professional assistant who was blinded to the patient group allocation.

### Study protocol

Patients were monitored by standard monitoring devices upon arrival at the operating room. A 22-gauge arterial catheter (Braun Co.) was inserted in the right or left radial artery. A central venous catheter was placed through the right internal jugular vein and therefore the tip would lie near the right atrium. After anesthesia was induced with midazolam (0.05 mg/kg), sufentanil (0.3–0.4  $\mu\text{g}/\text{kg}$ ), propofol (1.5–2 mg/kg) and cisatracurium (0.15 mg/kg), bronchial intubation was performed with a left-sided double lumen tube (size 37/35 for males and 35/33 for females), then the correct position was confirmed using fiberoptic bronchoscopy. Mechanical ventilation is used in a pressure-controlled mode for protective ventilation during the study. The ventilator parameters were as follow: inspiratory pressure ( $P_{\text{insp}}$ ) 20 cm H<sub>2</sub>O, respiratory quotient(I:E) 1:2, oxygen concentration (FO<sub>2</sub>) 100% and respiratory rate adjusted to maintain end-tidal carbon dioxide partial pressure ( $P_{\text{EtCO}_2}$ ) between 30 and 35 mmHg. 5 ml of the study drug was immediately administered via the ventilator circuit (Fig. 2) over 10 min after bronchial intubation during two-lung ventilation. OLV was initiated 15 min after bronchial intubation. During the study, anesthesia was maintained within a bispectral index (BIS) range of 40 to 50 using continuously infused propofol and intermittent administration of cisatracurium. Positive end expiratory pressure (PEEP) to the ventilated lung during OLV was applied in patients who failed to maintain adequate oxygenation ( $S_{\text{pO}_2} > 92\%$ ). Patients requiring PEEP or other recruitment maneuvers for oxygenation were excluded from final analysis. Atropine was administered if heart rate(HR) was less than 50, and ephedrine was required to maintain hemodynamic stability if mean arterial pressure (MAP) had more than 20% decrease from baseline.

### Outcome Measures

Arterial and central venous samples were obtained for blood gas analysis at four time points: 15 min after bronchial intubation during two-lung ventilation (TLV<sub>15</sub>), 30 min and 60min after OLV (OLV<sub>30</sub> and OLV<sub>60</sub>) and 15 min after reinstatement of TLV (ReTLV). Pulmonary shunt fraction ( $Q_s/Q_t$ ) was calculated using the following formula:



**Figure 1** CONSORT flow diagram among four groups. Placebo group, 0.9% saline. Dex<sub>0.5</sub> group, 0.5  $\mu\text{g}/\text{kg}$  Dex. Dex<sub>1</sub> group, 1  $\mu\text{g}/\text{kg}$  Dex. Dex<sub>2</sub> group, 2  $\mu\text{g}/\text{kg}$  Dex.

Full-size DOI: [10.7717/peerj.9247/fig-1](https://doi.org/10.7717/peerj.9247/fig-1)

$$Q_s/Q_t = (C_cO_2 - C_aO_2) / (C_cO_2 - C_vO_2) \times 100\%.$$

Whereby  $C_aO_2$  (oxygen content of arterial blood) =  $(P_aO_2 \times 0.0031) + (\text{Hb} \times 1.34 \times S_aO_2)$ .

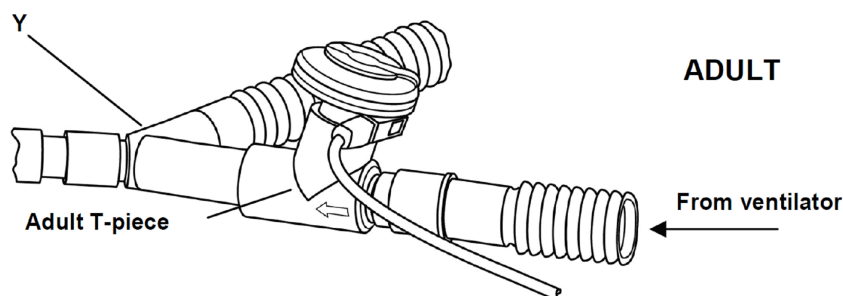
$$C_vO_2 \text{ (oxygen content of venous blood)} = (P_vO_2 \times 0.0031) + (\text{Hb} \times 1.34 \times S_vO_2).$$

$$C_cO_2 = ([F_iO_2 \times (P_B - p_{H_2O}) - (P_aCO_2/RQ)] \times 0.0031) + (\text{Hb} \times 1.34).$$

$P_B$  –Barometric pressure (760 mmHg),  $p_{H_2O}$ –47 mmHg,

Hb –Hemoglobin, RQ –Respiratory quotient (0.8).

Dynamic compliance( $C_{dyn}$ ) was obtained from the Primus ventilator at TLV<sub>15</sub>, OLV<sub>30</sub>, OLV<sub>60</sub>, and ReTLV. HR and MAP were recorded at these different times.



**Figure 2** The ventilator circuit. The vibrating mesh nebulizer (Aeroneb Solo, Aerogen, Galway, Ireland) was connected to the circuit with adult T-piece. The devices were placed in the inspiratory limb before the Y-piece.

Full-size  DOI: [10.7717/peerj.9247/fig-2](https://doi.org/10.7717/peerj.9247/fig-2)

### Statistical analysis

Sample size calculation was based on the difference of  $P_aO_2$  by 40 mmHg between groups with a power of 90% and two-sided  $\alpha$  of 0.05 by repeated measures analysis of variance (Lee et al., 2016). The enumeration data (gender, ASA and operative site) were measured by  $\chi^2$  test. Data with normal distributions were presented as mean  $\pm$  standard deviation. Intergroup comparisons were determined by LSD test. Variables with repeated measures such as  $P_aO_2$ ,  $C_{dyn}$ ,  $Q_s/Q_t$ , HR, MAP and BIS were analyzed using repeated measures analysis of variance. All statistical analyses were performed with SPSS version 23.0 (IBM Inc., Armonk, NY, USA) and  $P < 0.05$  was considered statistically significant.

## RESULTS

Here we enrolled and completed studies of total 128 patients during this study. The CONSORT flow diagram is shown in Fig. 1.

Demographic and perioperative data are detailed in Table 1. Overall, there were no differences among groups regarding age ( $P = 0.960$ ), ASA ( $P = 0.982$ ), gender ( $P = 0.919$ ), weight ( $P = 0.204$ ), height ( $P = 0.259$ ), operative site ( $P = 0.988$ ), operational time ( $P = 0.648$ ), crystalloid ( $P = 0.611$ ), colloid ( $P = 0.675$ ), urine ( $P = 0.291$ ), PH ( $P = 0.978$ ),  $P_aO_2$  ( $P = 0.547$ ),  $P_aCO_2$  ( $P = 0.791$ ), Hb ( $P = 0.934$ ),  $FEV_1$  ( $P = 0.705$ ), FVC ( $P = 0.417$ ) and  $FEV_1/FVC$  ( $P = 0.809$ ).

The values of HR, MAP and BIS weren't significantly different among groups ( $P = 0.397$ , 0.863 and 0.815, respectively). During the transition from TLV<sub>15</sub> to OLV,  $P_aO_2$  and  $C_{dyn}$  decreased and  $Q_s/Q_t$  increased significantly in the four groups ( $P = 0.000$ ). During OLV,  $P_aO_2$  and  $C_{dyn}$  had a significant increase in Dex<sub>0.5</sub>, Dex<sub>1</sub> and Dex<sub>2</sub> groups compared with the placebo group ( $P = 0.000$ ) while  $Q_s/Q_t$  decreased in the Dex<sub>1</sub> and Dex<sub>2</sub> groups compared with the placebo group ( $P = 0.000$ ).

Patients in the Dex<sub>1</sub> and Dex<sub>2</sub> group required significantly less propofol during surgery than patients in the placebo group to maintain BIS values between 40 and 50 ( $P = 0.000$ ) (Tables 2 and 3). However, the requirement of sufentanil, cisatracurium, ephedrine and atropine did not differ significantly among groups ( $P = 0.728$ , 0.204, 1.0 and 1.0, respectively) (Table 3).

**Table 1** Demographic and perioperative data ( $N = 32$ ). All data are expressed as means  $\pm$  SD.

Parameters	Groups				Significance ( $P$ )
	Placebo	Dex <sub>0.5</sub>	Dex <sub>1</sub>	Dex <sub>2</sub>	
Age(year)	55.5 $\pm$ 11.9	55.6 $\pm$ 13.0	56.9 $\pm$ 8.9	56.3 $\pm$ 12.3	0.960
ASA I/II(n)	27/5	26/6	27/5	27/5	0.982
Gender(male/female)	15/17	17/15	17/15	15/17	0.919
Weight(kg)	62.8 $\pm$ 11.4	65.0 $\pm$ 11.5	60.1 $\pm$ 9.6	60.1 $\pm$ 10.4	0.204
Height(cm)	164.4 $\pm$ 7.6	167.3 $\pm$ 7.7	165.1 $\pm$ 5.6	164.4 $\pm$ 5.2	0.259
Operative site(Right/Left)	14/18	13/19	14/18	13/19	0.988
Operational time(min)	117.9 $\pm$ 25.8	116.3 $\pm$ 25.9	112.3 $\pm$ 21.8	111.8 $\pm$ 19.0	0.648
Crystalloid(ml)	571.9 $\pm$ 172.7	521.9 $\pm$ 131.3	562.5 $\pm$ 164.1	553.1 $\pm$ 158.6	0.611
Colloid(ml)	440.6 $\pm$ 126.6	462.5 $\pm$ 100.8	435.9 $\pm$ 133.3	425.6 $\pm$ 128.4	0.675
Urine(ml)	168.1 $\pm$ 38.1	184.1 $\pm$ 43.5	168.1 $\pm$ 53.5	163.4 $\pm$ 45.6	0.291
PH	7.41 $\pm$ 0.03	7.41 $\pm$ 0.02	7.40 $\pm$ 0.03	7.40 $\pm$ 0.02	0.978
P <sub>a</sub> O <sub>2</sub> (mmHg)	84.3 $\pm$ 5.8	83.6 $\pm$ 6.3	82.9 $\pm$ 4.8	82.3 $\pm$ 6.2	0.547
P <sub>a</sub> CO <sub>2</sub> (mmHg)	35.3 $\pm$ 1.5	35.3 $\pm$ 1.5	35.2 $\pm$ 1.4	35.0 $\pm$ 1.0	0.791
Hb(mg l <sup>-1</sup> )	117.2 $\pm$ 12.0	117.2 $\pm$ 11.7	118.3 $\pm$ 12.5	118.8 $\pm$ 11.9	0.934
FEV <sub>1</sub> (%)	80.5 $\pm$ 10.3	82.0 $\pm$ 9.5	79.2 $\pm$ 10.4	80.0 $\pm$ 8.5	0.705
FVC(%)	88.2 $\pm$ 8.5	88.8 $\pm$ 7.8	86.1 $\pm$ 8.9	86.2 $\pm$ 6.9	0.417
FEV <sub>1</sub> /FVC(%)	84.3 $\pm$ 8.5	85.6 $\pm$ 8.2	83.7 $\pm$ 8.7	84.0 $\pm$ 7.5	0.809

**Notes.**

Compared with Placebo group.

\* $P < 0.05$ .ASA, American society of anesthesiologists physical status; PH, Hydrogen ion concentration; P<sub>a</sub>O<sub>2</sub>, Arterial oxygen partial pressure; P<sub>a</sub>CO<sub>2</sub>, Arterial partial pressure of carbon dioxide; Hb, Hemoglobin concentrations; FEV<sub>1</sub>, Forced expiratory volume in one second; FVC, Forced vital capacity.

## DISCUSSION

Intraoperative hypoxemia can lead to long term complications including end organ failure and increased mortality. One two-center study of a large non-cardiac surgical population estimated that one in fifteen patients experienced hypoxemia for at least 2 min and that one in sixty-four patients experienced hypoxemia for a minimum of 5 min (*Ehrenfeld et al., 2010*). The decreased arterial oxygen tension (PaO<sub>2</sub>) may be a reliable indicator of abnormal lung function and predict intraoperative hypoxemia during OLV (*Karzai & Schwarzkopf, 2009*). Anesthetics may negatively impact the hemodynamic changes that influence PaO<sub>2</sub>. For instance, isoflurane and halothane reduce HPV by up to 50% at 2 MAC and increase the shunt fraction and risk of hypoxia (*Saraswat, 2015*). Since a majority of intraoperative hypoxemia occurs during OLV, emphasis remains on the discovery and development of appropriate anesthetic agents.

Dex was applied to produce a level of sedation during the perioperative period and in mechanically ventilated patients (*Chen & Shen, 2014; Saraswat, 2015*). In a recent meta-analysis of 14 randomized controlled trials, Dex was found to increase oxygenation index in seven studies, decrease intrapulmonary shunt in five studies, decrease perioperative HR and MAP in nine studies, and reduce the concentration of the inflammatory factors TNF- $\alpha$  and IL-6 in four studies during OLV (*Huang et al., 2017*). Intravenous Dex along with isoflurane inhalation was shown to increase P<sub>a</sub>O<sub>2</sub> and significantly decrease Q<sub>s</sub>/Q<sub>t</sub>

**Table 2** Changes of hemodynamics and respiratory mechanics (N = 32). All data are expressed as means ± SD.

Parameters	Groups	TLV <sub>15min</sub>	OLV <sub>30min</sub>	OLV <sub>60min</sub>	ReTLV	P value
P <sub>a</sub> O <sub>2</sub> (mmHg)	Placebo	431.8 ± 54.3	168.6 ± 43.6	178.5 ± 41.3	402.1 ± 42.1	0.000 <sup>b</sup>
	Dex <sub>0.5</sub>	435.8 ± 44.1	217.9 ± 43.5 <sup>*</sup>	255.6 ± 47.0 <sup>*</sup>	418.7 ± 33.2	0.000
	Dex <sub>1</sub>	424.5 ± 38.7	242.5 ± 60.8 <sup>*</sup>	282.1 ± 54.6 <sup>*</sup>	405.8 ± 37.8	0.000
	Dex <sub>2</sub>	423.4 ± 53.3	262.7 ± 53.6 <sup>*</sup>	298.6 ± 38.4 <sup>*</sup>	409.1 ± 51.6	0.000
	P value	0.691	0.000	0.000	0.429	0.000 <sup>a</sup> (P = 0.000 <sup>c</sup> )
C <sub>dyn</sub> (ml/cmH <sub>2</sub> O)	Placebo	43.4 ± 7.1	21.0 ± 2.8	19.7 ± 2.8	32.4 ± 2.7	0.000
	Dex <sub>0.5</sub>	42.8 ± 6.0	26.7 ± 2.4 <sup>*</sup>	26.2 ± 2.4 <sup>*</sup>	38.7 ± 2.6 <sup>*</sup>	0.000
	Dex <sub>1</sub>	42.2 ± 5.3	26.4 ± 2.6 <sup>*</sup>	25.5 ± 2.6 <sup>*</sup>	37.8 ± 1.8 <sup>*</sup>	0.000
	Dex <sub>2</sub>	41.5 ± 4.3	26.9 ± 3.2 <sup>*</sup>	26.2 ± 2.9 <sup>*</sup>	38.5 ± 2.5 <sup>*</sup>	0.000
	P value	0.619	0.000	0.000	0.000	0.000 <sup>a</sup> (P = 0.000 <sup>c</sup> )
Q <sub>s</sub> /Q <sub>t</sub> (%)	Placebo	9.9 ± 2.2	30.4 ± 2.3	27.5 ± 1.4	9.5 ± 0.5	0.000
	Dex <sub>0.5</sub>	9.8 ± 1.2	30.0 ± 3.0	27.2 ± 2.5	9.4 ± 0.7	0.000
	Dex <sub>1</sub>	9.4 ± 2.0	24.6 ± 2.2 <sup>*</sup>	22.3 ± 3.6 <sup>*</sup>	9.4 ± 0.6	0.000
	Dex <sub>2</sub>	9.7 ± 2.3	22.6 ± 2.5 <sup>*</sup>	21.6 ± 3.1 <sup>*</sup>	9.8 ± 0.6	0.000
	P value	0.789	0.000	0.000	0.112	0.000 <sup>a</sup> (P = 0.000 <sup>c</sup> )
HR (bpm)	Placebo	68.9 ± 9.3	74.6 ± 11.4	76.0 ± 10.3	79.3 ± 10.9	0.002
	Dex <sub>0.5</sub>	70.4 ± 11.9	73.6 ± 13.2	72.8 ± 12.3	74.3 ± 13.1	0.640
	Dex <sub>1</sub>	72.1 ± 10.3	71.6 ± 11.0	71.0 ± 11.5	74.9 ± 9.7	0.478
	Dex <sub>2</sub>	68.3 ± 8.4	73.0 ± 10.0	70.3 ± 8.0	72.6 ± 9.0	0.121
	P value	0.424	0.772	0.143	0.086	0.397 <sup>a</sup> (P = 0.064 <sup>c</sup> )
MAP (mmHg)	Placebo	82.0 ± 8.2	84.1 ± 9.5	83.0 ± 9.2	92.0 ± 10.2	0.000
	Dex <sub>0.5</sub>	83.3 ± 10.6	81.5 ± 9.8	84.4 ± 8.7	88.3 ± 9.3	0.043
	Dex <sub>1</sub>	85.6 ± 18.1	84.2 ± 8.5	83.6 ± 9.3	90.0 ± 9.1	0.132
	Dex <sub>2</sub>	84.7 ± 6.8	82.2 ± 11.0	83.0 ± 9.3	90.7 ± 10.8	0.002
	P value	0.633	0.611	0.914	0.502	0.863 <sup>a</sup> (P = 0.580 <sup>c</sup> )
BIS	Placebo	45.6 ± 2.9	43.5 ± 2.2	44.1 ± 2.0	47.5 ± 2.0	0.000
	Dex <sub>0.5</sub>	45.4 ± 2.4	43.2 ± 2.4	43.9 ± 2.3	47.2 ± 1.3	0.000
	Dex <sub>1</sub>	45.6 ± 2.9	43.0 ± 2.4	44.8 ± 2.0	47.6 ± 2.0	0.000
	Dex <sub>2</sub>	45.3 ± 2.8	42.9 ± 2.2	44.9 ± 2.3	47.8 ± 2.5	0.000
	P value	0.974	0.727	0.171	0.759	0.815 <sup>a</sup> (P = 0.650 <sup>c</sup> )

**Notes.**

Compared with Placebo group.

<sup>\*</sup>P < 0.05.<sup>a</sup>P value of main effect(group).<sup>b</sup>P value of main effect(time).<sup>c</sup>P value of crossover effect.

**Table 3** Amount of anesthetic and hemodynamic agents administrated during OLV (N = 32). All data are expressed as means  $\pm$  SD.

Parameters	Groups				Significance (P)
	Placebo	Dex <sub>0.5</sub>	Dex <sub>1</sub>	Dex <sub>2</sub>	
Propofol(mg)	491.3 $\pm$ 25.6	494.5 $\pm$ 28.3	444.1 $\pm$ 20.8*	388.3 $\pm$ 23.7*	0.000
Sufentanil( $\mu$ g)	48.3 $\pm$ 6.4	47.5 $\pm$ 6.3	47.0 $\pm$ 5.3	46.8 $\pm$ 5.2	0.728
Cisatracurium(mg)	24.4 $\pm$ 1.7	24.8 $\pm$ 1.7	24.0 $\pm$ 1.4	24.0 $\pm$ 1.6	0.204
Ephedrine(mg)	0.3 $\pm$ 1.3	0.3 $\pm$ 1.2	0.3 $\pm$ 1.2	0.3 $\pm$ 1.2	1.0
Atropine(mg)	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1	1.0

**Notes.**

Compared with Placebo group.

\*P &lt; 0.05.

compared to a saline + isoflurane group in a population of adults undergoing elective thoracic surgery (Xia *et al.*, 2013), indicating its safety and feasibility during OLV.

Dex is commonly delivered intravenously but can also be administered as a nebulized premedication in uncooperative children. Inhalation of nebulized Dex is an alternative method of administration, which is related to high bioavailability of Dex (Anttila *et al.*, 2003; McCormick *et al.*, 2008). Nebulized respiratory administration may results in maximizing the surface area of absorption, less drug loss and increased clinical effectiveness (Wolfe & Braude, 2010). In pediatric populations, it has been demonstrated nebulized Dex (as a premedicant) significantly improved cannulating conditions such as parental separation, face mask acceptance and IV placement (Abdel-Ghaffar *et al.*, 2018), with no hemodynamic side-effects (Zanaty & El Metainy, 2015; Abdel-Ghaffar *et al.*, 2018). However, these studies were often applied to pediatric populations.

In the present study, we evaluated whether nebulized Dex could improve oxygenation in adult patients undergoing thoracic surgery. The major finding of this study was that nebulized Dex increased P<sub>a</sub>O<sub>2</sub> during OLV. This is consistent with the results of previous study done by Kernan *et al.* (2011) and Xia *et al.* (2013). We surmise this finding may be associated with the fact that intravenous Dex improved oxygenation and lung mechanics during OLV. Additionally, there was no marked systemic hemodynamic change in our study. This may be due to the tiny systemic effect of nebulized Dex. In contrast, Nguyen *et al.* (2017) found that intravenous Dex can cause hypotension and bradycardia. Thus, this is especially meaningful as nebulized Dex is superior to standard intravenous route.

We also found that 0.5–2  $\mu$ g/kg nebulized Dex significantly increased dynamic compliance during OLV. These results were in line with intravenous administration in chronic obstructive pulmonary disease (COPD) patients undergoing lung cancer surgery (Lee *et al.*, 2016). Similar results have been reported in a study of morbidly obese patients with restrictive lung disease undergoing bariatric surgery (Hasanin *et al.*, 2018). However, Groeben has been previously reported that inhalation of Dex caused significant bronchoconstriction in an animal study in contrast to intravenous administration (Groeben, Mitzner & Brown, 2004). This initial bronchoconstriction is because of a variety of factors. Firstly, aerosols of water generated ultrasonically to provoke bronchoconstriction in



persons without asthma (*Gonzalez et al., 1994; Groeben et al., 2000*). Secondly, the initial bronchoconstriction may result from release of inflammatory mediators on airway smooth muscle or activating reflexes mediated via afferent fibers of the vagus nerve (*Gonzalez et al., 1994; Bulut, Hirshman & Brown, 1996*). Nevertheless, subsequent bronchodilation can be demonstrated after airway was irritated by aerosolized drugs. Thus, it should be likely that Dex may directly improve oxygenation by stimulating bronchodilation to increase dynamic compliance during OLV, though this remains to be substantiated in future studies.

Another finding of this study was that the utilization of nebulized Dex significantly reduced the requirements of anesthetic, specifically propofol. This phenomenon has been previously characterized in intravenous Dex, which decreased the need of isoflurane (*Xia et al., 2013*) and propofol (*Sen et al., 2013*) during elective spinal surgery. Although bradycardia and hypotension have been reported in the adult population, patients receiving nebulized Dex did not require more atrophine and ephedrine to maintain adequate hemodynamic stability. Thus it's likely that nebulized Dex may reduce haemodynamic changes related to propofol (*Sherman & Barrick, 2019*).

Interestingly, 1–2  $\mu\text{g}/\text{kg}$  Dex reduced Qs/Qt and improved oxygenation during OLV. This may be due to a variety of factors. Firstly, the attenuation of local inflammation factors contributing to the hypoxic vasodilator effect of OLV may have been influenced by Dex as has been characterized to diminish the production of these pro-inflammatory factors (*Zhang et al., 2018; Meng et al., 2018*). Secondly, Dex may have played a direct role in pulmonary artery mechanics, promoting the occurrence of HPV by directly impacting bronchodilation (*Lee et al., 2016*). Finally, reduction in the requirement of propofol, which has been shown to attenuate HPV in a dose-dependent manner, may have contributed to decreased pulmonary shunt and improved HPV (*Huang et al., 2017*). All of the above mechanisms are based solely on pathophysiological speculations and remain to be further ascertained.

Despite the novel findings of the present study, there are several limitations to consider. Firstly, this study used central venous samples instead of mixed venous samples as pulmonary catheter placement isn't routine in thoracotomy cases at the participating hospital. However, this technique has been validated and used in many earlier studies (*Turnaoglu et al., 2001; Ozcan et al., 2007*). Secondly, both left and right thoracotomies and multiple lung pathologies were included in the study. In the future, designing a study aimed at patients with shared trauma and sided thoracotomy may bring to light more accurate results. Thirdly, studies with larger sample sizes are warranted to analyze the safety of nebulized Dex.

## CONCLUSION

Nebulized dexmedetomidine improved oxygenation not only by reducing intrapulmonary shunt but also by increasing lung compliance during OLV. This strategy simultaneously decreased the requirement of propofol without hemodynamic instability. Thus, this study demonstrated that nebulized dexmedetomidine can be used as a feasible strategy for improving oxygenation during OLV in patients undergoing thoracotomy. Nonetheless,

studies with larger sample sizes are necessary to clarify the effects and the safety of nebulized Dex used.

## ACKNOWLEDGEMENTS

The authors would like to thank the nurse anesthetists in the operating room of the Wuxi People's Hospital, Jiangsu, Republic of China, for their involvement and support.

## ADDITIONAL INFORMATION AND DECLARATIONS

### Funding

This work was supported by the Science and Technology Project Wuxi City (NO.WX18IVKN016). There was no additional external funding received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Grant Disclosures

The following grant information was disclosed by the authors:  
Science and Technology Project Wuxi City: WX18IVKN016.

### Competing Interests

The authors declare there are no competing interests.

### Author Contributions

- Bo Xu conceived and designed the experiments, performed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Hong Gao performed the experiments, prepared figures and/or tables, and approved the final draft.
- Dan Li analyzed the data, prepared figures and/or tables, and approved the final draft.
- Chunxiao Hu and Jianping Yang conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

### Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

The medical ethics committee of Wuxi People's Hospital granted ethical approval to carry out the study within its facilities (Ethical Application Ref: KYuKS201816).

### Data Availability

The following information was supplied regarding data availability:

The raw data are available in [Dataset S1](#).

### Clinical Trial Registration

The following information was supplied regarding Clinical Trial registration:

Chinese Clinical Trial Registry:ChiCTR1800020112.

## Supplemental Information

Supplemental information for this article can be found online at <http://dx.doi.org/10.7717/peerj.9247#supplemental-information>.

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