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Original Article / Özgün Makale

One-lung ventilation duration-dependent stress response in thoracotomies and the effect of a low-volume, high-frequency differentiated ventilation strategy on this response

Torakotomilerde tek akciğer ventilasyon süresine bağlı stres yanıtı ve düşük volüm, yüksek frekanslı diferansiye ventilasyon stratejisinin bu yanıta etkisi

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ABSTRACT

Background: This study aims to investigate the effect of ventilation of the non-ventilated lung in patients undergoing one-lung ventilation by a separate low-tidal-volume (1 mL/kg) ventilator at high frequency (30/min) on preventing the effect of one-lung ventilation-associated oxidative damage.

Methods: The study included 45 patients (24 males, 21 females; mean age 54.6±7.7 years; range, 18 to 65 years) with an American Society of Anesthesiologists risk group of 1 to 2 and scheduled for elective thoracotomy. Patients were randomly divided into three groups as those due for thoracotomy without one-lung ventilation (group 1, n=15), those due for thoracotomy with one-lung ventilation (group 2, n=15), and those due for thoracotomy in whom both lungs were ventilated (group 3, n=15). Blood specimens were collected for ischemia-modified albumin, malondialdehyde, and lactate measurements one minute before one-lung ventilation (t0), 30 minutes after one-lung ventilation (t1), 60 minutes after one-lung ventilation (t2), and at postoperative 24th hour (t3). For group 1, t0 was defined as the time at which the thorax was opened.

Results: A statistically significant increase in ischemia-modified albumin, malondialdehyde, and lactate levels occurred in group 2 as the duration of one-lung ventilation increased ($p<0.01$). Plasma ischemia-modified albumin and malondialdehyde levels in group 3 were statistically significantly lower at t1, t2, and t3 compared with group 2 ($p<0.01$). Plasma lactate levels were significantly lower in group 3 at t1 ($p<0.05$) and t3 compared with group 2 ($p<0.01$).

Conclusion: Separate ventilation of the non-ventilated lung with low tidal volume and high frequency reduces the response to one-lung ventilation-associated oxidative stress in thoracic surgery.

Keywords: Differentiated ventilation strategy, one-lung ventilation, oxidative damage.

ÖZ

Amaç: Bu çalışmada tek akciğer ventilasyonu uygulanan hastalarda ventile edilmeyen akciğerin düşük tidal volümlü (1 mL/kg) ayrı bir ventilatör tarafından yüksek frekansta (30/dak.) ventile edilmesinin tek akciğer ventilasyonuna bağlı oksidatif hasarı önlemedeki etkisi araştırıldı.

Çalışma planı: Çalışmaya Amerikan Anestezistler Derneği risk grubu 1-2 olan ve elektif torakotomi planlanan 45 hasta (24 erkek, 21 kadın; ort. yaş 54.6±7.7 yıl; dağılım, 18-65 yıl) dahil edildi. Hastalar; tek akciğer ventilasyonu olmaksızın torakotomi geçirecekler (grup 1, n=15), tek akciğer ventilasyonu ile torakotomi geçirecekler (grup 2, n=15) ve iki akciğerin ventile edilmesi ile torakotomi geçirecekler (grup 3, n=15) olmak üzere randomize şekilde üç gruba ayrıldı. İskemi modifiye albumin, malondialdehit ve laktat ölçümleri için kan örnekleri tek akciğer ventilasyonundan bir dakika önce (t0), tek akciğer ventilasyonundan 30 dakika sonra (t1), tek akciğer ventilasyonundan 60 dakika sonra (t2) ve ameliyat sonrası 24. saatte (t3) alındı. Grup 1 için t0 toraksın açıldığı zaman olarak tanımlandı.

Bulgular: Grup 2'de tek akciğer ventilasyon süresi arttıkça iskemi modifiye albumin, malondialdehit ve laktat düzeylerinde istatistiksel olarak anlamlı derecede artış gerçekleşti ($p<0.01$). Grup 3'te plazma iskemi modifiye albümin ve malondialdehit düzeyleri t1, t2 ve t3'te grup 2'ye kıyasla istatistiksel olarak anlamlı derecede daha düşüktü ($p<0.01$). Grup 3'te plazma laktat düzeyleri t1 ve t3'te grup 2'ye kıyasla anlamlı derecede daha düşüktü ($p<0.01$).

Sonuç: Toraks cerrahisinde ventile edilmeyen akciğerin düşük tidal volüm ve yüksek frekans ile ayrı ventile edilmesi tek akciğer ventilasyonuna bağlı oksidatif strese yanıtı azaltır.

Anahtar sözcükler: Farklılaştırılmış ventilasyon stratejisi, tek akciğer ventilasyonu, oksidatif hasar.

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One-lung ventilation (OLV) is widely used in thoracic surgery. With this method, surgical challenges and problems that might result from these difficulties are reduced. One-lung ventilation is generally maintained as long as blood gas parameters and saturation are appropriate. However, complications such as OLV-related hypoxemia and increased intrapulmonary shunting may develop.[1,2]

Ischemia-reperfusion (I/R)-associated oxidative damage has been shown to develop as a result of hypoperfusion of the non-ventilated lung in OLV and of reperfusion with reventilation after OLV. This damage increases in a duration-dependent manner.[3] Various techniques have been used to prevent OLV-associated complications. These include oxygenation of the non-ventilated lung and continuous positive airway pressure.[4,5] These studies have shown that oxygenation of the non-ventilated lung reduces OLV-related hypoxemia and shunting. However, to the best of our knowledge, the effect on oxidative damage has not been investigated. Therefore, in this study, we aimed to investigate the effect of ventilation of the non-ventilated lung in patients undergoing OLV by a separate low-tidal-volume (1 mL/kg) ventilator at high frequency (30/min) on preventing the effect of OLV-associated oxidative damage.

PATIENTS AND METHODS

Forty-five patients (24 males, 21 females; mean age 54.6±7.7 years; range, 18 to 65 years) with an American Society of Anesthesiologists (ASA) risk group of 1 to 2 and scheduled for elective thoracotomy were enrolled in this study that was conducted at Karadeniz Technical University Faculty of Medicine Farabi Hospital between February 2009 and October 2009. Patients were allocated randomly, using the sealed-envelope method, to one of three groups as those scheduled for thoracotomy but not to undergo routine OLV (group 1, n=15), those scheduled for thoracotomy and routine OLV (group 2, n=15), and those scheduled for thoracotomy and in whom the non-ventilated lung was to be ventilated with a separate ventilator at a low tidal volume (group 3, n=15). Patients with an ASA risk group of 3 or above or with metabolic, renal, or hepatic disease were excluded. The study protocol was approved by the Karadeniz Technical University Faculty of Medicine Farabi Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were intramuscularly premedicated with the standard 2 mg of midazolam and 0.5 mg of atropine sulphate. Patients were taken to the operating room, and venous access was secured with a 16- or 18-gauge intravenous catheter from the antecubital vein. Intraoperative fluid replacement was performed through this catheter with 0.09% saline. The requisite drugs for anesthesia maintenance were administered via the same route. Electrocardiogram, invasive blood pressure, and pulse oximetry monitoring were performed for all patients. Anesthesia was induced with 3 mg of midazolam, 2 mcg/kg of fentanyl, 2 mg/kg of propofol, and 0.2 mg/kg of cisatracurium. Three minutes after induction, patients were intubated with a Robertshaw double-lumen tube and monitored with chest auscultation and fiberoptic bronchoscopy. Following induction, all patients' respiration rates were set at 12/min with a mechanical ventilator (OAV 7710, Ohmeda, Essex, UK) for controlled respiration, with an inspiration/expiration ratio of 1:2 and tidal volume of 10 mL/kg. Anesthesia was maintained with 50% oxygen (3 L/min), 50% air (3 L/min), and 1.2 minimum alveolar concentration sevoflurane. The muscle relaxation requirement was met with cisatracurium at a dose of 0.01 mg/kg. The settings in group 1 were 50% oxygen (3 L/min), 50% air (3 L/min), tidal volume of 8 to 10 mL/kg, and arterial carbon dioxide (CO2) pressure (arterial partial pressure of CO_2) of 35 to 40 mmHg. In group 2, the settings were 100% oxygen (6 L/min), sevoflurane at 1.2 MAC, respiration rate at 16 to 20/min, and tidal volume at 6 to 8 mL/kg. In group 3 (after standard OLV; the other deflated lung was ventilated with a different ventilator in volume control mode), the settings were a tidal volume of 1 mL/kg, frequency of 39, and 50% oxygen.

Blood specimens from all groups were collected for ischemia-modified albumin (IMA), malondialdehyde (MDA), and lactate measurements one min before OLV (t0), 30 min after OLV (t1), 60 min after OLV (t2), and at postoperative 24 hour (t3). For group 1, t0 was defined as the time at which the thorax was opened.

Cobalt's decreasing albumin-binding capacity was evaluated using the rapid and colorimetric method developed by Bar-Or et al.[6] A total of 200 μL of patient serum was added to a glass tube followed by 50 μL of 0.1% cobalt chloride hexahydrate ($CoCl2{\cdot}6H_2O$) (Sigma Aldrich, St. Louis, MO, USA). After light stirring, this was left to stand for 10 min to permit sufficient cobalt–albumin binding. A total of 50 mL of 1.5-mg/mL dithiothreitol (DTT) (Sigma Aldrich, St. Louis, MO, USA) was added as coloring agent. After waiting for two minutes, the reaction

was halted by the addition of 1 mL of 0.9% sodium chloride (NaCl) to stop the bonding between cobalt and albumin. Blind sampling was performed for each specimen. At the DTT addition stage, serum cobalt blanks without DTT were prepared with the addition of 50 µL of distilled water instead of 50 µL of 1.5-mg/mL DTT. Specimen absorbance at 470 nm was measured with a spectrophotometer (UV-1601, Shimadzu, Tokyo, Japan). Color formation in specimens with DTT was compared with color formation in the blanks, and the results were reported as absorbance units.

The level of MDA in plasma specimens was determined using the thiobarbituric acid (TBA)-reactive substance method developed by Yagi[7] The red color that formed as a result of the reaction between the lipid peroxidation product (MDA) and TBA was measured spectrophotometrically. To remove water-soluble materials that might produce the same color by entering into reaction with TBA, serum lipids and proteins were dissolved with the phosphotungstic acid/sulfuric acid system.

To a test tube were added 150 μL of plasma, 1.2 mL of sulfuric acid (H_2SO_4), and 150 mL of phosphotungstic acid. This was left to stand for five min after thorough mixing. The mixture was centrifuged at 1500 × g for 10 min, and the upper phase was removed. To the remaining precipitate was added 2 mL of distilled water, and this was vortexed until dissolution. To the tube was added 500 μL TBA, and this was incubated at 100°C for one h. Following incubation, the tubes were centrifuged at 1000 × g for 10 min. The transparent part on the top was removed, and absorbances were read at a wavelength of 532 nm. Subsequently, 1 mmol of 1,1,3,3-tetramethoxypropane was incubated in 100 mL of 0.01 molar HCl (hydrogen chloride) at 50°C for one h, and 10-, 5-, 3-, 2-, 1-, and 0.5-nmol/mL study standards were prepared from the MDA solution that formed as a result of hydrolysis of that compound. A standard chart was created from the results obtained. Plasma MDA levels were expressed as nmol MDA/mL on the basis of that chart.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine normality and homogeneity of data distribution. Parametric data (age, weight, height, IMA, MDA and lactate) were compared using one-way analysis of variation (ANOVA). Post-hoc comparisons were performed using the Dunnett's two-tailed t-test with the controls as the reference control group. Nonparametric data (gender) were compared using the Kruskal-Wallis test. Repeat measured ANOVA was used for statistical analysis. *P* values <0.05 were considered statistically significant.

RESULTS

No differences were found among the groups in terms of demographic characteristics (Table 1). Baseline MDA, IMA, lactate, blood gas, and hemodynamic values were not statistically different among the groups (p>0.05).

In group 2, there was a statistically significant increase in IMA, MDA, and lactate levels as the duration of OLV increased (p<0.01). In group 3, plasma IMA levels were statistically significantly lower at t1, t2, and t3 compared with group 2 (p<0.01) (Figure 1). Malondialdehyde levels were also significantly lower in group 3 at t1, t2, and t3 compared with group 2 (p<0.01) (Figure 2). Plasma lactate levels at t1 and t3 were also significantly lower in group 3 compared to group 2 (p<0.01) (Figure 3).

Plasma IMA at t1 in group 2 was compared with groups 1 and 3 (p<0.05). Ischemia-modified albumin at t2 in group 2 was compared with groups 1 and 3 (p<0.01). Ischemia-modified albumin at t2 was compared with t1 and t3 in group 2 (p<0.05) (Figure 1).

Plasma MDA at t1 in group 2 was compared with groups 1 and 3 (p<0.05). Malondialdehyde at t2 in

Table 1. Demographic data of patients in three groups

	Group 1 (n=15)		Group 2 (n=15)		Group 3 (n=15)	
	n	Mean±SD	n	Mean±SD	n	Mean±SD
Age (year)		54.7±9.9		55.2±8.5		54.4±5.6
Gender						
Male	8		7		9	
Female	7		8		6	
Weight (kg)		67.8±2.6		67.1±2.4		66.5±2.4
Height (cm)		167±4.3		167.3±3.4		167.2±2.9

SD: Standard deviation.

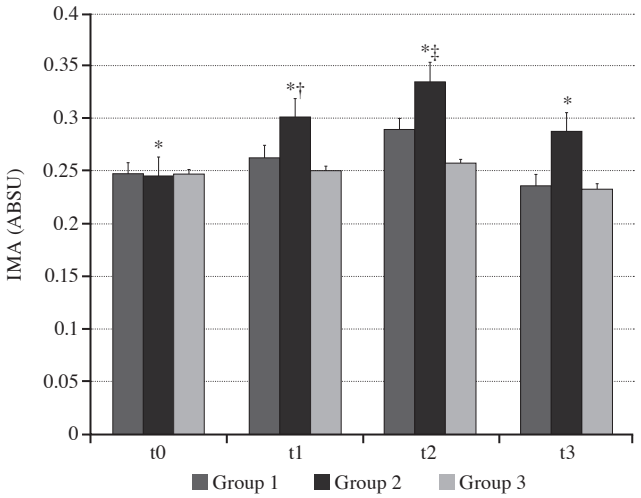

Figure 1. Plasma concentration of ischemia-modified albumin. Ischemia-modified albumin at t1 in group 2 compared with groups 1 and 3 †(p<0.05). Ischemia-modified albumin at t2 in group 2 compared with groups 1 and 3 ‡(p<0.01). Ischemia-modified albumin at t2 compared with t1 and t3 in group 2 *(p<0.05).
ABSU: Absorbance unit; IMA: Ischemia-modified albumin.

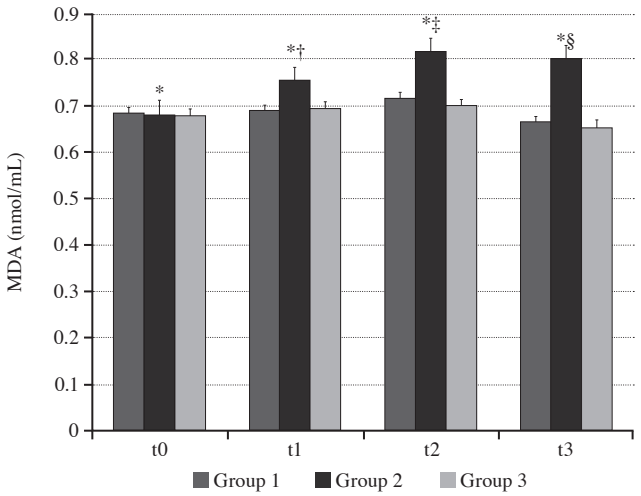

Figure 2. Plasma concentration of malondialdehyde. Malondialdehyde at t1 in group 2 compared with groups 1 and 3 †(p<0.05). Malondialdehyde at t2 in group 2 compared with groups 1 and 3 ‡(p<0.01). Malondialdehyde at t3 in group 2 compared with groups 1 and 3 §(p<0.01). Malondialdehyde at t2 compared with t0, t1 and t3 in group 2 *(p<0.05).
MDA: Malonyldialdehyde.

group 2 was compared with groups 1 and 3 (p<0.01). Ischemia-modified albumin at t3 in group 2 was compared with groups 1 and 3 (p<0.01). Malondialdehyde at t2 was compared with t0, t1 and t3 in group 2 (p<0.05).

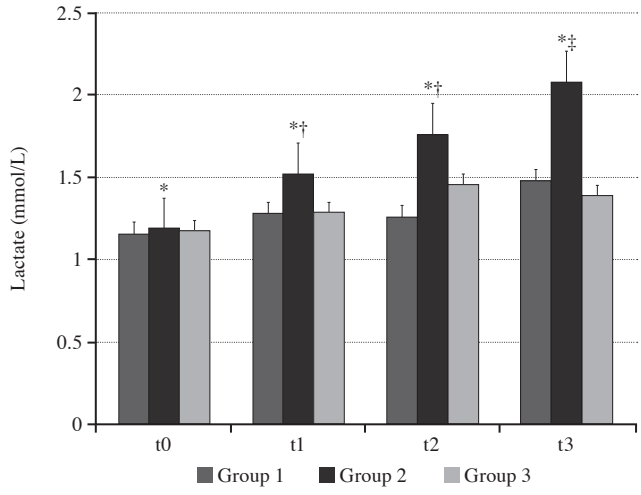

Figure 3. Plasma concentrations of lactate. Lactate at t1 and t2 in group 2 compared with groups 1 and 3 †(p<0.05). Lactate at t3 in group 2 compared with groups 1 and 3 ‡(p<0.01). Lactate at t3 compared with t0, t1 and t2 in group 2 *(p<0.05).

Plasma lactate at t1 and t2 in group 2 compared with groups 1 and 3 (p<0.05). Lactate at t3, in group 2 compared with groups 1 and 3 (p<0.01). Lactate at t3 compared with t0, t1 and t2 in group 2 (p<0.05) (Figure 3).

DISCUSSION

Oxidative damage has been shown to rise in association with ischemia and subsequent reperfusion throughout OLV.[3] In this prospective, randomized study, we investigated the development of OLV-associated oxidative damage by measuring IMA, MDA, and lactate levels. We also investigated the effect on plasma IMA, MDA, and lactate levels during separate ventilation of the non-ventilated lung with a different ventilator at low tidal volume and high frequency on the prevention of that damage.

We identified an increase in plasma IMA, MDA, and lactate levels with increasing oxidative damage as the length of OLV increased. We showed that separate ventilation of the non-ventilated lung with a different ventilator at low tidal volume and high frequency led to a decrease in plasma IMA, MDA, and lactate levels.

One-lung ventilation is widely used in thoracic surgery because it improves the surgical field of vision, allowing the operation to be performed more easily. It can be used to the extent permitted by the patient's hemodynamic status. One-lung ventilation is performed when all monitoring criteria are appropriate: vital findings, oxygen saturation values,

and blood gas parameters. However, the presence of abnormalities in these criteria is not an indicator of probable cellular damage. Studies have investigated oxidative damage associated with ischemia and subsequent reperfusion throughout OLV.[3,8-10] Various biochemical parameters have been examined to investigate this damage. We used IMA, which is increasingly being used as an oxidative stress marker and has been placed on the list of tests approved for the diagnosis of myocardial ischemia by the United States Food and Drug Administration. Ischemia-modified albumin is based on the identification of a decrease in the human serum albumin N-terminal binding capacity to cobalt during myocardial ischemia.[11,12] Cellular alterations such as the formation of free radicals, acidosis, and impairment of the sodium-calcium pump during ischemia or reperfusion have been held responsible for modifications affecting the N-terminal region.[11-13] Several studies have shown that IMA indicates the presence of I/R-associated oxidative damage.[13-15] Also, IMA is more sensitive than other oxidative stress markers (e.g., MDA, total antioxidant status [TAS], total oxidant status [TOS], and oxidative stress index [OSI]) for detection of I/R-associated oxidative damage.[16]

We found no studies of IMA levels in OLV-associated oxidative damage. We identified a statistically significant rise in IMA levels with increasing OLV duration. Plasma IMA levels were also significantly lower in the group in which the non-ventilated lung was ventilated separately. Another biochemical parameter associated with I/R-associated oxidative damage is MDA. Free radicals and other powerful oxidants form as a normal product of aerobic metabolism in biological systems. The term "free radicals" in fact suggests free oxygen radicals (or reactive oxygen species, to use a more general term). Free oxygen radicals have toxic effects on proteins, deoxyribonucleic acid, carbohydrates, and particularly lipids. The effect of free radicals on lipids involves lipid peroxidation, which is a result of the effect of oxidizing agents on fatty acids in the structure of lipoproteins and the membrane. Lipid peroxidation leads to the formation of such highly toxic products as MDA and 4-hidroxynonenal. Malondialdehyde is therefore a powerful marker of oxidative damage.[14,16,17]

In one experimental study, Tekinbas et al.[3] showed that OLV gives rise to cellular damage and that this damage increases with the duration of OLV: biochemically with a rise in plasma MDA and plasma myeloperoxidase levels, and histopathologically based on examination of pulmonary tissue. In our clinical study, there was an OLV duration-dependent rise in plasma MDA levels. Malondialdehyde levels were significantly lower in the group in which the non-ventilated lung was ventilated separately. Misthos et al.[8] showed that oxidative damage increased with the duration of OLV and that there was a pronounced rise in plasma MDA levels. Those authors measured plasma MDA, a marker replacing free oxygen radicals, in patients undergoing pulmonary resection. Rising MDA levels and the degree of oxidative stress measured were associated with performance of OLV and its duration. Reventilation of the lungs after OLV gives rise to severe oxidative stress by supporting the concept of reperfusion damage.

Another parameter we examined was blood lactate level. Lactate is a byproduct of carbohydrate metabolism. The blood lactate concentration depends on its production speed and metabolism in the liver and kidneys. A moderate rise in lactate production results in hepatic lactate elimination. Lactic acidosis arises in two clinical conditions: type A hypoxia (together with decreasing tissue oxygenation, such as that occurring in shock, hypovolemia, and left ventricular failure) and type B metabolic diseases (such as diabetes mellitus and neoplasia) due to drug toxins (such as methanol, ethanol, and salicylates) or inherited metabolic disorders. Hypoxia-related elevated lactate levels are frequently encountered, and the levels rise in I/R injury.[14,18,19] We identified a rise in lactate levels associated with duration of OLV.

Various studies have been performed for the purpose of reducing OLV-related pulmonary injury. Different ventilator modes or different anesthetic methods and agents have been tested.[20,21] The establishment of a different ventilation strategy that will not eliminate the advantages bestowed by OLV during surgery and in which OLV-related local and systemic pathological effects do not arise or else are reduced to a minimum is of great importance. Pardos et al.[20] investigated the effectiveness of the use of pressure control and volume control in OLV. They showed that ventilator mode variation did not affect arterial oxygenation during OLV or oxygenation in the early postoperative period. In our study, we used a volume-controlled ventilator mode in all groups. In group 3, we ventilated the non-ventilated lung with another ventilator in a volume-controlled mode (1 mL/kg). Misiolek et al.[22] investigated double-lung jet ventilation as a possible alternative to OLV for thoracotomy. They showed that double-lung jet ventilation was reliable in thoracotomy and possessed advantages over OLV. In addition to

these studies, research regarding the oxygenation of the non-ventilated lung in patients administered OLV has also been conducted. Pfitzner and Pfitzner[23] showed that apnoeic oxygenation of the non-ventilated lung in OLV delayed desaturation. Kim et al.[5] showed that the administration of continuous positive airway pressure (CPAP) to the non-ventilated lung in OLV improved arterial oxygenation. These studies did not examine the effect on oxidative damage of different procedures on the non-ventilated lung. Our study determined that oxidative stress rose in association with duration of OLV in patients who undergo OLV (using plasma IMA, MDA, and lactate levels). Ventilation of the non-ventilated lung at low tidal volume (1 mL/kg) and high frequency prevents this OLV-related damage.

This study has some limitations. Firstly, it would have been better to show tissue damage histopathologically. Therefore, this clinical study should be supported by experimental studies. A second limitation is our small sample size. Another limitation is the lack of measurement of other oxidative stress parameters such as myeloperoxidase, total oxidant status, and total antioxidant status.

In conclusion, our data suggest that one-lung ventilation gives rise to oxidative damage and that this damage increases with one-lung ventilation duration. In addition, a low-volume (1 mL/kg), high-frequency. ventilation strategy was capable of providing the advantages of one-lung ventilation and of reducing oxidative damage developing secondary to ischemia/reperfusion. We believe that its clinical use can reduce postoperative pulmonary damage and associated mortality.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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