Effects of volatile versus intravenous anesthesia on oxygenation and hemodynamic response during thoracotomy with one-lung ventilation

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Background The aim of this study was to evaluate the effects of total intravenous anesthesia by propofol and ketamine (ketofol) versus that of inhalational anesthetic technique using sevoflurane on oxygenation and hemodynamics before, during, and after one-lung ventilation (OLV) in adults undergoing thoracic surgery.

Patients and methods Twenty-eight patients (American Society of Anesthesiologists) II–III were undergoing thoracic surgery requiring OLV. Each patient was randomly allocated to one of two groups: ketofol group, in which induction was performed with 1% propofol 1.5–2.5 mg/kg, with ketamine 1 mg/kg and, in the second group (sevoflurane), 8% sevoflurane. Fentanyl 2 μg/kg and cisatracurium 0.1 mg/kg was administered to both groups. Anesthesia was maintained with ketamine and propofol in the ketofol group and 2% sevoflurane in the sevoflurane group.

Results Arterial blood gas analysis, end-tidal carbon dioxide concentration, heart rate, mean arterial pressure, and end-tidal concentration of sevoflurane were noted in the sevoflurane group. In patients receiving ketofol, fentanyl requirements were decreased when compared with the sevoflurane group. However, the total dose of phenylephrine was greater in patients receiving sevofluran when compared with those receiving ketofol (5 μg/kg/patient vs. 1.1 μg/kg/patient). Mean arterial pressure was reduced during the course of OLV in both groups, as compared with levels found before OLV ($P<0.05$). Sevoflurane anesthesia induced a significant reduction in heart rate, whereas no significant difference in heart rate was found in the ketofol group. Initiation of OLV caused a significant decrease in PaO_2 and SpO_2 in both groups, especially in the sevoflurane group, as compared with the ketofol group.

Conclusions The combination of ketamine and propofol anesthesia has a relatively mild influence on hypoxic pulmonary vasoconstriction and more hemodynamic stability compared with conventional inhalational anesthetics with sevoflurane for OLV anesthesia.

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Introduction

One-lung ventilation (OLV) is commonly used during open thoracic surgery to improve surgical exposure. Hypoxic pulmonary vasoconstriction (HPV) allows for shunting of blood away from the nonventilated lung to the ventilated one and thus allows for the maintenance of adequate oxygenation [1,2].

HPV is felt by most investigators to be the most important intraoperative variable [3]. A large number of factors (anesthetic agents, acid/base imbalance, lung manipulation, vasodilators, etc.) can be involved in the magnitude of HPV in the nonventilated lung. In many studies, volatile anesthetics have been shown to impair HPV, and increase intrapulmonary shunt fraction or reduce arterial oxygen tension in a dose–response manner [4,5], whereas propofol does not seem to affect HPV [6]. Moreover, ketamine has little effect or may actually potentiate HPV and thereby improve oxygenation [7].

Propofol remains the mainstay drug for total intravenous anesthesia (TIVA). In addition to its favorable pharmacodynamic and pharmacokinetic profile, propofol offers distinct benefits over inhaled anesthetics. In studies comparing propofol with inhaled anesthetics in thoracic procedures, propofol reduced the postoperative decline of lung function after lung resection and inhibited the catecholamine surge and adrenocorticotropic hormone response during lung lobectomy [8,9]. In addition, propofol reduced coughing during emergence from anesthesia and the depression in bronchial mucus transport velocity associated with general anesthesia [10,11].

Ketamine is an N-methyl-D-aspartate receptor antagonist. It has profound analgesic, sedative, and amnestic properties [12,13]. It is occasionally used as an adjunct to propofol in TIVA regimens. Ketamine is particularly valuable for thoracic surgery because it has

bronchodilating properties, does not depress respiration, reduces narcotic requirement, and exerts sympathomimetic effects, which may be beneficial in thoracic trauma and in situations wherein perfusion pressure must be maintained in the presence of volume restriction. Recent advances in surgical techniques, coupled with the introduction of high-resolution microchip cameras and smaller endoscopic instruments, have facilitated the application of video-assisted thoracoscopy in pediatric patients [14,15].

The purpose of this study was to determine whether there was a difference among volatile anesthetics using sevoflurane and ketofol with regard to oxygenation and hemodynamics during OLV.

Patients and methods

This study was approved by the local research ethics committee of Al-Zahraa University Hospital, Egypt. Twenty-eight patients according to the American Society of Anesthesiologists classification II–III patients were admitted for an elective anterolateral thoracotomy after giving written informed consent. Each patient was randomly allocated to one of two groups. Patients were randomized preoperatively by computer-generated random sequence. The assignment of study groups was placed in serially numbered opaque envelopes. Patients with a history of adverse reaction to inhalation anesthetics or propofol were excluded from the study. Patients with severe chronic obstructive pulmonary disease (forced expiratory volume in 1 s <40% of predicted value) and anemia (hemoglobin <100 g/l) were excluded; 40 patients were assessed for eligibility; 10 patients were excluded, as one had a history of adverse reaction to propofol, four had anemia, and five patients had severe chronic obstructive pulmonary disease; hence, 30 patients were randomized into two groups, 16 patients in the first group and 14 patients in the second group; two patients were lost of follow-up in the first group and no patient was lost of follow up in the second group; thus, 14 patients were analyzed in each group.

One hour before surgery, all patients were given 0.1 mg/kg of intravenous midazolam. An intravenous catheter, a central venous catheter, and a radial artery catheter were introduced into the forearm contralateral to the side of surgery. Arterial blood was withdrawn for determination of hemoglobin and blood gases.

Before induction, all patients received oxygen for 1 min from a face mask at a flow rate of 5 l/min. In first group (ketofol) of patients, induction was performed with injection of 1% propofol at a dose of 1.5–2.5 mg/kg, lidocaine 1 mg/kg and ketamine 1 mg/kg. In the second group (sevoflurane) induction was performed with 8% sevoflurane (Sevorane; Abbott Laboratories, Abbott Park, Illinois, USA). Fentanyl 2 μg/kg was administered to both groups. Once at adequate depth using eye signs (such as corneal lash or light reflex), respiration pattern and abdominal wall tone, cisatracurium 0.1 mg/kg was injected.

OLV was performed via a double-lumen endobronchial tube (Broncho-Cath; Mallinckrodt, Made in Ireland, Convidien II c, 15 Hamsphire Street, Mansfield, MA, USA). Its position was checked using a fiberoptic bronchoscope. A Dräger volume-cycled ventilator (Dräger, Lübeck, Germany) was used with the tidal volume set to 8 ml/kg of ideal body weight, the inspiratory to expiratory ratio to 1 : 2, and the positive end-expiratory pressure to 5 cmH_2O. Arterial hemoglobin oxygen saturation was maintained above 98% by administering 80–100% oxygen. $ETCO_2$ levels were kept in the range of 30–45 mmHg by adjusting the tidal volume and the respiratory rate.

Anesthesia was maintained in the ketofol group with 0.03 ml/kg/min (15 μg/kg/min of ketamine+60 μg/kg/min of propofol). In the (sevoflurane) group, anesthesia was maintained with 2% sevoflurane. Both groups received fentanyl in additional boluses of 1 μg/kg every 30–60 min, and cisatracurium at a rate of 0.1 μg/kg/min. Intraoperative arterial pressure was maintained within 20% of baseline management with intravenous fluid or intravenous fentanyl, as required.

Measurement of the investigated parameters was carried out before induction while breathing room air (preinduction), 15 min after induction while in the lateral decubitus position with two-lung ventilation (TLV1), then at 15, 30, 45, and 60 min after start of OLV and again 15 min after institution of two-lung ventilation while they were in the lateral decubitus position (TLV2).

The following variables were recorded at the same intervals: arterial blood gas analysis, end-tidal carbon dioxide concentration, heart rate, mean arterial pressure, central venous pressure (CVP), supplemental fentanyl to maintain hemodynamic stability, and phenylephrine used to treat hypotension and keep the mean arterial pressure within 20% of baseline values. End-tidal

concentration of sevoflurane was noted in the sevoflurane group.

CONSOLT chart

Outcome

The effects of TIVA by propofol and ketamine (ketofol) versus inhalational anesthetic technique using sevoflurane on oxygenation is the primary outcome, and its effect on the hemodynamics is the secondary outcome.

Table 1 Demographic data of ketofol and sevoflurane groups

	Ketofol group 1 (*n*=14)	Sevoflurane group 2 (*n*=14)
Age (years)	53.8±13.5	51.5±17.8
Weight (kg)	82.3±25.2	81.17±18.6
Height (cm)	160.1±7.14	161±7.3
Sex (male/female)	9/5	10/4
Preoperative arterial blood gases		
pH	7.42±0.04	7.41±0.03
PaO_2	75.4±1.5	77.5±1.7
$PaCO_2$	35.3±1.3	37.4±1.3
HCO_3 (mEq/l)	22.1±0.3	21.3±1.3
Preoperative spirometric tests		
FEV_1 (% of predicted value)	83±18	86±17
FVC (% of predicted value)	88±18	93±19
FEV_1/FVC (%)	83±14	82±15
Type of surgery		
Lobectomy	10	10
Atypical pulmonary resection	4	4
OLV (duration) (min)	71±35	68±42
Operation time (min)	132±63	120±73

Values are mean±SD, or absolute numbers. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; OLV, one-lung ventilation.

Statistical analysis

Data were checked, entered, and analyzed using SPSS software statistical computer package 19 (IBM SPSS), Released 2015 for Windows, version 23.0, Armonk, NY: IBM Corporation. Data were expressed as mean ±SD, numbers, percentages, median, and range. χ^2, Student's *t* test, Mann–Whitney, Kruskal–Wallis, and ANOVA tests were used when appropriate. *P* value less than 0.05 was considered statistically significant.

On the basis of previous literature (Supplementary Material, Supplemental digital content 2, http://links.lww.com/AA/A912), we considered a reduction from 65 to 40% as clinically relevant, assuming a two-sided type I error rate of 5% and a power of 80%.

Results

No significant difference was found between groups with regard to age, weight, height, preoperative lung function, and preoperative arterial blood gases (Table 1).

In patients receiving ketofol, fentanyl requirements were decreased when compared with sevoflurane (2.6 μg/kg/patient vs. 4.1 μg/kg/patient). However, more patients receiving sevoflurane required

Table 2 Fentanyl and phenylephrine data and expired sevoflurane concentration

Variables	Ketofol	Sevoflurane
Fentanyl (μg/kg/patient)	2.6±1.0	4.1±1.8
Phenylephrine (number receiving)	2	5
Phenylephrine (μg/kg/patient)	1.1±2.2	5.2±9.1
Expired sevoflurane concentration (%)		2.1±1.2

Values are mean±SD or absolute numbers.

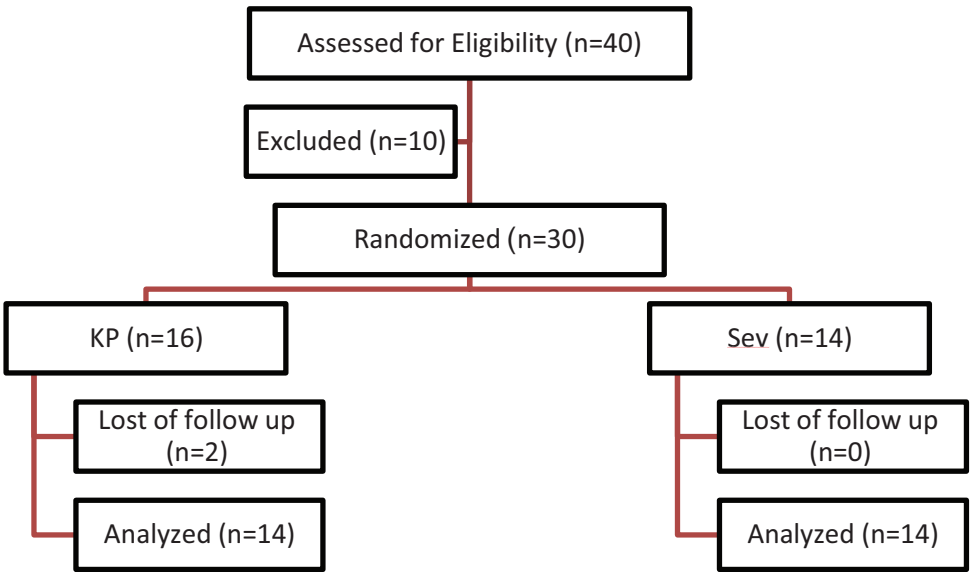
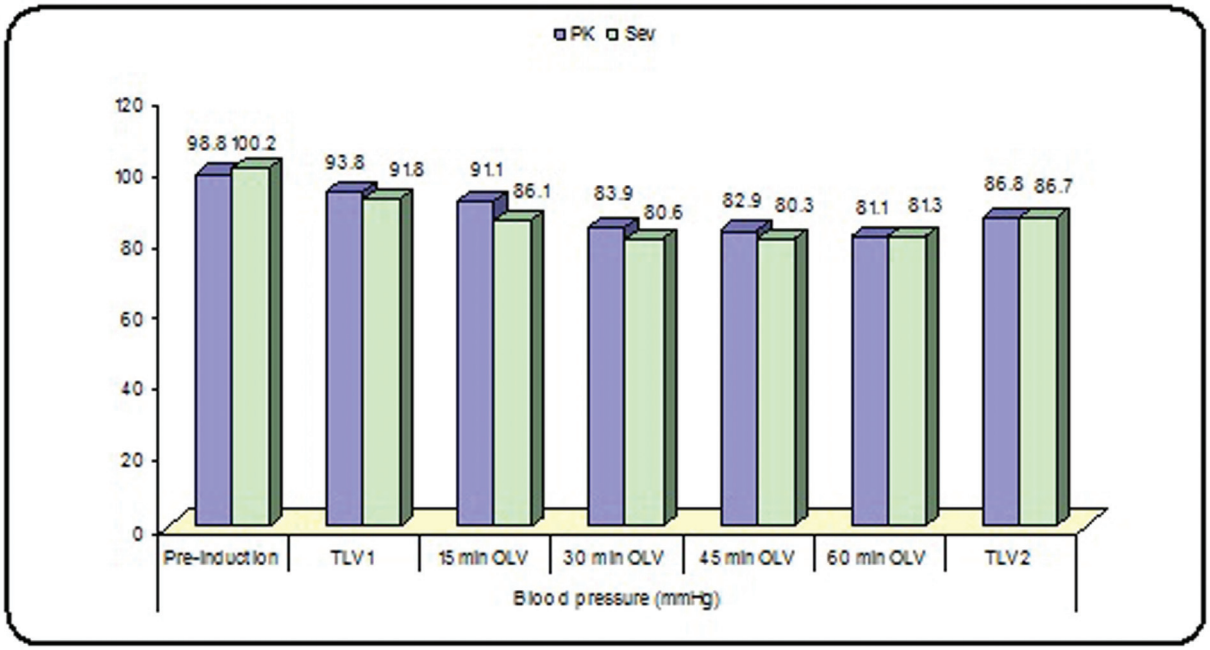


Table 3 Heart rate

Time (min)	Heart rate (beats/min)		
	Ketofol (*n*=14)	Sevoflurane (*n*=14)	Intergroup *P* value
Preinduction	84.1±5.4	83.1±7.2	0.58
TLV1	82.7±6.5	75.7±6.5*	0.04
15 min OLV	83.4±7.2	73.5±6.3*	0.03
30 min OLV	81.8±6.3	72.2±8.3*,**	0.02
45 min OLV	82.3±7.5	71.3±7.9*,**	0.001
60 min OLV	81.9±4.2	68.4±7.2*,**	0.000
TLV2	82.4±5.3	73.8±5.8*	0.7

Data are presented as mean±SD. OLV, one-lung ventilation; TLV, two-lung ventilation. **P* value less than 0.05 for versus preinduction. ***P* value less than 0.05 for versus baseline (TLV1).

Figure 1



Blood pressure. Data are presented as mean±SD.

phenylephrine to maintain hemodynamic stability (5 of 14 patients vs. 2 of 14 patients), and the total dose of phenylephrine was greater in patients receiving sevoflurane when compared with ketofol (5.2 μg/kg/patient vs. 1.1 μg/kg/patient) (Table 2).

Sevoflurane anesthesia induced a significant reduction in heart rate ($P<0.001$) and reached its maximum after 60 min of OLV, whereas no significant difference in heart rate was found in the ketofol group (Table 3). Mean arterial pressure was reduced during the course of OLV in both groups, as compared with levels found before OLV ($P<0.05$) (Fig. 1).

CVP was significantly increased in both groups, as compared with levels found before OLV ($P<0.05$) (Table 4). The observed rise during OLV was greater in the sevoflurane group.

Initiation of OLV caused a significant decrease in PaO_2 and SpO_2 in both groups, especially in the sevoflurane group ($P<0.001$), as compared with levels found before OLV. There was a significant decrease in PaO_2 and SpO_2 with the sevoflurane group ($P<0.05$), as compared with the ketofol group (Table 5). There was no significant difference in $ETCO_2$, $PaCO_2$, and O_2Hb in both groups.

Discussion

Our study was performed on patients undergoing open lung surgery. An open lung operation is a complicated procedure, which often results in circulatory instability with consequent tissue hypoperfusion [16]. OLV carried out during these operations frequently leads to serious complications. It would be advantageous to use anesthetics that have the least effect on hemodynamics.

Our study showed that patients anesthetized with ketofol were hemodynamically more stable than patients given sevoflurane (Fig. 1). There was a slight decrease in heart rate in the sevoflurane group as compared with the ketofol group. A similar result was reached by Aouad *et al.* [17], who found hemodynamic stability with ketofol in children undergoing cardiac catheterization. This is consistent with the result of Kishnani and Dave [18] who found the combination of propofol and ketamine, as well as propofol and dexmedetomidine, to be equally effective in TIVA, caused less hemodynamic effects and minimal side effects, and was found to be safe.

In the present study, hemodynamic parameters were measured after the induction of anesthesia and at the beginning of OLV, when hemodynamic instability is especially frequent. After induction, the hemodynamic values in both groups of patients decreased but remained within the normal range. However, the patients anaesthetized with sevoflurane required substantially more ephedrine to maintain the hemodynamic parameters within the normal range and thus ensure normal tissue perfusion. This implies that the patients in the sevoflurane group were hemodynamically less stable than the patients in the ketofol group and needed support. The combination of propofol-ketamine may be recommended as an effective and safe induction agent for attenuating hemodynamic responses to laryngoscopy and intubation with better hemodynamic stability [19,20]. Sevoflurane causes a dose-dependent depression of right ventricular function [21]. Hazrati *et al.* [22] findings showed that isoflurane as a volatile agent provides a bloodless field better than does propofol through TIVA. Similar results about the effects of sevoflurane on heart rate and mean arterial pressure were reached by Andolfatto and Willman [23] The combination of ketamine and propofol seeks to limit the adverse effects of each of the two drugs, and synergize their analgesic, hypnotic, and sedative effects because they use less dose of each to achieve the same anesthetic and cardiovascular effects [24]. Several studies support the concept of synergy because similar quality of anesthesia was achieved with lower doses of propofol and ketamine. Propofol is an excellent sedative but has no analgesic effects. Hypotension and respiratory depression of propofol may be offset by the sympathomimetic effects of ketamine. Arora [25], and Arora *et al.* [26] studies confirm the synergistic protective effect of ketamine on propofol-induced hypotension.

Table 4 Changes in central venous pressure (mmHg)

Time (min)	Ketofol (*n*=14)	Sevoflurane (*n*=14)	Intergroup *P* value
Preinduction	8.5±1.5	8.0±1.5	0.23
TLV1	7.6±3.6	9.3±2.9	0.14
15 min OLV	10.3±1.5	12.3±1.7*	0.03
30 min OLV	12.2±1.3*	12.8±2.3*	0.64
45 min OLV	11.3±1.7*	12.9±1.5*	0.16
60 min OLV	11.8±2.1*	12.5±2.4*	0.61
TLV2	10.1±1.3*	11.3±1.7*	0.24

Data are presented as mean±SD. OLV, one-lung ventilation; TLV, two-lung ventilation. **P* value less than 0.05 for versus preinduction.

In the present study, CVP was increased during anesthesia in both groups, especially during OLV. This may be due to the effect of the lateral decubitus position and the effect of pre-existing lung pathology, which affects the compliance of the pulmonary vessels. The CVP was increased slightly in the sevoflurane group of patients as compared with the ketofol group. This rise may be due to the inhibiting effect of sevoflurane on the HPV mechanism. However, the changes in CVP were acceptable, as they were within the normal range.

The present study showed that PaO_2 was significantly higher in patients who received mixtures of propofol and ketamine for open lung surgery than in those who received sevoflurane. Several studies have shown an

Table 5 Time course changes of blood samples and end-tidal CO_2

Time (min)	Ketofol (*n*=14)					Sevoflurane (*n*=14)				
	PaO_2	SpO_2	O_2Hb	$PaCO_2$	$ETCO_2$	PaO_2	SpO_2	O_2Hb	$PaCO_2$	$ETCO_2$
TLV1	340±9.8	99±1	98±2	40±6	34±2	336±12.5	98±7	98±2	39±4	34±3
15 min OLV	211±12.6*	98±2*	97±9	39±8	32±2	158±11.9*,**	98±4*	97±9	39±1	33±2
30 min OLV	189±11.7*	98±2*	97±9	38±4	31±2	130±18.1*,**	98±2*	97±9	37±3	34±2
45 min OLV	175±8.3*	97±2*	97±7	37±4	31±3	135±10.2*,**	98±2*	97±8	36±4	31±2
60 min OLV	179±8.5*	97±1*	97±8	37±4	33±1	132±12.1*,**	98±1*	97±	36±5	31±3
TLV2	302±9.8	98±9	98±1	41±8	35±1	312±9.8	98±5	98±1	39±9	35±1

Data are presented as mean±SD. OLV, one-lung ventilation; TLV, two-lung ventilation. **P* value less than 0.05 significant for versus baseline (TLV1). ***P* value less than 0.05 significant for versus ketofol group.

advantage to using TIVA for open lung surgery. Cho *et al*. [27] found that desflurane-remifentanil anesthesia resulted in decreased arterial oxygenation compared with that of propofol-remifentanil anesthesia during OLV for thoracoscopic surgery in patients with lung cancer. In another study, PaO_2 was also significantly higher in patients who received TIVA in patients undergoing esophagectomy than in those who received volatile anesthetics [28]. Ozcan and collogues compared oxygenation and shunt fraction in 100 patients undergoing one of four anesthesia techniques during OLV: TIVA with or without thoracic epidural anesthesia (TEA), and isoflurane with or without TEA. Patient oxygenation was significantly higher and shunt was significantly lower in the two groups receiving TIVA; the addition of TEA in either study group had no significant effect [29].

Alternatively, a few studies failed to support any advantage of TIVA. Sharifian Attar *et al*. [30] concluded that using intravenous propofol or inhaled isoflurane as a maintenance anesthetic agent does not have a different effect on pressure of arterial oxygen and patients' hemodynamics during two-lung ventilation or OLV. Pruszkowski and colleagues compared oxygenation levels in patients undergoing lung lobectomy. The patients received a thoracic epidural and either sevoflurane or propofol at levels required to maintain a bispectral index between 40 and 60. The authors found no difference in PaO_2 levels between the sevoflurane and propofol groups. They suggest that the titration of anesthetics to appropriate bispectral index levels (which distinguished their study) could avoid potential negative effects of inhalational anesthetics on hemodynamics that affect shunt [31]. Lastly, Lee *et al*. [32], concluded that the quality of recovery for female thyroid surgery patients is significantly better with TIVA compared with desflurane anesthesia.Hypercapnia during OLV seems to act as a vasoconstrictor drug by selectively increasing the nonventilated lung vascular resistance. Mild hypercapnia and respiratory acidosis may minimize the deleterious effects of CO_2 insufflation in pediatric patients undergoing VATS closure of PDA [15]. As the $PaCO_2$ level all through the study was kept at a fixed level, 35–40 mmHg, therefore the lower arterial oxygen tension with sevoflurane is due to its more direct inhibiting effect on HPV.

Two potential limitations should be considered first; the sample size enrolled in our study was limited to adult patients; hence, further studies are needed on a wider population with different ages to concur with our results to confirm their efficacy and incidence of complications. Second, there were difficulties in adequately blinding studies. However, neither the surgeon nor the anesthesiologist conducting the assessment was aware of the group allocation.

Conclusion

In conclusion, the combination of ketamine and propofol anesthesia has a relatively mild influence on HPV, and more hemodynamic stability, compared with conventional inhalational anesthetics with sevoflurane for major lung surgeries needing thoracotomy with periods of OLV.

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Conflicts of interest

There are no conflicts of interest

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