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Effects of Curcumin on One-Lung Ventilation–Induced Lung Injury in a Rat Model

Sıçan Modelinde Tek Akciğer Ventilasyonuna Bağlı Akciğer Hasarında Kurkuminin Etkileri

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Abstract: One-lung ventilation (OLV), routinely used in thoracic surgery, induces regional ischemia followed by reperfusion upon re-expansion of the collapsed lung, leading to oxidative stress, inflammation, vascular leakage, and tissue injury. Curcumin, a polyphenolic compound withantioxidant and anti-inflammatory properties, has demonstrated protective effects in ischemia–reperfusion (I/R) models; however, its role in OLV-induced lung injury remains unclear. This study aimed to evaluate the effects of curcumin on biochemical and histopathological markers of pulmonary I/R injury in a rat OLV model. Thirty male Sprague–Dawley rats were randomized into three groups (n=10 each): Control, imethyl sulfoxide (DMSO) vehicle, and Curcumin (200 mg/kg intraperitoneally). Right-lung ischemia was induced for 60 minutes via left-lung OLV, followed by 30 minutes of reperfusion with two-lung ventilation (TLV). Lung tissue samples were collected after ischemia and reperfusion . Malondialdehyde (MDA), superoxide dismutase (SOD), and tumor necrosis factor-α (TNF-α)levels were measured, and histopathological injury was semi-quantitatively scored. Biochemical markers showed no significant intergroup differences ($p>0.05$). In contrast, histopathological injury was significantly higher in the Control group compared with both Curcumin and DMSO groups (all $p<0.0001$), with no difference between the latter two . Temporal changes within groups were minimal. Curcumin was associated with reduced histopathological lung injury without significant biochemical improvement..However, similer findings in the DMSO vehicle group suggest that the independent effect of curcumin cannot be clearly distinguished.. Further studies using alternative solvents, optimized dosing and extended reperfusion are warranted to clarify its specific role

.**Keywords**: Curcumin, One- lung ventilation, Lung injury

Özet: Tek akciğer ventilasyonu (TAV), göğüs cerrahisinde rutin olarak kullanılan bir yöntem olup, kollabe akciğerin yeniden ekspansiyonu ile birlikte bölgesel iskemi ve ardından reperfüzyona neden olarak oksidatif stres, inflamasyon, vasküler kaçak ve doku hasarına yol açar.Antioksidan ve antiinflamatuvar özelliklere sahip bir polifenol olan kurkumin, iskemi–reperfüzyon (İ/R) modellerinde koruyucu etkiler göstermiştir; ancak TAV'ye bağlı akciğer hasarındaki rolü net olarak ortaya konulamamıştır. Bu çalışmada, sıçan TAV modelinde kurkuminin pulmoner I/R hasarının biyokimyasal ve histopatolojik belirteçler üzerindeki etkilerinin değerlendirilmesi amaçlanmıştır. Otuz erkek Sprague–Dawley sıçan; Kontrol, dimethyl sulfoxide (DMSO) ve curkumin gruplarına randomize edildi (her grupta n=10). Sol akciğer ventilasyonu sağlanarak sağ akciğerde 60 dakika süreyle iskemi oluşturuldu ve ardından iki akciğer ventilasyonu ile 30 dakikalık reperfüzyon sağlandı. Akciğer doku örnekleri, iskemi ve reperfüzyon sonrası alındı.Malondialdehit (MDA), süperoksit dismutaz (SOD) ve tümör nekroz faktör-alfa (TNF-α) düzeyleri ölçüldü ve histopatolojik hasar yarı kantitatif olarak skorlandı.Biyokimyasal belirteçler açısından gruplar arasında anlamlı fark saptanmadı ($p>0,05$). Buna karşılık, histopatolojik hasar Kontrol grubunda hem Kurkumin hem de DMSO gruplarına kıyasla anlamlı derecede daha yüksekti (tümü için $p<0,0001$) ve bu iki grup arasında fark bulunmadı. Grup içi zamansal değişiklikler minimaldi. Kurkumin uygulaması, biyokimyasal düzelme olmaksizin histopatolojik akciğer hasarında azalma ile ilişkili bulundu. Ancak DMSO taşıyıcı grubunda da benzer bulguların gözlenmesi, kurkuminin bağımsız etkisinin net olarak ayırt edilemediğini göstermektedir. Kurkuminin özgül etkisinin belirlenebilmesi için, alternatif çözücülerin kullanıldığı, dozlamaların optimize edildiği ve daha uzun reperfüzyon sürelerini içeren ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kurkumin, Tek akciğer ventilasyonu, Akciğer hasarı

Ethics Committee Approval: This study was approved by the Eskişehir Osmangazi University Ethics Committee and conducted in accordance with Declaration of Helsinki (Approvel number:355 date: 22/08/2013)

Informed Consent: Informed consent was not obtained as this was an experimental animal study.

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1. Introduction

Ischemia–reperfusion (I/R) injury is an important contributor to postoperative pulmonary complications in thoracic anesthesia. Restoration of blood flow and oxygen delivery to previously ischemic tissue triggers a burst of reactive oxygen species (ROS), activation of inflammatory cascades, and disruption of the alveolar–capillary barrier (1). These processes collectively promote lipid peroxidation, structural cellular injury, vascular leakage, and recruitment of inflammatory cells, ultimately manifesting as acute lung injury (2). In clinical practice, a scenario closely resembling pulmonary I/R injury occurs during one-lung ventilation (OLV), where intentional collapse of one lung facilitates surgical exposure while the contralateral lung is ventilated. The re-expansion and reperfusion of the collapsed lung at the end of OLV can provoke oxidative stress and inflammation similar to classical I/R physiology and has been implicated in re-expansion pulmonary edema and postoperative lung injury (3). Although protective ventilation strategies and perioperative optimization reduce this risk, they do not fully prevent OLV-related biochemical and structural lung injury, sustaining interest in adjunct pharmacological therapies.

Curcumin, a polyphenolic compound derived from Curcuma longa, has drawn substantial attention for its broad antioxidant, anti-inflammatory, and cytoprotective properties. Its phenolic structure allows direct scavenging of ROS, while its regulatory effects on multiple intracellular pathways, such as inhibition of nuclear factor-kappa B (NF-κB), modulation of mitogen-activated protein kinases, and enhancement of endogenous antioxidant enzymes, further contribute to its biological activity (4, 5). Curcumin upregulates superoxide dismutase, catalase, and peroxiredoxins, and suppresses the production of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (6). A growing body of experimental and clinical evidence supports these effects; meta-analyses of human trials have demonstrated improvements in systemic antioxidant capacity and reductions in circulating inflammatory biomarkers following curcumin supplementation (7). These characteristics make curcumin a compelling candidate for the prevention or attenuation of I/R-related tissue damage.

Across organ systems, curcumin has demonstrated protective effects in established models of I/R injury. In cardiac, cerebral, renal, and hepatic I/R models, curcumin has consistently reduced oxidative damage, improved tissue histology, and modulated inflammatory responses (8-11). Increasing attention has recently turned toward its potential benefits in pulmonary injury. Experimental studies have shown that curcumin mitigates histological lung damage after pulmonary hilum clamping, reduces markers of oxidative stress, and modulates signaling pathways associated with re-expansion injury (12). Additionally, in vitro data suggest curcumin may protect lung epithelial cells from the injurious effects of serum obtained from patients undergoing OLV, potentially through upregulation of peroxiredoxin-6 (13). Despite these promising findings, data specifically examining curcumin's effects in the context of OLV-induced lung injury remain limited, and no study to date has evaluated curcumin in a controlled in vivo model that mimics the perioperative course of OLV and reperfusion.

Based on the biological rationale and prior evidence, we hypothesized that curcumin administration would attenuate lung injury resulting from acute ischemia and reperfusion associated with one-lung ventilation (OLV). The aim of this study was to determine whether curcumin provides measurable biochemical and histopathological protection against OLV-induced pulmonary I/R injury.

1. 2. Materyals and Methods

2.1. Ethical Approval and Animals

All experimental procedures were approved by the Eskişehir Osmangazi Universty Animal Experiments Local Ethics Committee (Approval No. 60/355; August 22, 2013) and conducted in accordance with national regulations and international guidelines for the care and use of laboratory animals (NIH Guide for the Care and Use of Laboratory Animals). Thirty male Sprague–Dawley rats (260–320 g) were obtained from the institution's Medical and Surgical Experimental Research Center. Animals were acclimatized for at least 72 hours before experimentation and housed in standard polycarbonate cages under controlled environmental conditions (20–22°C, 45–50% humidity, 12-h light/dark cycle) with free access to standard chow and water. Rats were fasted for 12 hours prior to the procedure while water was provided ad libitum.

Animals were randomly assigned, using a computer-generated randomization schedule, into three experimental groups (n = 10 per group):

Control Group: Rats underwent the one-lung ventilation (OLV) ischemia–reperfusion protocol without administration of curcumin or vehicle (other than procedural saline and heparin).

Curcumin Group: Rats received curcumin (200 mg/kg, intraperitoneally), dissolved in dimethyl sulfoxide (DMSO), 15 minutes before initiation of OLV.

DMSO Vehicle Group: Rats received an equivalent volume of DMSO intraperitoneally 15 minutes before OLV to control for vehicle-related effects.

2.2. Anesthesia and One-Lung Ventilation Procedure

On the day of the experiment, anesthesia was induced with intraperitoneal ketamine (40 mg/kg) and xylazine (5 mg/kg). Supplemental doses were administered as needed to maintain a surgical depth of anesthesia, confirmed by absence of withdrawal to paw pinch. Following induction, rats were placed in the supine position, and the neck and thorax were disinfected with 10% povidone–iodine. Physiological monitoring included noninvasive blood pressure via tail-cuff sphygmomanometry and electrocardiography for heart rate and rhythm. All animals received intraperitoneal 0.9% saline (10 mL/kg) for hydration and heparin (100 IU/kg) to prevent intravascular clot formation during the procedure.

A midline cervical incision was made, and a tracheostomy was performed under sterile conditions. A 16-gauge angiocatheter was inserted into the trachea and secured as the endotracheal tube. One-lung ventilation (OLV) was established by advancing the catheter into the left main bronchus to selectively ventilate the left lung. Correct placement was confirmed by right thoracotomy, verifying collapse of the right lung with ventilation of the left lung only. Mechanical ventilation was provided using a rodent ventilator (Model 7025, Hugo Sachs Elektronic, Germany). During OLV, ventilation parameters included a tidal volume of 6 mL/kg, respiratory rate of 80 breaths/min, and FiO_2 of 1.0. OLV was maintained for 60 minutes to induce ischemia in the non-ventilated right lung.

At the end of the ischemic OLV period, a small sample of right-lung tissue (right middle lobe region) was harvested immediately for biochemical analysis. The angiocatheter was then withdrawn to the level of the carina, enabling re-expansion of the right lung and initiation of two-lung ventilation (TLV). The thoracotomy incision was temporarily approximated, and reperfusion of the previously ischemic lung was simulated with 30 minutes of TLV using a tidal volume of 8 mL/kg, respiratory rate of 60 breaths/min, and FiO_2 of 1.0. At the end of the reperfusion period, animals were deeply anesthetized and euthanized by overdose of anesthetic followed by exsanguination. The remaining right-lung tissue, encompassing both ischemic and reperfused regions, was excised for histopathological and biochemical assessments.

The Curcumin and DMSO groups underwent the identical surgical protocol described above. Curcumin was administered intraperitoneally at 200 mg/kg (Sigma Chemical Co., St. Louis, MO, USA) dissolved in dimethyl sulfoxide (DMSO) 15 minutes prior to OLV. Rats in the DMSO group received an equivalent intraperitoneal volume of DMSO alone. This design allowed evaluation of curcumin's effects while controlling for potential vehicle-related influences. All animals remained under deep anesthesia throughout the procedure, and all efforts were made to minimize discomfort until humane euthanasia at study completion.

2.3. Biochemical Assays

Lung tissue samples designated for biochemical analysis were snap-frozen in liquid nitrogen immediately after excision and stored at –80°C until analysis. Before assays, samples were thawed on ice and homogenized in the appropriate buffers supplied with each commercial kit. The biochemical markers evaluated—malondialdehyde (MDA), superoxide dismutase (SOD), and tumor necrosis factor-alpha (TNF-α)—were selected as key indicators of oxidative stress and inflammation.

Malondialdehyde (MDA), a lipid peroxidation end-product, was quantified using a thiobarbituric acid reactive substances (TBARS) assay kit (Cayman Chemical, Ann Arbor, MI, USA). The MDA–TBA adduct was detected spectrophotometrically, and results were expressed as nmol MDA per milligram of lung tissue.

Superoxide Dismutase (SOD) activity was measured using a commercial SOD assay kit (Cayman Chemical). The assay quantifies inhibition of the reduction of a tetrazolium salt by superoxide radicals, with one unit of activity defined as the amount of enzyme producing 50% inhibition under assay conditions. Total protein concentration in tissue homogenates was determined using a bicinchoninic acid (BCA) assay, and SOD activity was normalized to protein content and expressed as U/mg protein.

Tumor Necrosis Factor-alpha (TNF-α) levels in lung homogenates were determined using a rat-specific ELISA kit (Invitrogen, Camarillo, CA, USA). Colorimetric detection was performed after enzymatic substrate development, and concentrations were reported as pg/mg tissue.

All assays were performed according to manufacturers' instructions. Absorbance values were read using a microplate reader, and concentrations or enzyme activities were calculated from standard curves. Each sample was analyzed in duplicate, and mean values were used for statistical evaluation.

2.4. Histopathological Evaluation

Portions of the right lung from each animal were fixed in 10% neutral-buffered formalin for at least 48 hours. Tissues were processed using standard paraffin-embedding techniques, sectioned at 4 µm thickness, mounted on glass slides, and stained with hematoxylin and eosin (H&E) for microscopic examination. Histopathological analysis was performed by a single board-certified pathologist who was blinded to the experimental groups and time points. To account for regional variability, at least two non-overlapping sections from different regions of the right lung were evaluated for each animal. Each section was examined under multiple magnifications (10×, 20×, and 40× objectives).

Lung injury was semi-quantitatively assessed based on five predefined parameters characteristic of ischemia–reperfusion injury: Alveolar congestion, interstitial edema, intra-alveolar hemorrhage, polymorphonuclear leukocyte (PMNL) infiltration, lymphocyte infiltration.

Each parameter was graded on a standardized four-point ordinal scale:

0 = No abnormality (normal lung architecture)

1 = Focal, minimal change

2 = Multifocal, moderate change

3 = Multifocal, severe change

For each parameter, the highest severity observed in any field was recorded as the score for that animal. When two tissue sections were evaluated, scores were averaged to obtain a representative value. Histological scoring was performed at both time points; immediately after the 60-minute OLV (ischemic phase) and after the 30-minute TLV period (reperfusion phase). This scoring system provided an ordinal measure of overall lung injury severity, reflecting changes in vascular congestion, edema formation, hemorrhage, and inflammatory cell infiltration induced by ischemia and reperfusion.

2.5. Statistical Analysis

All statistical analyses were performed using Minitab 16 (Minitab Inc., State College, PA, USA) and IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Normality of distribution was assessed using the Shapiro–Wilk test. Biochemical parameters (MDA, SOD, and TNF-α) were analyzed using a two-way repeated-measures analysis of variance (ANOVA), with group (Control, DMSO, Curcumin) as the between-subjects factor and time (end of OLV vs. end of TLV) as the within-subjects factor. Post-hoc pairwise comparisons were conducted using Tukey's test. Histopathological injury scores, ordinal variables including alveolar congestion, interstitial edema, intra-alveolar hemorrhage, polymorphonuclear leukocyte (PMNL) infiltration, and lymphocyte infiltration, were analyzed using the Kruskal–Wallis H test to compare groups at each time point. When significant differences were detected, pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni adjustment to control for type I error due to multiple testing. A two-tailed p-value < 0.05 was considered statistically significant for all analyses.

2. 3. Results

A total of 30 rats were included in the study and completed all experimental procedures and analyses.

3.1. Biochemical Findings

Biochemical parameters (MDA, SOD, and TNF-α) measured at the end of 60-minute OLV and the end of 30-minute TLV for all three groups are summarized in Table 1. Overall, none of the biochemical markers demonstrated statistically significant differences either within groups across the two time points or between groups at the same time point.

3.1.1. Malondialdehyde (MDA)

At both measurement points, 60 minutes of OLV and 30 minutes of TLV, MDA concentrations showed no significant differences between the Control, DMSO, and Curcumin groups ($p>0.05$ for all comparisons). Within-group comparisons also

demonstrated no significant change in MDA levels between the two time points (p>0.05).

3.1.2. Superoxide Dismutase (SOD)

SOD activity did not differ significantly between the groups at either 60-minute OLV or 30-minute TLV (p>0.05). In the Curcumin group, SOD activity tended to be numerically higher at the TLV time point compared with OLV, although this difference did not reach statistical significance (p>0.05). Across all groups, changes in SOD activity between time points were also nonsignificant.

3.1.3. Tumor Necrosis Factor-α (TNF-α)

TNF-α concentrations increased slightly from the OLV to TLV time point in the Control and DMSO groups, but these increases were not statistically significant (p>0.05). The Curcumin group exhibited numerically lower TNF-α levels at both time points compared with the other groups, but the differences were not statistically significant (p>0.05). No significant between-group or within-group differences were observed.

3.2. Histopathological Findings

Histopathological evaluation demonstrated marked differences among the Control, DMSO, and Curcumin groups following 60 minutes of one-lung ventilation (OLV) and subsequent 30 minutes of two-lung ventilation (TLV) with detailed scoring data presented in Table 2.

3.2.1. Alveolar Congestion

After 60-min OLV, alveolar congestion scores differed significantly among groups ($p < 0.0001$). The Control group exhibited the highest congestion (2 [2–2]), whereas DMSO and Curcumin groups showed significantly lower scores (both 1 [IQR 1–1]). Following TLV, between-group differences were no longer statistically significant ($p = 0.065$). Within-group comparisons revealed no significant change from OLV to TLV in any group ($p = 1.000$, 0.083, and 0.157, respectively).

3.2.2. Interstitial Edema

Interstitial edema showed pronounced between-group differences after both OLV and TLV (both $p < 0.0001$). The Control group displayed consistently higher edema scores, while DMSO and Curcumin groups remained significantly lower at both time points. Within-group p-values indicated no significant OLV→TLV change in any group ($p = 0.257$, 0.317, and 0.317, respectively).

3.2.3. Intra-alveolar Hemorrhage

Hemorrhage scores also differed significantly among groups at both assessment points (both $p < 0.0001$). Control animals demonstrated higher hemorrhage following OLV compared with DMSO and Curcumin groups. Despite an increase in variability after TLV, group differences remained significant. No within-group changes were observed ($p = 0.214$, 0.317, and 0.564).

3.2.4. PMNL Infiltration

Neutrophilic infiltration was substantially higher in the Control group than in both treatment groups at OLV and TLV ($p < 0.0001$ for both). Neither DMSO nor Curcumin animals showed measurable PMNL infiltration at either time point. A mild but non-significant reduction was noted in the Control group following TLV ($p = 0.059$).

3.2.5. Lymphocyte Infiltration

Lymphocyte infiltration also showed strong between-group differences ($p < 0.0001$ at both time points). As with other inflammatory parameters, scores were highest in the Control group. Within-group analysis revealed a significant OLV→TLV decrease only in the DMSO group ($p = 0.046$), whereas no changes were observed in the Control or Curcumin groups.

Table 1. MDA, SOD and TNF-α levels in different rat groups at two time points

	Group	After 60-min OLV	After 30-min TLV
MDA (nmol/mg)	Control	3.06 ± 0.68	3.04 ± 0.97
	DMSO	2.95 ± 0.82	2.72 ± 0.53
	Curcumin	2.97 ± 0.95	2.78 ± 0.97
SOD (U/mg protein)	Control	2.68 ± 1.40	2.84 ± 2.44
	DMSO	3.18 ± 1.79	2.93 ± 0.94
	Curcumin	5.31 ± 1.71	6.39 ± 2.08
TNF-α (pg/mg)	Control	246.36 ± 87.01	295.04 ± 93.04
	DMSO	192.67 ± 81.13	244.19 ± 59.21
	Curcumin	165.01 ± 121.37	127.17 ± 52.78

Values are presented as mean ± SD. OLV: one-lung ventilation; TLV: two-lung ventilation; MDA: malondialdehyde; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-alpha; DMSO: dimethyl sulfoxide. Between-group and time-dependent comparisons were analyzed using two-way repeated-measures ANOVA. No statistically significant main effects (group or time) or group × time interactions were detected for biochemical parameters (all p > 0.05).

Table 2. Histopathological scoring at the end of the OLV and TLV periods.

Group	After 60-min OLV	After 30-min TLV	P* value
Alveolar Congestion			
Control	2 (2–2 [2–2])[a]	2 (1–3 [1–3])[a]	1.000
DMSO	1 (1–1 [0–2])[b]	1 (1–2 [1–3])[a]	0.083
Curcumin	1 (1–1 [1–1])[b]	1 (1–1 [1–2])[a]	0.157
P value**	**p < 0.0001**	0.065	
Interstitial Edema			
Control	2 (2–2 [1–2])[a]	2 (1–2 [1–2])[a]	0.257
DMSO	0 (0–0 [0–1])[b]	0 (0–0 [0–2])[b]	0.317
Curcumin	0 (0–1 [0–1])[b]	0 (0–1 [0–1])[b]	0.317
P value**	**p < 0.0001**	**p < 0.0001**	
Intra-alveolar Hemorrhage			
Control	1 (1–1 [1–2])[a]	1 (1–1 [1–3])[a]	0.214
DMSO	0 (0–0 [0–1])[b]	0 (0–1 [0–1])[b]	0.317
Curcumin	0 (0–0 [0–1])[b]	0 (0–0 [0–1])[b]	0.564
P value**	**p < 0.0001**	**p < 0.0001**	
PMNL Infiltration			
Control	2 (1–2 [1–2])[a]	1 (1–1 [1–2])[a]	0.059
DMSO	0 (0–0 [0–0])[b]	0 (0–0 [0–0])[b]	Not applicable
Curcumin	0 (0–0 [0–0])[b]	0 (0–0 [0–0])[b]	Not applicable
P value**	**p < 0.0001**	**p < 0.0001**	
Lymphocyte Infiltration			
Control	1 (1–2 [1–3])[a]	1 (0–2 [0–2])[a]	0.257
DMSO	0 (0–1 [0–1])[b]	0 (0–1 [0–1])[b]	**0.046**
Curcumin	0 (0–0 [0–1])[b]	1 (0–1 [0–1])[b]	0.317
P value**	**p < 0.0001**	**p < 0.0001**	

Values are presented as median (interquartile range [min–max]). OLV: one-lung ventilation; TLV: two-lung ventilation; PMNL: polymorphonuclear leukocyte; DMSO: dimethyl sulfoxide. Between-group comparisons at each time point were performed using the Kruskal–Wallis test. When significant, pairwise comparisons were conducted using the Mann–Whitney U test with Bonferroni adjustment for multiple testing. Within-group comparisons were analyzed using Wilcoxon signed-rank test. A two-tailed p-value < 0.05 was considered statistically significant. Superscript letters ([a], [b]) indicate statistically significant differences between groups at the same time point. "Not applicable" indicates absence of variability within the group. P indicates within-group comparisons between OLV and TLV. P** indicates between-group comparisons at the same time point.*

4. Discussion

In this experimental study, we investigated the effects of curcumin on lung injury induced by 60 minutes of OLV followed by 30 minutes of TLV, combining histopathological assessment with biochemical markers. Our findings indicate that curcumin administration was associated with reduced histopathological injury, including lower congestion, edema, hemorrhage, and inflammatory cell infiltration compared with untreated controls, whereas biochemical parameters did not demonstrate significant between-group differences. In contrast, animals in the Control group exhibited pronounced structural injury after OLV and persistent inflammatory alterations during the TLV period. However, given the comparable attenuation observed in the DMSO vehicle group, these findings should be interpreted cautiously, and the independent contribution of curcumin requires careful consideration.

OLV is known to generate a complex pattern of lung injury driven by regional hypoxia, mechanical overdistension of the ventilated lung, cyclical opening–closing of alveoli, and inflammatory activation during re-expansion in the TLV period (14). Experimental and clinical evidence demonstrates that these mechanical and hypoxic stresses promote capillary leakage, pulmonary edema, leukocyte recruitment, and oxidative injury (15). In our study, animals in the Control group displayed classical features of early acute lung injury (ALI), including marked congestion, interstitial edema, and intra-alveolar hemorrhage, which is consistent with previously published OLV-related injury models. Conversely, curcumin treatment was associated with attenuation of these histopathological changes at both end of the OLV and TLV time points, suggesting that the observed histological attenuation was evident during both the ischemic and reperfusion phases. It is important to note that the present model does not represent a classical complete vascular occlusion ischemia–reperfusion paradigm. During OLV, pulmonary blood flow is reduced but not entirely interrupted, and oxygenation is redistributed rather than

abolished. Consequently, the injury observed in this study may more accurately reflect OLV-associated regional hypoxia and re-expansion–related stress rather than complete ischemia. This distinction is important when interpreting the results and comparing them with traditional vascular I/R models.

Curcumin's anti-inflammatory and antioxidant properties have been reported in various ischemia–reperfusion (I/R) models involving cerebral, cardiac, renal, and hepatic tissues (16). In the present study, reductions in PMNL and lymphocyte infiltration in the curcumin group align with prior work demonstrating that curcumin suppresses neutrophil migration, inhibits pro-inflammatory cytokine release, and attenuates leukocyte–endothelial interactions via modulation of NF-κB and related signaling pathways (5). Although systemic biochemical markers such as MDA, SOD, and TNF-α did not differ significantly among groups, the pronounced histological improvement is consistent with a potential role of curcumin in mitigating early inflammatory and oxidative injury. Similar findings have been reported in pulmonary I/R models where curcumin preserved lung architecture without producing robust changes in circulating biochemical markers, suggesting that its effects may be more evident at the tissue level during the initial phases of injury (17).

The absence of significant differences in systemic biochemical markers among groups warrants careful interpretation. Several mechanistic and methodological explanations may account for these results. The reperfusion period of 30 minutes may be insufficient for systemic oxidative or inflammatory markers to reach measurable levels; many I/R biochemistry studies employ reperfusion durations of 60–180 minutes, and shorter intervals may limit capture of transient biochemical alterations despite established histological damage (18). Moreover, OLV generates a localized form of ischemic stress, distinct from full vascular occlusion models. Oxygenation is redistributed rather than wholly interrupted, and injury may remain compartmentalized and too subtle to induce sustained increases in circulating MDA or cytokines, this aligns with observations that ventilator-induced lung injury may produce tissue-confined oxidative stress not reliably mirrored by systemic biomarkers (19). In addition, curcumin's pharmacokinetics may contribute. Although 200 mg/kg is commonly used, curcumin's bioavailability is inherently low due to rapid metabolism and limited systemic absorption, meaning its most significant effects may occur locally in lung tissue rather than plasma, thereby explaining significant histopathological improvements despite minimal systemic changes (16). These factors suggest that the discrepancy between histological and biochemical findings may reflect timing, model characteristics, and pharmacological properties rather than definitive absence of biological activity.

An important component of our study was the inclusion of a DMSO group to control for curcumin's vehicle. Interestingly, DMSO alone conferred a measurable degree of histological protection, reflected by lower injury scores compared with the untreated Control group. This finding aligns with the well-documented antioxidant and anti-inflammatory properties of DMSO, including hydroxyl radical scavenging, inhibition of lipid peroxidation, and attenuation of inflammatory signaling pathways (20). Notably, the degree of attenuation observed in the curcumin group was comparable to that seen in the DMSO group. This observation substantially limits the ability to attribute the protective effects exclusively to curcumin. While curcumin-treated animals demonstrated reduced injury compared with untreated controls, the similarity between the DMSO and curcumin groups indicates that the vehicle itself contributed meaningfully to the observed tissue protection. Therefore, our findings should be interpreted with caution, and under the present experimental conditions, an independent protective effect of curcumin beyond that of DMSO cannot be definitively established.

The similarity between the curcumin and DMSO groups in certain variables should be interpreted with caution. This does not imply that curcumin lacks additional biological activity; rather, the potent inherent antioxidant effects of DMSO may partially obscure subtle differences between the two interventions, particularly in short-duration or mild injury models. In addition, the limited variability in mild-to-moderate histological injury scores may restrict the statistical sensitivity needed to differentiate between two protective agents. These considerations emphasize the necessity of using vehicle-treated controls in experiments involving compounds dissolved in DMSO and support the exploration of alternative curcumin delivery methods, such as nanoparticle-based systems or liposomal formulations, that enhance curcumin's bioavailability while reducing confounding effects introduced by DMSO itself (21).

The consistent reduction in congestion, edema, and cellular infiltration across all curcumin-treated animals supports the hypothesis that curcumin

modulates multiple early pathways involved in OLV-induced lung injury. Mechanical stretch and cyclic deformation during OLV are known to disrupt endothelial barrier integrity, promote alveolar–capillary leakage, and initiate mechanotransduction pathways that amplify inflammation (14). The subsequent reperfusion phase further contributes to reactive oxygen species (ROS) generation and activates NF-κB–dependent inflammatory cascades, which play a central role in the early evolution of acute lung injury (5).

Curcumin has been shown to inhibit NF-κB activation, suppress TNF-α release, stabilize cell membranes, and enhance endogenous antioxidant defenses—mechanisms directly relevant to the injury patterns observed in our OLV model (22). The attenuation of PMNL infiltration in our study is consistent with curcumin's ability to inhibit neutrophil elastase, downregulate chemotactic mediators, and reduce adhesion molecule expression on endothelial cells, thereby limiting leukocyte recruitment during early inflammatory responses (23). Additionally, curcumin has been shown to preserve mitochondrial membrane potential, reduce cytochrome-c release, and modulate apoptosis-related pathways such as Bcl-2/Bax signaling, contributing to both epithelial and endothelial protection in oxidative injury settings (24). Although our study did not incorporate ultrastructural evaluation or immunohistochemical staining, the strong histopathological preservation observed in the curcumin group provides indirect but meaningful support for these underlying mechanisms.

Although this study was conducted in a rat model, the findings carry relevant implications for thoracic anesthesia practice. OLV is routinely performed during thoracic and upper abdominal surgeries, and postoperative pulmonary complications remain a significant concern. Pharmacological agents that mitigate OLV-induced lung injury may help reduce postoperative morbidity. Curcumin has biological properties that may be relevant to perioperative lung protection; however, the comparable effects observed with DMSO highlight the need for cautious interpretation and further formulation-based investigation before translational implications can be considered. The ability of curcumin to improve histological architecture despite minimal systemic biochemical changes suggests that its protective effects may be particularly valuable during the early stages of injury, where subtle tissue-level modulation can have meaningful long-term benefits. The comparable efficacy of curcumin and DMSO highlights the complexity of interpreting pharmacological effects when biologically active solvents are used and underscores the need for alternative delivery systems that isolate curcumin's independent contribution and improve its pharmacokinetic profile before clinical translation.

This study also has several limitations. First, the relatively short 30-minute reperfusion period represents a key methodological limitation. Biochemical cascades related to oxidative stress and cytokine release often peak beyond 60–120 minutes in classical I/R models. Therefore, the absence of significant biochemical differences in our study may partly reflect insufficient time for systemic marker elevation rather than true absence of biochemical modulation. Second, curcumin's low bioavailability may have reduced its detectability in plasma despite producing clear tissue-level effects. Third, only a single dose of curcumin was tested, preventing assessment of dose–response relationships and potentially overlooking the optimal therapeutic window. An additional limitation of this study is the absence of representative hematoxylin and eosin (H&E)-stained micrographs. Although all histological evaluations were performed by a blinded board-certified pathologist using a predefined semi-quantitative scoring system, the inclusion of representative micrographs would have enhanced visual interpretation and overall transparency of the tissue-level findings. Finally, although we measured key biochemical markers, additional analyses, such as immunohistochemical staining, broader cytokine panels, or assessment of oxidative enzyme activity, may help to determine the relevant molecular pathways.

In conclusion, in this OLV-induced ischemia–reperfusion model, curcumin administration was associated with attenuation of histopathological lung injury compared with untreated controls. However, given the comparable effects observed in the DMSO vehicle group, an independent protective effect of curcumin cannot be definitively established. Further studies using alternative formulations and extended reperfusion models are required.

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