ORIGINAL ARTICLE

Effects of dexmedetomidine on oxygenation and lung mechanics in patients with moderate chronic obstructive pulmonary disease undergoing lung cancer surgery

A randomised double-blinded trial

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BACKGROUND Chronic obstructive pulmonary disease (COPD) is a risk factor that increases the incidence of postoperative cardiopulmonary morbidity and mortality after lung resection. Dexmedetomidine, a selective α_2-adrenoreceptor agonist, has been reported previously to attenuate intrapulmonary shunt during one-lung ventilation (OLV) and to alleviate bronchoconstriction.

OBJECTIVE The objective is to determine whether dexmedetomidine improves oxygenation and lung mechanics in patients with moderate COPD during lung cancer surgery.

DESIGN A randomised, double-blinded, placebo-controlled study.

SETTING Single university hospital.

PARTICIPANTS Fifty patients scheduled for video-assisted thoracoscopic surgery who had moderate COPD. Patients were randomly allocated to a control group or a Dex group ($n = 25$ each).

INTERVENTIONS In the Dex group, dexmedetomidine was given as an initial loading dose of $1.0\,\mu g\,kg^{-1}$ over 10 min followed by a maintenance dose of $0.5\,\mu g\,kg^{-1}\,h^{-1}$ during OLV while the control group was administered a comparable volume of 0.9% saline. Data were measured at 30 min (DEX-30) and 60 min (DEX-60) after dexmedetomidine or saline administration during OLV.

MAIN OUTCOME MEASURES The primary outcome was the effect of dexmedetomidine on oxygenation. The secondary outcome was the effect of dexmedetomidine administration on postoperative pulmonary complications.

RESULTS Patients in the Dex group had a significantly higher PaO_2/FiO_2 ratio (27.9 ± 5.8 vs. 22.5 ± 8.4 and 28.6 ± 5.9 vs. 21.0 ± 9.9 kPa, $P < 0.05$), significantly lower dead space ventilation (19.2 ± 8.5 vs. 24.1 ± 8.1 and 19.6 ± 6.7 vs. $25.3 \pm 7.8\%$, $P < 0.05$) and higher dynamic compliance at DEX-30 and DEX-60 ($P = 0.0001$ and $P = 0.0184$) compared with the control group. In the Dex group, the PaO_2/FiO_2 ratio in the postoperative period was significantly higher ($P = 0.022$) and the incidence of ICU admission was lower than in the control group.

CONCLUSION Dexmedetomidine administration may provide clinically relevant benefits by improving oxygenation and lung mechanics in patients with moderate COPD undergoing lung cancer surgery.

TRIAL REGISTRATION ClinicalTrial.gov identifier: NCT 02185430.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a risk factor that increases the incidence of postoperative cardiopulmonary morbidity and mortality after lung resection.[1–3] COPD is a physiological condition in which patients display airflow limitations because of narrowing of peripheral bronchioles. Decreased elastic recoil and structural changes of the small airways and alveoli cause air trapping and pulmonary hyperinflation,[4] and the

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chronic alveolar hypoxia results in medial hypertrophy of the pulmonary arteriole and structural changes, such as muscularisation.[5] In COPD patients, hypoxaemia is caused by intrapulmonary right-to-left shunt and the uneven distribution of alveolar ventilation and pulmonary perfusion. The high ventilation/perfusion area interferes with effective CO_2 elimination, possibly resulting in hypercapnia.[6,7] One-lung ventilation (OLV) aggravates the intrapulmonary shunt and dead space, whereas gravitational effects and hypoxic pulmonary vasoconstriction (HPV) act as protective mechanisms.[8,9] However, decreased pulmonary artery compliance and increased pulmonary artery stiffness are reported in early COPD without pulmonary hypertension,[10,11] and the HPV responses have been reported to be less efficient in patients with COPD.[12] Furthermore, the treatment strategies for hypoxaemia induced by OLV, such as positive end-expiratory pressure (PEEP) and alveolar recruitment, cannot be applied to COPD patients because of concern about high intrinsic PEEP development.

In addition to β-adrenoreceptors in the smooth muscle of the bronchus, α_1 and α_2-adrenoreceptors are found in the bronchial mucosa and ganglia. Bronchodilators that are currently used target the β-adrenoreceptors of the bronchial wall, as bronchodilator effects of α-adrenoreceptors have not yet been proved. Dexmedetomidine, which is a selective α_2-adrenoreceptor agonist, was reported to effectively inhibit histamine-induced bronchoconstriction in an animal study[13] and to decrease the intrapulmonary shunt during OLV in healthy patients.[14] In addition, dexmedetomidine is known to decrease pulmonary arterial pressure directly,[15] and it does not increase pulmonary arterial pressure in patients with pre-existing pulmonary hypertension.[16–18] However, whether or not dexmedetomidine can exert beneficial effects on oxygenation and lung mechanics in COPD during OLV remains unclear.

The primary object of this randomised trial was to assess the effects of dexmedetomidine on oxygenation and lung mechanics during OLV in patients with moderate COPD. The secondary end point was to assess the effects of dexmedetomidine administration on postoperative pulmonary complications.

Methods

This study received approval from the institutional review board of Severance Hospital, Yonsei University Health System, Seoul, South Korea (Ref. 4-2014-0306) in July 2014 and was registered at Clinical Trials.gov (NCT 02185430). All participants provided written informed consent before participation. Patients expected to undergo video-assisted thoracoscopic surgery for lung lobectomy were included. The inclusion criteria were as follows: age more than 40 years, American Society of Anaesthesiologists' physical status 2 or 3, a diagnosis of COPD of moderate grading, and a forced expiratory volume in 1 s (FEV_1) of at least 50% and less than 80% of predicted with the presence of a post-bronchodilator FEV_1/forced vital capacity ratio less than 0.70 in a preoperative pulmonary function test.[19] The exclusion criteria were heart failure (New York Heart Association class > II), a history of arrhythmia or treatment with antiarrhythmic drugs, bradycardia [heart rate (HR) <45 beats min^{-1}] or atrioventricular block, severe functional liver or kidney disease, obesity (body mass index >30 $kg\,m^{-2}$), restrictive lung disease and/or decreased lung diffusion capacity for carbon monoxide (DL$_{CO}$ <70%).

Enrolled patients were randomly allocated to a control (0.9% saline) group or a Dex (dexmedetomidine) group using a randomised sequence generated by a computer, and the randomisation process was centralised. A concealed envelope for random allocation was sent to the anaesthesia nurses who prepared the dexmedetomidine or saline. Therefore, the anaesthesiologist administered the drug in a blind manner. The participating anaesthetists, nurses, surgeons and patients were blinded to the treatment allocation.

Patients were monitored with standard monitoring devices upon arrival at the operating room. Anaesthesia was induced with propofol, remifentanil and rocuronium. Tracheal intubation was performed with a left-sided double-lumen tube (Broncho-Cath, Mallinckrodt, Dublin, Ireland), and the position of the double-lumen tube was confirmed with a fibre-optic bronchoscope before OLV. After induction of anaesthesia, a 20-gauge radial artery catheter was inserted, and a 7-FG central venous catheter (Arrow, Teleflex Incorporated, Wayne, PA, USA) was inserted through the right internal jugular vein. The inserted length of the central venous catheter was calculated using a height-based formula so that the tip would lie near the right atrium.[20] Anaesthesia was maintained with 1.0 to 3.0% sevoflurane, remifentanil and rocuronium. The lungs were initially ventilated in autoflow pressure-controlled ventilation mode (Primus i ventilator, Dräger[TM] Medical, Lübeck, Germany) with a tidal volume of 8 ml kg^{-1} and an inspiratory : expiratory (I : E) ratio of 1 : 2.5. During OLV, the lungs were ventilated in autoflow pressure-controlled ventilation mode with a tidal volume of 6 ml kg^{-1} and PEEP of 3 cm$H_2$0 for protective ventilation. In all patients, PEEP of 3 cm$H_2$0 was applied but discontinued if the peak airway pressure exceeded 30 mmHg. The fraction of inspired oxygen (FiO_2) was initially set at 0.6 and in cases of desaturation to SaO_2 less than 95%, FiO_2 was increased by 0.2 up to 1.0. The respiratory rate was adjusted to maintain an end-tidal CO_2 tension ($EtCO_2$) of 5 to 6 kPa. During the study, the depth of anaesthesia was adjusted to maintain a bispectral index of 40 to 60. If the bispectral index decreased below 40, the concentration of sevoflurane was reduced. The concentration of sevoflurane in exhaled gas was monitored. In the Dex group, dexmedetomidine

Fig. 1
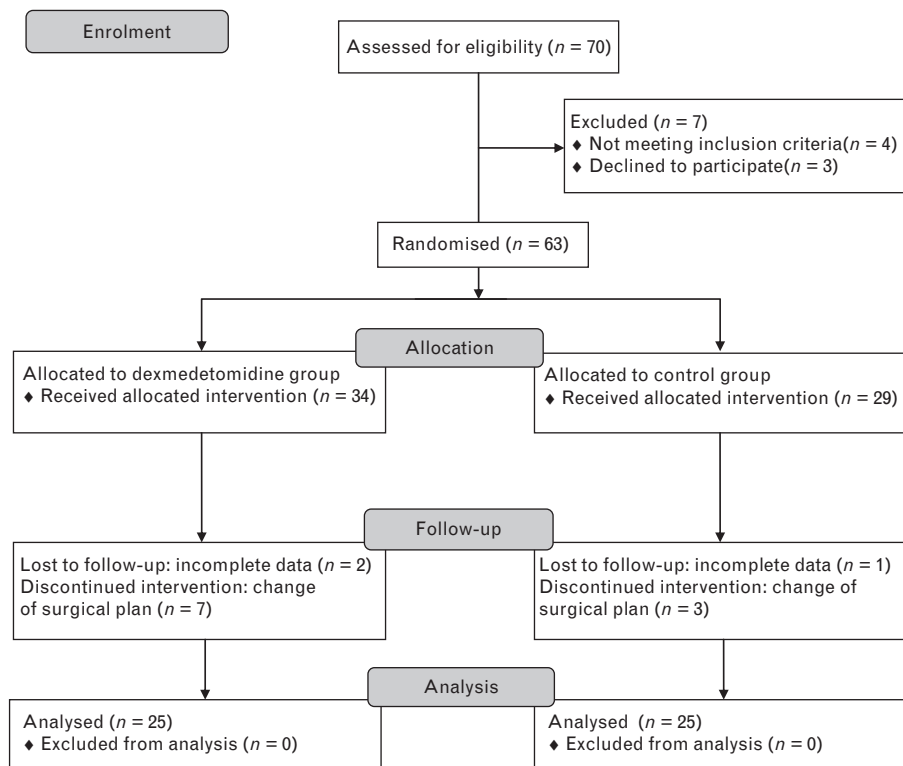
Study flow diagram.

(Precedex, Hospira, Lake Forest, IL, USA) was started once the patient was haemodynamically stable 30 min after the initiation of OLV; a bolus of $1.0\,\mu g\,kg^{-1}$ was administered over 10 min followed by a continuous infusion at $0.5\,\mu g\,kg^{-1}\,h^{-1}$ for 1 h. A comparable volume of 0.9% saline was administered to patients in the control group.

The object of this trial was to evaluate the effects of dexmedetomidine on patients with moderate COPD undergoing lung cancer surgery. The primary outcome was lung oxygenation expressed as the PaO_2/FiO_2 ratio. The secondary outcome was to assess the effects of dexmedetomidine administration on postoperative pulmonary complications. Arterial blood gases were analysed (GEM Premier 4000, Instrumentation Laboratory, Lexington, MA, USA) at three time points: 30 min after the initiation of OLV (OLV), 30 min after dexmedetomidine administration during OLV (DEX-30) and 60 min after dexmedetomidine administration during OLV (DEX-60). The respiratory variables included PaO_2/FiO_2 ratio, $PaCO_2$, $EtCO_2$, dead space ventilation, peak airway pressure, tidal volume and dynamic compliance. The physiological dead space ventilation (Vd/Vt) was calculated as follows according to the Hardman & Aitkenhead equation:[21] $Vd/Vt = 1.14 \times (PaCO_2 - EtCO_2)/PaCO_2 -$

0.005. Dynamic compliance and plateau airway pressure were obtained from the Primus i ventilator. Dynamic compliance was automatically calculated as tidal volume/ (plateau airway pressure – PEEP). The haemodynamic measurements included HR and systolic and diastolic blood pressures. Vasoactive drugs, such as ephedrine, were administered if the mean arterial pressure decreased by more than 20% from baseline arterial pressure, and atropine was administered if HR decreased to less than 45 beats min^{-1}. If the SaO_2 measured by pulse oximetry decreased to less than 90% during OLV, two-lung ventilation was reinstuted, and the event was recorded. The double-lumen tube was removed after the end of surgery.

To evaluate the secondary end point of pulmonary complications, respiratory rate and PaO_2/FiO_2 ratio were recorded 20 min after arrival at the post-anaesthetic care unit (PACU), and incidences of postoperative atelectasis, pneumonia and acute lung injury (ALI) were assessed for 72 h. In the PACU, if the patient showed signs of dyspnoea with a concurrent PaO_2/FiO_2 ratio less than 40 kPa, the patient required ICU admission. ALI was defined as the following: PaO_2/FiO_2 ratio less than 40 kPa (300 mmHg); diffuse pulmonary infiltration at 72 h; exclusion of hydrostatic pulmonary oedema because of other primary causes, including cardiac insufficiency or fluid overload.[22]

Statistical analysis

The primary outcome was lung oxygenation expressed by PaO_2/FiO_2 ratio during OLV. A previous study[23] showed that the mean $\pm$ SD value of PaO_2/FiO_2 ratio during OLV in patients with COPD was 22.7 ± 7.0 kPa. A PaO_2/FiO_2 ratio difference of 6.7 kPa between the two groups is considered to be significant. We calculated that a sample size of 23 patients was required in each group at a power of 90%, with a two-sided significance level of 0.05 by an independent t-test. To account for a 10% dropout rate, we included 25 patients in each group. Results are expressed as mean $\pm$ SD or median (IQR). Adjusted odds ratios (OR) and 95% confidence intervals (CIs) were calculated for independent variables. Intergroup comparisons at each time point were determined by unpaired t-tests, Mann–Whitney U-tests and χ^2 or Fisher exact tests. Variables with repeated measures were analysed using a linear mixed model with patient indicator as a random effect and group, time, and group-by-time as fixed effects. The statistical analyses were performed with SPSS 20.0 software (IBM Corporation, Armonk, NY, USA), and P values less than 0.05 were considered statistically significant.

Results

Seventy patients were determined to be eligible for this study, but four patients were excluded at initial screening and three patients declined to participate. Of the 63 patients, 13 were excluded from the study because of incomplete data and/or changes of surgical plan. Data from 25 patients in each group were analysed (Fig. 1). There were no differences between groups regarding baseline characteristics. The frequency of ephedrine administration was significantly greater in the Dex group (Table 1).

Intraoperative data are shown in Table 2. In comparison with the control group, there were significant haemodynamic changes in patients in the Dex group. HR at DEX-30 and DEX-60 was significantly lower compared with values at the same times in the control group ($P < 0.001$). In addition, mean blood pressure was significantly lower in the Dex group than in the control group ($P < 0.05$). The end-tidal concentrations of sevoflurane were similar in the two groups.

Results of blood gas analysis and lung mechanics are shown in Fig. 2 and Table 2. The PaO_2/FiO_2 ratio was significantly higher at DEX-30 and DEX-60 in the Dex group compared with the control group (27.9 ± 5.8 vs. 22.5 ± 8.4 and 28.6 ± 5.9 vs. 21.0 ± 9.9 kPa, $P = 0.026$ and 0.009). In the Dex group, dead space ventilation at DEX-30 and DEX-60 was significantly lower compared with the control group (19.2 ± 8.5 vs. 24.1 ± 8.1 and 19.6 ± 6.7 vs. $25.3 \pm 7.8\%$, $P = 0.046$ and 0.013). Dynamic compliance was higher at DEX-30 and DEX-60 in the Dex group compared with the control group. Plateau airway

Table 1 Patients' characteristics and operative data

	Dex group (n = 25)	Control group (n = 25)
Age (years)	68.4 ± 6.4	69.4 ± 8.7
Sex (M/F)	12/13	11/14
Height (cm)	162.9 ± 6.9	162.3 ± 8.4
Weight (kg)	60.8 ± 8.9	61.3 ± 8.9
BMI (kg m^{-2})	22.3 ± 2.7	22.7 ± 2.1
ASA physical status, 2/3	11/14	12/3
Hypertension	10	11
Cardiovascular medication		
RAAS inhibitor	8	8
Calcium channel blocker	1	2
β-adrenergic antagonists	0	1
Furosemide	2	2
Smoking		
Ex-smoker/current smoker	11/12	14/10
Smoking index, pack-years	36.7 ± 27.1	35.8 ± 28.9
Non-smoker	2	1
Medication		
Inhaled corticosteroid	42.7%	39.5%
Oral corticosteroid	18.6%	14.3%
Inhaled bronchodilator	21.3%	17.9%
Oral bronchodilator	33.6%	34.2%
Muscarinic antagonists	3.7%	3.2%
Preoperative SpO$_2$, %	93.8 ± 1.2	94.1 ± 1.3
Preoperative spirometry		
FEV$_1$, % predicted	60.8 ± 5.2	61.4 ± 4.1
FVC, % predicted	82.7 ± 8.6	83.1 ± 7.2
FEV$_1$/FVC, %	55.9 ± 3.2	56.1 ± 5.7
FEF$_{25-75\%}$, l s^{-1}	26.4 ± 18.9	27.1 ± 19.3
FEF$_{50\%}$, l s^{-1}	18.9 ± 11.3	19.3 ± 12.7
DLco, % predicted	93.6 ± 8.2	92.3 ± 7.6
Intraoperative data		
Anaesthesia time (min)	193.6 ± 24.6	189.7 ± 44.1
Operation time (min)	163.8 ± 39.4	158.1 ± 33.2
OLV time (min)	125.6 ± 37.1	124.7 ± 41.2
Fluid intake (ml)	791.4 ± 92.3	813.2 ± 79.5
Urine output (ml)	274.5 ± 132.6	354.6 ± 132.7
Estimated blood loss (ml)	122.4 ± 55.6	125.6 ± 84.7
Number receiving ephedrine	9*	1
Right/left lobectomy	17/8	16/9
Right upper lobe	8	5
Right middle lobe	2	5
Right lower lobe	7	6
Left upper lobe	4	6
Left lower lobe	4	3

Values are mean $\pm$ SD, number or percentage of patients. ASA, American Society of Anesthesiologists; DLco, diffusion capacity of lung for carbon monoxide; FEF$_{25-75\%}$, forced expiratory volume between 25 and 75% of the FVC; FEF$_{50\%}$, forced expiratory volume 50% of the FVC; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; OLV, one-lung ventilation; RAAS, renin–angiotensin–aldosterone system; SpO$_2$, oxygen saturation (pulse oximetry). * $P < 0.05$ vs. control group.

pressure was significantly lower in the Dex group at DEX-30 and DEX-60.

Postoperative data are shown in Table 3. In the PACU, PaO_2/FiO_2 ratio was significantly higher in the Dex group than in the control group. Seven patients in the control group had episodes in which SaO_2 was less than 95% and PaO_2/FiO_2 ratio was less than 40 kPa while breathing room air, eventually resulting in respiratory care in the ICU, with one patient ultimately diagnosed with ALI. In comparison, only one patient in the Dex group required respiratory care in the ICU after lung

Table 2 Haemodynamic and respiratory changes in 50 patients with moderate chronic obstructive pulmonary disease during one-lung ventilation

	Dex group ($n = 25$)	Control group ($n = 25$)	$P_{\text{Group} \times \text{Time}}$
Heart rate (beats min^{-1})			<0.001
OLV	76.6 ± 7.6	81.1 ± 11.6	
DEX-30	63.2 ± 9.8*,**	76.4 ± 8.3	
DEX-60	58.8 ± 6.0*,**	77.0 ± 8.5	
MBP (mmHg)			0.014
OLV	84.8 ± 13.6	81.1 ± 12.1	
DEX-30	70.7 ± 10.9*,**	82.2 ± 6.3	
DEX-60	68.9 ± 9.5*,**	76.5 ± 5.1	
Et SEVO (vol%)			0.078
OLV	2.0 ± 0.5	2.0 ± 0.4	
DEX-30	1.8 ± 0.2	2.0 ± 0.4	
DEX-60	1.9 ± 0.2	2.2 ± 0.4	
BIS			0.022
OLV	56.9 ± 8.9	54.6 ± 6.6	
DEX-30	41.5 ± 5.5*,**	53.6 ± 8.6	
DEX-60	40.2 ± 7.3*,**	52.5 ± 5.8	
PaCO$_2$ (kPa)			0.027
OLV	6.2 ± 0.3	6.1 ± 0.3	
DEX-30	5.6 ± 0.3*,**	5.9 ± 0.5	
DEX-60	5.7 ± 0.3*,**	6.1 ± 0.6	
P$_{\text{peak}}$ (cmH$_2$O)			0.001
OLV	22.3 ± 3.9	22.5 ± 4.9	
DEX-30	18.2 ± 3.2*,**	23.0 ± 4.1	
DEX-60	18.2 ± 2.7*,**	21.7 ± 4.3	
Compliance (ml cmH$_2$O^{-1})			0.018
OLV	19.5 ± 4.9	19.2 ± 5.2	
DEX-30	22.5 ± 3.5*,**	17.7 ± 3.4	
DEX-60	21.4 ± 4.2*,**	18.1 ± 4.6	

Values are mean ± SD. BIS, bispectral index; Compliance, dynamic compliance; Control, control group; Dex, dexmedetomidine group; DEX-30, 30 min after dexmedetomidine administration during OLV; DEX-60, 60 min after dexmedetomidine administration during OLV; Et SEVO, concentration of sevoflurane in exhaled gas; MBP, mean blood pressure; OLV, 30 min after initiation of OLV; PaCO$_2$, arterial carbon dioxide tension; P$_{\text{peak}}$, peak airway pressure. *$P < 0.05$ versus Control group. **$P < 0.05$ versus OLV within the same group.

Fig. 2
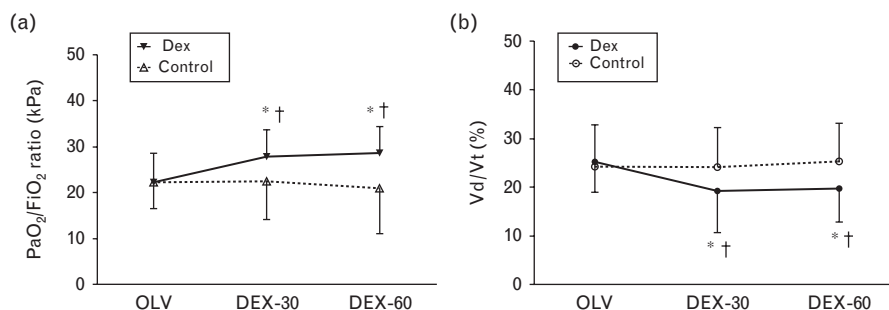
Respiratory changes in 50 patients with moderate COPD during OLV. (a) PaO$_2$/FiO$_2$ ratio, (b) deadspace ventilation (Vd/Vt). Data are mean with error bars showing SD. *$P < 0.05$ versus OLV, †$P < 0.05$ vs. control group. COPD, chronic obstructive pulmonary disease; Dex, dexmedetomidine group; Control, control group; OLV, 30 min after initiation of OLV; DEX-30, 30 min after dexmedetomidine administration during OLV; DEX-60, 60 min after dexmedetomidine administration during OLV; OLV, one-lung ventilation; Vd, dead space volume; Vt, tidal volume.

Table 3 Postoperative outcome of 50 patients with moderate chronic obstructive pulmonary disease undergoing lung cancer surgery

	Dex group ($n = 25$)	Control group ($n = 25$)	P	OR
PaO$_2$/FiO$_2$ ratio at PACU (kPa)	47.5 ± 7.1*	42.2 ± 5.9	0.022	
Need for ICU stay	1	7	0.049	9.33 (1.05 to 82.78)
Atelectasis	0	4	0.110	10.67 (0.54 to 209.65)
Length of hospital stay (days)	6.5 (5 to 10)	7.1 (6 to 11)	0.102	
Focal lung infiltration	1	2	>0.99	2.09 (0.18 to 24.61)
ALI	0	1	>0.99	3.12 (0.12 to 80.39)

Values are mean ± SD, number of patients, median (IQR) OR (95% CI). ALI, acute lung injury; Dex, dexmedetomidine; OR, odds ratio; PACU, post-anaesthetic care unit. *$P < 0.05$ vs. control group.

surgery. Patients in the Dex group had fewer incidences of atelectasis (Dex group 0%, control group 16%), focal lung infiltration (Dex group 4%, control group 8%). The duration of hospital stay did not differ between groups.

Discussion

This randomised trial assessed the effects of dexmedetomidine on oxygenation and lung mechanics of patients with moderate COPD undergoing lung cancer surgery. Dexmedetomidine improved oxygenation by decreasing dead space ventilation and dynamic compliance in patients with moderate COPD during the surgery, with significantly higher postoperative PaO_2/FiO_2 ratios and fewer pulmonary complications.

High ventilation/perfusion mismatch, which is caused by luminal narrowing of pulmonary arterioles and air-trapping hyperinflation, is considered the cause of hypoxaemia and hypercapnia in COPD.[6] In patients with COPD, the response to HPV does not activate effectively because of the remodelled pulmonary vascular structure and altered pulmonary vascular reactivity.[24] Furthermore, even in patients with early COPD without coexisting pulmonary hypertension, decreased pulmonary vascular resistance and increased pulmonary artery stiffness can possibly inhibit the activation of HPV.[11] According to the global initiative for [chronic obstructive] lung disease classification,[19] COPD is assessed as moderate when FEV_1 is at least 50%, and 80% or less of predicted, and severe if FEV_1 is more than 30%, and 50% or less of predicted with a post-bronchodilator FEV_1/ forced vital capacity ratio less than 0.70.

Previous studies of COPD have focused on hyperinflation and intrinsic PEEP because of air trapping during OLV in patients with severe COPD.[25,26] Our results revealed that the PaO_2/FiO_2 ratio in the control group was comparable with that of previously reported PaO_2/FiO_2 ratios in COPD patients during OLV.[23,25,26] However, there is controversy in the literature regarding the results of some studies which have claimed significantly higher PaO_2/FiO_2 ratios than we found.[27] Furthermore, there is a continuing dispute over intrinsic PEEP and oxygenation during OLV in COPD patients. Although Bardoczky *et al.*,[26] assert that intrinsic PEEP and oxygenation have a negative correlation, other views have been expressed by, for example, Aschkenasy *et al.*,[27] who stated that intrinsic PEEP may delay events of hypoxaemia in severe COPD patients when compared with healthy patients. Some authors have explained that intrinsic PEEP caused by the hyperinflation of ventilated lungs in patients with severe COPD increases the functional residual capacity and improves oxygenation during OLV.[27,28] However, they did not evaluate the statistical difference.[28] In light of this, Michelet *et al.*[23] insisted that moderate to severe COPD patients had better PaO_2/FiO_2 ratios than healthy patients during OLV. This hypothesis was based on the idea that high intrinsic PEEP could induce more entrapped lung volume in severe COPD. In our study, intrinsic PEEP rarely occurred during OLV. In addition, Yokota *et al.*[29] could not confirm the correlations between intrinsic PEEP and oxygenation, and preoperative forced expiratory volume and oxygenation have not been shown to correlate during OLV.[30] There are larger numbers of patients with mild to moderate COPD than severe COPD.[31,32] Thus, further studies are required to explore the physiological consequences of mild to moderate COPD during OLV.

In this study, dexmedetomidine administration decreased dead space ventilation and improved dynamic compliance and oxygenation. Dexmedetomidine has been reported to have a bronchodilator effect in histamine-induced bronchoconstriction when it was administered intravenously in an animal study,[13] but no clinical studies have confirmed this effect. Some authors have found that dexmedetomidine improves oxygenation and respiratory dynamics during OLV in healthy patients.[14,33] They suggested that a sparing effect of the inhalational agent by dexmedetomidine administration ameliorated HPV inhibition or increased perfusion in the ventilated lung by vasodilatation. However, the concentrations of sevoflurane were similar in both groups in the present study, and it seems more likely that dexmedetomidine affects lung mechanics directly in COPD to increase the threshold of hypoxaemia during OLV, rather than having an inhalation anaesthetic-sparing effect.

There is limited data about how dexmedetomidine affects the pulmonary vasculature and perfusion. Although perioperative dexmedetomidine administration is known to increase systemic blood pressure temporarily, its effect on pulmonary arterial pressure has rarely been studied. A previous study showed that dexmedetomidine administration decreased pulmonary arterial pressure when given through a peripheral vein, and it did not increase pulmonary arterial pressure even after direct injection into the pulmonary artery.[15] Several studies have reported that dexmedetomidine does not elevate pulmonary arterial pressure after cardiac surgery.[34,35] Clinically, administration of dexmedetomidine decreases pulmonary arterial pressure effectively in patients with existing pulmonary hypertension after cardiac surgery.[18] Recently, it was reported that dexmedetomidine does not affect the pulmonary vasculature in patients with existing pulmonary hypertension.[36,37] Furthermore, Nathan *et al.*[17] reported that dexmedetomidine improved respiratory status during sedation in patients without pulmonary arterial pressure elevation. As we did not have direct evidence to verify pulmonary arterial pressure and pulmonary vascular resistance in this study, we cannot determine whether dexmedetomidine improved oxygenation by increasing pulmonary perfusion. However, considering the decrease of dead space ventilation and improvement of PaO_2/FiO_2 ratio after dexmedetomidine administration, dexmedetomidine

could act as a pulmonary vasodilator which increases perfusion to the dead space ventilation portion of the ventilated lung in moderate COPD patients. Therefore, further study regarding the mechanism of dexmedetomidine on the pulmonary vasculature and bronchoalveolar system is needed.

Regardless of the novel findings of the present study, there are several limitations to take into account. First, although high F_IO_2 can possibly increase the risk of pulmonary atelectasis, lead to absent ventilation in low ventilation/perfusion areas of the lung and result in a high alveolar-arterial O_2 tension difference,[38] we allowed for an increase of F_IO_2 at an increment of 0.2 up to F_IO_2 1.0 in response to hypoxaemia. Because our goal was to prevent hypoxaemia during OLV, we set our focus on detection of intraoperative hypoxaemia rather than postoperative hypoxaemia. Second, this study was conducted on patients with moderate COPD. Consequently, we cannot assume the same results of dexmedetomidine administration in patients with severe COPD, which is characterised by irreversibility of airflow limitation, hyperdynamic inflation and resultant high intrinsic PEEP. Third, we could not confirm whether the enrolled patients had pulmonary hypertension before surgery. Because pulmonary artery catheters are not inserted routinely in clinical settings, we could not measure the pulmonary vascular resistance, or directly measure mixed venous oxygen tension. Fourth, the primary outcome of this trial was lung oxygenation expressed by PaO_2/F_IO_2 ratio and respiratory mechanics during OLV. Thus, the results from this study are underpowered to confirm the secondary outcome of postoperative pulmonary complications. Fifth, it is currently recognised that inhaled anaesthetics have an effect on intrapulmonary shunt during OLV. To minimise the effects of inhaled anaesthetics and focus on the direct effects of dexmedetomidine on lung mechanics, we maintained anaesthesia with the lowest possible concentration of sevoflurane in both groups. Nonetheless, we cannot exclude possible effects of deep anaesthesia by inhaled anaesthetics on lung mechanics. Finally, this study included a relatively small number of patients and further studies will be needed to verify our findings in both moderate and severe COPD patient groups.

In conclusion, dexmedetomidine provides clinically relevant benefits in patients with moderate COPD undergoing lung cancer surgery. Dexmedetomidine administration during OLV not only improved oxygenation but also reduced dead space ventilation in patients with moderate COPD. The positive effects of dexmedetomidine extended to the postoperative period, with the potential for better outcome after lung surgery.

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