Which Anesthesia Regimen Is Best to Reduce Morbidity and Mortality in Lung Surgery? A Multicenter Randomized Controlled Trial

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ABSTRACT

Background: One-lung ventilation during thoracic surgery is associated with hypoxia–reoxygenation injury in the deflated and subsequently reventilated lung. Numerous studies have reported volatile anesthesia–induced attenuation of inflammatory responses in such scenarios. If the effect also extends to clinical outcome is yet undetermined. We hypothesized that volatile anesthesia is superior to intravenous anesthesia regarding postoperative complications.

Methods: Five centers in Switzerland participated in the randomized controlled trial. Patients scheduled for lung surgery with one-lung ventilation were randomly assigned to one of two parallel arms to receive either propofol or desflurane as general anesthetic. Patients and surgeons were blinded to group allocation. Time to occurrence of the first major complication according to the Clavien-Dindo score was defined as primary (during hospitalization) or secondary (6-month follow-up) endpoint. Cox regression models were used with adjustment for prestratification variables and age.

Results: Of 767 screened patients, 460 were randomized and analyzed (n = 230 for each arm). Demographics, disease and intraoperative characteristics were comparable in both groups. Incidence of major complications during hospitalization was 16.5% in the propofol and 13.0% in the desflurane groups (hazard ratio for desflurane *vs.* propofol, 0.75; 95% CI, 0.46 to 1.22; $P = 0.24$). Incidence of major complications within 6 months from surgery was 40.4% in the propofol and 39.6% in the desflurane groups (hazard ratio for desflurane *vs.* propofol, 0.95; 95% CI, 0.71 to 1.28; $P = 0.71$).

Conclusions: This is the first multicenter randomized controlled trial addressing the effect of volatile *versus* intravenous anesthetics on major complications after lung surgery. No difference between the two anesthesia regimens was evident. **(ANESTHESIOLOGY 2016; XXX:00-00)**

ONE-LUNG ventilation (OLV) is a standard method that allows selective exclusion of one lung during anesthesia to assist the surgeon with his or her procedure. However, this method is associated with hypoxia and ischemia in the nonventilated lung tissue. Upon reventilation, the deflated lung is reoxygenated, which triggers a well-characterized hypoxia–reoxygenation injury similar to ischemic organ damage.

Patients undergoing lung surgery need general anesthesia with either a volatile (isoflurane, sevoflurane, and desflurane) or an intravenous anesthetic such as propofol. The choice between the different regimens for anesthesia maintenance

What We Already Know about This Topic

- Recovery from surgery involving one-lung ventilation can be complicated by acute pulmonary inflammatory processes. Some data suggest that such injury might be less if volatile (*vs.* intravenous) anesthesia is used. It was hypothesized that clinical outcome can be influenced.

What This Article Tells Us That Is New

- Four hundred and sixty patients (five centers) undergoing one-lung ventilation during thoracic surgery were randomized to receive either propofol or desflurane. There was no difference in major complications between the two groups.

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(volatile *vs.* intravenous) is mostly based on the anesthesiologists' habits and hospital practices. There is no evidence supporting superiority of the use of either a volatile or an intravenous anesthetic.

Because of the hypnotic effects of volatile anesthetics, attention has generally been focused on their use as general anesthetics. In the last decades, however, numerous studies have described an incremental value of volatile anesthetics: They provide protection to organs like the heart,[1] liver,[2,3] lung,[4,5] and kidney[6] in the intraoperative period in situations of ischemia–reperfusion (hypoxia–reoxygenation)-induced tissue damage. Volatile anesthetics have been effectively used before or after the onset of injury (pre- or postconditioning),[1] but also during the entire surgical procedure (conditioning).[7] All three volatile anesthetics isoflurane, sevoflurane, and desflurane have significantly decreased organ injury as expressed by biomarkers such as plasma levels of troponin,[7,8] transaminases,[3,9] or inflammatory mediators in bronchoalveolar lavage fluid.[4,5,10] Although these studies suggest that volatile anesthetics are immunomodulatory substances, it still has to be confirmed if they are potent enough to have an effect not only on biomarkers, but also on relevant clinical outcome parameters.

A large number of retrospective or prospective studies have already been performed, but all of them were clearly underpowered with regard to clinical outcomes. Our aim was to conduct the first adequately powered multicenter randomized controlled trial (RCT) to compare the effects of a volatile (desflurane) *versus* an intravenous anesthetic (propofol) on major complications during hospitalization and within the first 6 months after surgery in patients undergoing lung surgery with a well-defined hypoxia/ischemia period (OLV time) during surgery.

Materials and Methods

Study Design

This multicenter RCT was conducted in five thoracic surgery centers in Switzerland, the University Hospitals of Zurich, Bern, and Basel and the Cantonal Hospitals of St. Gallen and Muensterlingen. Patients enrolled were randomly assigned to one of two parallel arms to receive either the intravenous anesthetic propofol (control group) or the volatile anesthetic desflurane (intervention = conditioning group) for lung resections performed either in open fashion or thoracoscopically.

The goal of this trial was to test the hypothesis of whether conditioning with desflurane leads to fewer major complications when compared to the control group during hospitalization (primary endpoint) and during the 6 months after lung resection surgery with OLV (secondary endpoint). We hypothesized that patients would experience fewer major complications during desflurane anesthesia.

The institutional boards approved this trial for human studies in all five centers (principal investigator and sponsor: University Hospital Zurich, Zurich, Switzerland, protocol KEK-ZH no. 2011-0092; Swissmedic notification 2011DR4094). The study was registered at ClinicalTrial.gov NCT01452256 and is reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[11] In all five centers, the Clinical Trial Unit of the University of Zurich, Zurich, Switzerland, routinely monitored the study. An interim analysis after inclusion of 150 patients was performed by an independent data safety monitoring board.

Study Population

Patients were assessed for eligibility by the study team during routine preoperative visits between December 6, 2011, and March 28, 2014. All adults able to provide written informed consent, aged 18 to 80 yr, with American Society of Anesthesiologists physical status classification I to III and scheduled for elective lung resection surgery requiring OLV were eligible for study inclusion. Exclusion criteria were known or suspected allergy to propofol, soy, or egg, as well as hypersensitivity to volatile anesthetics (malignant hyperthermia). Therapy with cyclosporine or high dosages of statins as well as oral steroids (present or discontinued less than 3 months before surgery) was regarded as exclusion criteria. Patients suffering from severe renal impairment with a glomerular filtration rate less than 30 ml kg^{-1} min^{-1} 1.73 m^{-2} and/or with inflammatory processes (nonpulmonary and pulmonary), defined as increased C-reactive protein level (greater than 20 mg/l) or leukocytosis (leukocytes greater than $10 \times 10^3/\mu l$) or body temperature greater than 37°C, were not included. Breast feeding, pregnancy, and intention to become pregnant over the following 60 days or lack of safe contraception in women of childbearing potential were also defined as exclusion criteria. Finally, patients involved in any other clinical trial within a period of 30 days before or 30 days after completion of the current study were excluded.

Randomization

A web-based computerized and central randomization service was used for the allocation of the participants (http://www.randomizer.at). The minimization procedure ensured balanced groups (1:1 ratio) with respect to the number of patients in each arm and the three factors: center, number of comorbidities (coronary heart disease, chronic obstructive pulmonary disease, and mild to moderate renal impairment defined as glomerular filtration rate of 30 to 59 ml kg^{-1} min^{-1} 1.73 m^{-2}, chronic kidney disease), and pneumonectomy. Patients were randomized immediately before entering the operating room or, if this was not possible, on the evening before surgery. Concealment of random allocation was ensured by the computerized and central randomization service.

Blinding

Patients and surgeons were blinded to group allocation throughout surgery and follow-up. Induction of anesthesia

was performed in a similar way in both groups. Propofol or desflurane were applied only after the patient lost consciousness, thus making it impossible to know the correspondent arm of the study. Surgeons were blinded to the vaporizer or the propofol infusion by concealment of the respective device.

Anesthesia

Patients received oral premedication 30 min before anesthesia induction with midazolam. Standard monitoring (continuous 5-lead electrocardiogram, noninvasive blood pressure, and pulse oximetry) as well as bispectral index monitoring (Covidien, USA) was installed in the induction room. Intravenous peripheral access was gained through a forearm vein. Cannulation of the radial artery was performed before or immediately after anesthesia induction according to the clinical needs of the individual patient and at the discretion of the anesthesiologist. Epidural anesthesia was indicated and performed following respective departmental guidelines. Central venous catheters were placed when deemed clinically necessary following respective departmental guidelines in each center. Crystalloids at a rate of 8 ml kg^{-1} h^{-1} were infused throughout the procedure. Colloid solution was applied when regarded as clinically necessary by the responsible anesthesiologist.

General anesthesia was induced in both groups with 0.3 to 0.5 mg/kg etomidate (B. Braun Medical AG, Switzerland); suppression of laryngoscopic stress response was achieved with intravenous application of 3 μg/kg fentanyl (Sintetica SA, Switzerland). 0.5 mg/kg atracurium (GlaxoSmithKline AG, Switzerland) or 0.6mg/kg rocuronium (Organon, Switzerland) was applied to facilitate tracheal intubation. In the setting of a rapid-sequence induction, 0.9 mg/kg rocuronium or 0.8 mg/kg succinylcholine (Takeda Pharma AG, Switzerland) was chosen.

In the propofol group (control), anesthesia was maintained using propofol (AstraZeneca AG, Switzerland) at a rate of 4 to 10 mg kg^{-1} h^{-1} or as target-controlled infusion (2 to 6 μg/ml), while in the desflurane arm (intervention), desflurane (Baxter AG, Switzerland) was applied with end-tidal concentrations of 4.5 to 7.0%. Analgesia was achieved by applying boluses of fentanyl 1 to 2 μg/kg and/or continuous infusion of remifentanil (GlaxoSmithKline AG, Switzerland) up to 20 μg kg^{-1} h^{-1}, according to the patient needs. Muscle relaxation was monitored with train-of-four stimulation of the ulnar nerve. When train-of-four response was two or more, 5 to 10 mg atracurium or rocuronium was readministered.

Ventilation

Ventilation was performed *via* double-lumen endotracheal tubes (different manufacturers) of sizes Ch35-41 according to patient height. Right-sided tubes were preferred for left pneumonectomies or lung resections with left-sided lymphadenectomies.

During two-lung ventilation, settings were as follows: pressure-controlled mode; positive end-expiratory pressure, 5 cm H_2O; positive inspiratory pressure (PIP), less than or equal to 30 cm H_2O; target-tidal volume, 6 to 8 ml/kg; inspiratory oxygen fraction (F_{IO_2}), 0.6 to 1.0 with target Sp_{O_2} greater than 90%; and respiratory rate, 10 to 20/min, with a target arterial carbon dioxide partial pressure of 33.7 to 41.2 mmHg.

During OLV, settings were as follows: pressure-controlled mode, positive end-expiratory pressure, 5 cm H_2O; PIP, less than 35 cm H_2O; target-tidal volume, 4 to 6 ml/kg; F_{IO_2}, 0.6 to 1.0, with target Sp_{O_2} greater than 90%; respiratory rate, 10 to 20/min, with a target arterial carbon dioxide partial pressure of 33.7 to 41.2 mmHg. In case of hypoxia (Sp_{O_2} less than 90% and Pa_{O_2} less than 60 mmHg), the following strategies were implemented successively until sufficient oxygenation was achieved: (1) recruitment maneuver in the ventilated lung applying PIP, 40 cm H_2O, for 10 s, (2) insufflation of O_2, 1 to 5 l/min, in the nonventilated lung, (3) continuous positive airway pressure, 5 cm H_2O, in the nonventilated lung, and (4) reventilation of the collapsed lung.

For patients in the propofol group, an exit strategy switching the hypnotic to desflurane was implemented in patients with suspected anaphylactic reactions to propofol or its carrier substances and with hemodynamic instability, and for those with inadequate sedation despite high doses of propofol infusion. Protocol violations were noted, and patients in the randomized group were followed up according to the intention-to-treat principle.

Complications

Complications were assessed using the Clavien-Dindo classification with grade 0 (no complication) to grade V (death).[12] The Clavien-Dindo classification is widely used in surgical and anesthesiological research and captures the severity of complications by considering the intensity of the therapeutic consequences. Complications graded I to II are defined as minor since they require only symptomatic postsurgical treatments (grade I, *e.g.*, antiemetics or analgetics) or nonsurgical but more intensive treatments (grade II, *e.g.*, blood transfusions). IIIa to V are major events comprising reinterventions without (grade IIIa) or with general anesthesia (grade IIIb), single-organ (grade IVa) or multiorgan failure (grade IVb), as well as all-cause mortality (grade V). This composite measure of complications has been used in hundreds of studies and is attractive since it overcomes the limitations of considering complications separately, which include the wide range of severity a specific complication may have and the insurmountable sample-size requirements. As it is standard, only the highest complication that patients experienced was analyzed.

To better reflect the fact that a patient could suffer from several complications, we also used the more recent comprehensive complication index (CCI)[13] that considers all postsurgical complications as well as their severity on a scale

from 0 (no complication) to 100 (maximum burden from multiple complications). The CCI is more responsive to detect treatment effects than the traditional outcome (major complication yes/no).[14]

Complications were considered "related" when two different physicians who were blinded to group allocation independently determined potential causality relationship between lung resection surgery and major complication.

Endpoints

The primary study endpoint was the time to the occurrence of the first major complication (grade IIIa to V) during hospitalization, while the time to the first major complication up to 6 months was defined as secondary endpoint. Further secondary endpoints were the time to the first major complication related to lung resection during hospitalization and in the 6-month follow-up, CCI, and the length of intensive care unit and of the hospital stay.

Data Collection

Standardized web-based case report forms (secuTrial, interActive Systems GmbH, Germany) were used in all five centers to collect the data during surgery. An independent study nurse or anesthesiologist supervised data entry on a daily basis.

Complications were documented based on objective data such as (serum) markers or X-ray/computed tomography scan documentation. All major complications were recorded in the secuTrial. For the 6-month follow-up, the patient electronic chart system, which reliably provides information about the patient's follow-up, was scanned again for any complications. Additionally, family doctors/general practitioners of each patient were contacted by the local study team of the center and were systematically interviewed regarding complications and the details of such events (standard letter). If the answer was not clear, a second inquiry was performed by phone. All complications were documented in the secuTrial in the same way as during the hospitalization period.

The study was officially monitored by the clinical trial unit of the University Hospital Zurich.

Sample Size Calculation

In a previous trial that compared sevoflurane and propofol in patients undergoing liver surgery, we observed that anesthesia with sevoflurane decreased the risk of any major complications by more than 50%.[3] Based on these data, and assuming that 20% of patients in the propofol group would experience a major complication during hospitalization (primary outcome) and 10% in the desflurane group, we estimated that a sample size of 219 patients in each group would allow showing a relative risk of 2.0 with a power of 80% at a significance level of 5% (two-sided) (minimal sample size of 440) using a chi-square test. Assuming a drop-out rate of 10%, the sample size increased to 486. This sample size was also large enough to detect a hazard ratio (HR) of 2.0 (minimal sample size of 96) or a HR of 1.5 (minimal sample size of 264).

Statistical Analysis

The nature of the analyses is based on the superiority of the intervention. We used descriptive statistics (median and interquartile range [IQR] for continuous variables and percentages for categorical variables) to characterize the study population, the intervention and endpoints, stratified by group allocation. Kaplan–Meier curves were used to examine the time to occurrence of the first major complication in the two groups. For the comparison of time with regard to such complications between groups (any and related), we used a Cox proportional hazard regression analysis with treatment allocation as independent variable. Cox models were calculated without further adjustment and additionally with adjustment for prestratification variables and age. Similarly, we used linear regression analyses to compare the groups in terms of their CCI. Two-sided P values less than 0.05 were considered statistically significant. We conducted a number of prespecified subgroup analyses that included effect modification by age, the presence of a major disease, pneumonectomy, and OLV time. We assessed subgroup effects by introducing interactions with the treatment into the regression model and considered subgroup effects to be significant if $P \leq 0.10$ because of the low power of interaction testing to detect subgroup effects. All analyses were performed with the statistics program R, version 3.2.0.[15]

Results

Patient Recruitment

Between December 6, 2011, and March 28, 2014, of 767 patients undergoing lung resection with OLV who were screened for recruitment at the five Swiss study centers, a total of 465 patients were enrolled (fig. 1). Three hundred and two patients had to be excluded based on the following criteria: enrollment in other studies or missing willingness to participate. There were 5 patients (1.1%) who dropped out due to rejection for randomization. These patients had been enrolled before an exclusion criterion was identified.

According to the surgical volume of the center, 46 patients were randomized and analyzed in Basel, 70 in Bern, 27 in Muensterlingen, 120 in St. Gallen, and 197 in Zurich—460 patients in total with 230 subjects per arm as necessary according to the power analysis.

A change of the allocated procedure was necessary in one patient, but data were analyzed in an "intention-to-treat" manner based on the original allocation.

Patient Characteristics

No important difference between the propofol and desflurane arm was observed, including the criteria age, sex, body mass index, American Society of Anesthesiologists classification, diagnosis (benign and malignant), and preexisting major diseases (coronary heart disease, chronic obstructive pulmonary disease, and chronic kidney disease; table 1).

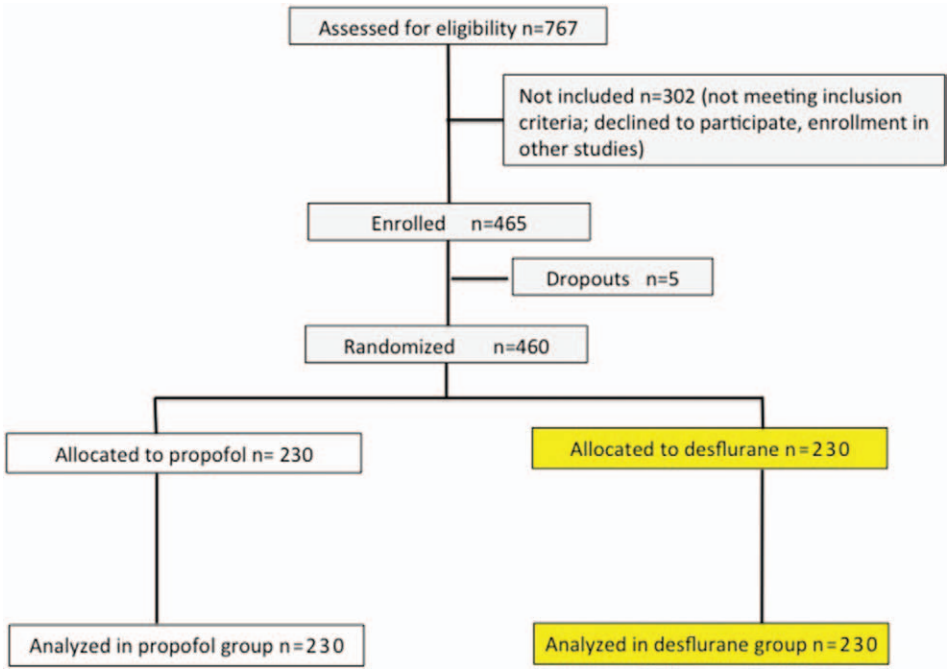

Fig. 1. Enrollment of patients. Of note is that one patient of the propofol group was anesthetized with desflurane; however, the patient was evaluated in an intention-to-treat manner as a propofol patient.

Intraoperative Data

Intraoperative characteristics were comparable (table 1). Particularly, there was no difference between OLV time (mean of 155 [IQR, 78 to 245) min for propofol and 140 [IQR, 58 to 241] min for desflurane) as well as the duration of surgery and anesthesia. Approximately 40% of the patients underwent thoracotomy (without pneumonectomy) in both groups. Nine patients (4%) had a pneumonectomy in the propofol and seven (3%) in the desflurane groups. Overall, 103 patients (45%) experienced major surgery in the propofol and 98 (43%) in the desflurane groups. Blood loss and transfusion requirements were comparable in both groups (table 1).

Major Complications

Primary and Secondary Outcomes. Overall the proportion of patients experiencing at least one major complication during hospitalization (primary outcome) was 13% in the desflurane and 16.5% in the propofol groups (table 2). For a descriptive comparison of the time to occurrence of the first major complication during hospitalization, Kaplan–Meier curves are shown in figure 2A. Both in the unadjusted and in the adjusted Cox models, the difference between groups was not statistically significant (unadjusted HR, 0.77; 95% CI, 0.47 to 1.24; $P = 0.28$; adjusted HR, 0.75; 95% CI, 0.46 to 1.22; $P = 0.24$) (table 2).

Major complications within 6 months after surgery were 40% (see also Kaplan–Meier curve in fig. 2B). Again no significant difference between groups could be found (unadjusted HR, 0.96; 95% CI, 0.72 to 1.28; $P = 0.76$; adjusted HR, 0.95; 95% CI, 0.71 to 1.28; $P = 0.75$) (table 2). When complications related to surgery were analyzed separately, results were similar (table 3) with no difference between groups.

The median CCI was 22.6 in the desflurane (IQR, 0 to 37.9) and 26.0 in the propofol group (IQR, 8.7 to 39.5). There was no significant difference between groups for the CCI nor for all major complications during hospitalization ($P = 0.33$) or over 6 months ($P = 0.82$), Again, we did not observe any statistically significant difference for study-related complications during hospitalization ($P = 0.78$) or over 6 months ($P = 0.53$).

Finally, the length of intensive care unit (median of 0 days [IQR, 0 to 1] in both groups; $P = 0.21$) and hospital stay (median of 8 days [IQR, 5 to 12] in the desflurane and median of 7.5 days [IQR, 5 to 11] in the propofol group; $P = 0.52$) did not differ between groups, either.

Subgroup Analyses. None of the prespecified variables suggested a subgroup effect. Interaction terms were not statistically significant for age ($P = 0.22$ for interaction term during hospitalization and $P = 0.59$ for 6-month follow-up), the presence of a major disease ($P = 0.29$ for interaction term during hospitalization and $P = 0.75$ for 6-month follow-up), pneumonectomy ($P = 0.80$ for interaction term during hospitalization and $P = 0.74$ for 6-month follow-up), or OLV time ($P = 0.92$ for interaction term during hospitalization and $P = 0.19$ for 6-month follow-up).

Discussion

Promising results from clinical trials have emerged, showing that expression of inflammatory mediators is less pronounced after pulmonary ischemia–reperfusion in the presence of

Table 1. Baseline Characteristics of Patients and Intraoperative Parameters for Propofol and Desflurane Groups

	Propofol (n = 230)	Desflurane (n = 230)
Age (yr), median (IQR)	65 (57–70)	63 (54–70)
Sex: male, n (%)	144 (63)	145 (63)
BMI (kg/m^2), median (IQR)	25 (23–28)	25 (22–29)
ASA, n (%)		
I	12 (5)	13 (6)
II	107 (47)	116 (50)
III	107 (47)	99 (43)
IV	3 (1)	2 (1)
Diagnosis, n (%)		
Benign lesion	50 (22)	53 (23)
Malignant lesion	180 (78)	177 (77)
CHD, n (%)		
No	196 (87)	201 (89)
Yes	30 (13)	26 (11)
COPD, n (%)		
No	151 (66)	157 (68)
Yes	79 (34)	73 (32)
Diabetes, n (%)		
No	203 (88)	209 (91)
Yes	27 (12)	21 (9)
CKD, n (%)		
No	205 (89)	208 (91)
Yes	24 (11)	21 (9)
Major disease, n (%)		
0	119 (52)	133 (58)
1	87 (38)	71 (31)
2	22 (10)	21 (9)
3	2 (1)	5 (2)
OLV time (min), median (IQR)	155 (78–245)	140 (58–241)
Surgery time (min), median (IQR)	215 (110–309)	205 (105–300)
Anesthesia time (min), median (IQR)	333 (237–440)	330 (230–440)
Procedures, n (%)		
Thoracoscopy	127 (55)	132 (57)
Thoracotomy	94 (41)	91 (40)
Pneumonectomy	9 (4)	7 (3)
Blood loss (ml), median (IQR)	100 (20–250)	100 (30–200)
Patients with transfusion, n (%)		
No	226 (98)	227 (99)
Yes	4 (2)	3 (1)

The following data were missing: American Society of Anesthesiologists (ASA) classification for one patient in the propofol group; coronary heart disease (CHD) of four patients in the propofol and of three patients in the desflurane group; one patient for both groups with regard to chronic kidney disease (CKD). ASA IV: Although being an exclusion criterion, this classification was chosen by the responsible anesthesiologist, which obviously was in discrepancy to the first evaluation.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; OLV = one-lung ventilation.

volatile anesthetics. Based on the suggestions of potential clinical benefit, we performed the first large and adequately powered multicenter RCT to address the effect of volatile anesthetics on major complications after lung surgery. No significant difference was observed between the volatile and intravenous anesthesia regimen, and complication rate was comparable. The proportion of patients with complications was similar.

Clinical studies on anesthesia in lung surgery revealed that volatile anesthetics decrease pulmonary inflammation in the deflated-reoxygenated operated or the nonoperated lung, based on surrogate markers.[4,5,10] One of our former trials also suggested improved clinical outcomes[4] but was not powered for a strong endpoint such as major complications. The current study includes an appropriate number of patients and demonstrates unequivocally that organ protection is not significant enough to have an impact on measurable clinical outcomes.

Several explanations for our findings may be given. At the same time, these considerations also highlight the limitations of the trial. One might argue that desflurane should have been given for pre- or postconditioning, while we have applied desflurane during the entire surgical procedure. We believe, however, that with OLV, the anesthetic supply to the deflated lung is interrupted and therefore comparable to a pre- or postconditioning scenario. Additionally, we intended to use a protocol that can be performed without the need for additional communication between the surgeon and the anesthesiologist, which may prolong the procedure unnecessarily.

Another explanation for our finding may be the type of the volatile anesthetic chosen, desflurane. However, desflurane just like sevoflurane has actually been shown to provide protection in ischemia–reperfusion-like injury.[7,16] Former *in vitro* and *in vivo* studies from our group have highlighted that fluorinated carbon groups in all volatile anesthetics may be responsible for the protection.[17,18] While sevoflurane consists of two such groups, only one is present in desflurane. However, since the alveolar desflurane concentration required for deep anesthesia is at least three times as high as that of sevoflurane, desflurane might therefore provide similar amounts of protective fluorinated groups to the alveoli.

Another explanation concerns the degree of injury incurred by thoracic surgery and whether it is too little to allow us to detect a protection from injury at all. Compared to former studies in liver surgery,[3,9] where we clearly found a positive impact of volatile anesthetics on major complications, the rate of serious adverse events in thoracic surgery seems certainly lower, which is also underlined by other studies.[19] This suggests the explanation that protection is not effective when relevant injury is missing. We recently performed a large multicenter study with similar findings in liver transplant patients.[20] Increase of transaminases after reperfusion was mild, with a peak median aspartate aminotransferase of only 1,000 U/l and an alanine aminotransferase of only 750 U/l. This study did not even show a difference of the primary endpoint (peak transaminases) between sevoflurane and propofol anesthesia. Yet another study in line with these negative findings is the multicenter clinical trial, which has been performed in patients at high cardiac risk undergoing noncardiac surgery, randomizing 385 patients to either sevoflurane or propofol anesthesia.[21] The incidence of

Table 2. Comparisons of Incidence of Major Complications (Any Events) for Propofol and Desflurane Groups

	Propofol (n = 230)	Desflurane (n = 230)	Unadjusted Incidence Rate Ratio	Adjusted Incidence Rate Ratio*
Incidence of major complications during hospitalization:				
Overall (%)	38 (16.5)	30 (13.0)	0.77 (95% CI, 0.47–1.24; *P* = 0.28)	0.75 (95% CI, 0.46–1.22; *P* = 0.24)
Overall per 100 person-days	0.402	0.348		
Incidence of all major complications up to 6 months follow-up:				
Overall (%)	93 (40.4)	91 (39.6)	0.96 (95% CI, 0.72–1.28; *P* = 0.76)	0.95 (95% CI, 0.71–1.28; *P* = 0.75)

*Adjusted for prestratification variables (study cite, major disease, and pneumonectomy) and age.

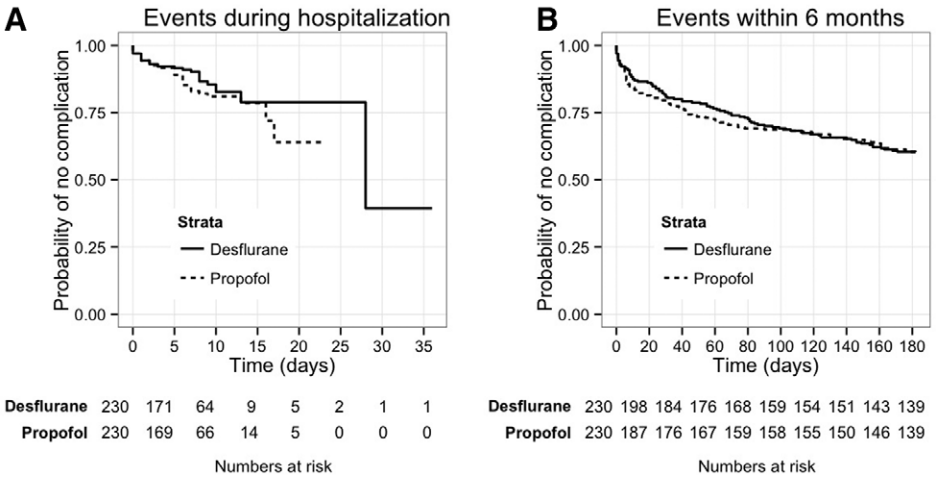

Fig. 2. Kaplan–Meier survival curves, not adjusted for covariates. They represent occurrence of the first major complication after lung surgery, (*A*) during hospitalization and (*B*) within 6 months.

Table 3. Comparisons of Incidence of Related Major Complications for Propofol and Desflurane Groups

	Propofol (n = 230)	Desflurane (n = 230)	Unadjusted Incidence Rate Ratio	Adjusted Incidence Rate Ratio*
Incidence of related major complications during hospitalization:				
Overall (%)	22 (9.6)	20 (8.7)	0.94 (95% CI, 0.52–1.73; *P* = 0.85)	0.94 (95% CI, 0.51–1.74; *P* = 0.85)
Incidence of related major complications up to 6 months follow-up:				
Overall (%)	33 (14.3)	36 (15.7)	1.10 (95% CI, 0.68–1.76; *P* = 0.70)	1.09 (95% CI, 0.68–1.76; *P* = 0.71)

*Adjusted for prestratification variables (study cite, major disease, and pneumonectomy) and age.

myocardial ischemia was similar in both groups at 40%, and the Q-wave infarction rate was 0.5%.

One could also raise the concern or claim a limitation of the trial that we did not exclusively focus on respiratory complications after thoracic surgery. Our goal was to use a composite measure of complications, which allows comparison with hundreds of other study results using the same scoring system. Also the Clavien-Dindo classification is of high clinical relevance as it was established based on the treatment consequences a complication has.

A surgical procedure, which evokes numerous major complications, is pneumonectomy.[22] Thanks to the advances in diagnostic and screening methods, the incidence of patients needing such an invasive procedure was low. We included seven patients undergoing pneumonectomy in the desflurane and nine in the propofol arms. In the pneumonectomy subgroup, there were four complications in the desflurane group, one of minor and three of major grade (1xII, 2xIIIa, and 1xIIIb), and 18 complications were found in the propofol group (nine of minor and nine of major grade: 2xI,

7xII, 1xIIIa, 2xIIIb, 4xIVa, and 2xV). Similar results were observed for the 6-month follow-up period with seven minor and three major events (3xI, 4xII, 2xIIIa, and 1xIIIb) in the desflurane and 12 and 11, respectively, in the propofol group (2xI, 10xII, 3xIIIa, 2xIIIb, 4xIVa, 2xV). The mortality rate of these pneumonectomy patients in the 6-month follow-up was 2/9 in the propofol group, while there was no mortality found in the desflurane group. The relevance of this subgroup analysis is unclear, and this finding should not be overemphasized but warrants future studies focusing on patients with higher severity of injury like those undergoing pneumonectomy.

Even though this trial presents negative results, these findings should not be ignored. Once more, results of small and large retrospective studies with their intrinsic biases extensively demonstrate protective effects, while an adequately powered randomized study cannot confirm these findings. It may well be that only patients with severe injuries benefit from the frequently invoked antiinfammatory effects of volatile anesthetics.

In summary, this is the first adequately powered RCT showing that desflurane compared to propofol anesthesia does not reduce the number of short- and long-term major complications after standard lung surgery. Equivalence of both regimens can now be confidently established in anesthetic management protocols.

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Competing Interests

Dr. Beck-Schimmer has received a grant from Baxter AG (Volketswil, Switzerland), not related to this work. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Bonvini: john.bonvini@usz.ch. Raw data available from Dr. Bonvini: john.bonvini@usz.ch.

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