Study Protocol

Contribution of chemical and mechanical power to postoperative pulmonary complications: post hoc analysis of three randomized clinical trials of intraoperative ventilation

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A collaborative research project of the Department of Outcomes Research, Cleveland Clinic and the Departments of Anesthesiology and Intensive Care, Amsterdam University Medical Center.

1. BACKGROUND

Supplemental oxygen exposes lung tissue to increased oxidative stress which may provoke hyperoxia-induced lung injury (HILI).[1] Intraoperative exposure to high inspiratory oxygen concentrations is associated with postoperative pulmonary complications, multiorgan injury, and mortality.[2,3] While some trials did not detect substantial pulmonary harm,[4–6] others showed higher severities of postoperative pulmonary concentrations and an increase in postoperative atelectasis after exposure to high inspiratory oxygen concentrations.[7,8] Despite potential risks, high intraoperative inspiratory oxygen fractions are frequently applied,[9] most often justified by increased safety margins for airway complications and low-grade evidence for a reduction in postoperative wound infections.[10,11] Although best practice for the use of intraoperative oxygen remains controversial, guidelines recommend rather high inspiratory oxygen fractions to reduce the risk of postoperative surgical complications.[12–15]

Stretching lung tissue is the major mechanism by which mechanical ventilation injures the lung.[16] The relatively new concept of mechanical power summarizes the mechanical energy transferred from the ventilator to the respiratory system which is associated with lung injury.[17–22] However, mechanical power disregards potential oxygen-related harm. Therefore, an equivalent concept for the exposure to oxygen – chemical power – was recently proposed.[23] Chemical power estimates the exposure of lung tissue to the amount of energy produced by reactive oxygen species resulting from supplemental inspiratory oxygen.[23] Given the controversial discussion on the intraoperative use of oxygen and the limited number of studies on its relationship with lung injury, an evaluation of how harm is balanced between chemical and mechanical power is of considerable interest.

Preclinical experiments suggest that lung tissue exposed to high mechanical power may be especially susceptive to oxidative injury, whereas lung tissue might be resilient to high oxygen concentrations when mechanical power is low.[24–31] An evaluation of harm from chemical and mechanical power should thus include the extent to which hyperoxia-induced lung injury depends on the concomitant exposure to mechanical power.

We therefore aim to evaluate the effects of the chemical and mechanical power on postoperative pulmonary complications in combined data from three randomized trials that were designed to assess relationships between intraoperative ventilator settings, especially positive end-expiratory pressure (PEEP), and postoperative pulmonary complications. Additionally, we will test for harm thresholds and evaluate the interaction between chemical and mechanical power. Specifically, we seek to identify harm thresholds for chemical and mechanical power and will test the hypothesis that there is a synergistic interaction between chemical and mechanical power, such that lung injury is most apparent when the two are combined.

1.1 Significance

More than 300 million surgeries are performed world-wide each year, mostly with general anesthesia and mechanical ventilation.[32] Despite frequent use of supplemental intraoperative oxygen, best practice remains unclear. Previous research largely focused on the effect of intraoperative supplemental oxygen on postoperative wound infections, while leaving potentially detrimental effects on the lung aside. Results of this analysis will provide indispensable evidence for clinicians about the effects of

intraoperative supplemental oxygen on postoperative lung injury, its balance and interaction with mechanical forces dissipated to the lung, and thresholds of harm.

2. STUDY OBJECTIVES

2.1 Primary Aim & Hypothesis

Primary Aim: To evaluate the relative contributions of intraoperative chemical and mechanical power on postoperative pulmonary complications within seven days after surgery.

Primary Hypothesis: Compared to intraoperative mechanical power, chemical power contributes less to postoperative postoperative pulmonary complications within seven days after surgery.

2.2 Secondary Aims & Hypotheses

Secondary Aim 1: To identify the thresholds of harm for the associations of intraoperative chemical and mechanical power with postoperative pulmonary complications within seven days after surgery.

Secondary Hypothesis 1: The exposures to intraoperative chemical and mechanical power have thresholds of harm (inflection points) from which on the risk for postoperative pulmonary complications within seven days after surgery increases substantially.

Secondary Aim 2: To evaluate the interaction between the intraoperatively applied chemical and mechanical power on postoperative pulmonary complications within seven days after surgery.

Secondary Hypothesis 2: Chemical power-related harm largely depends on the concomitantly applied mechanical power, meaning that chemical power causes significantly more postoperative pulmonary complications within seven days after surgery when exposed to high intraoperative mechanical power.

3. METHODS

3.1 Study Design and Population

We will perform a post hoc analysis of the previously combined dataset named 'Re–evaluation of the Effects of High PEEP with Recruitment Manoeuvres versus Low PEEP without Recruitment Manoeuvres During General Anaesthesia for Surgery' (REPEAT), registered at ClinicalTrials.gov: NCT03937375 on 3rd May 2019. This dataset merged the individual patient data from three RCTs, the 'High versus low positive end–expiratory pressure during general anesthesia for open abdominal surgery' (PROVHILO) study (registered with Controlled-Trials.com: ISRCTN70332574), the 'Individualized perioperative open–lung approach versus standard protective ventilation in abdominal surgery' (iPROVE) study (registered with ClinicalTrials.gov: NCT02158923) and the 'Effect of intraoperative high positive end–expiratory pressure with recruitment manoeuvres vs low PEEP on postoperative pulmonary complications in obese patients' (PROBESE) study (registered with ClinicalTrials.gov: NCT02148692).

3.2 Ethics

The Amsterdam UMC institutional review board (IRB) is the IRB of reference. According to local standards at Amsterdam UMC, no additional IRB approval and no additional individual consent aside those previously obtained for the underlying prospective trials are necessary.

3.3 Data Management

Data will be made available in an Amsterdam UMC remote working environment equipped with the applicable statistical software to perform the statistical analysis (R, Rstudio, etc.). Investigators of the Cleveland Clinic that are involved in the statistical analysis will get an Amsterdam UMC guest account enabling access to the remote working environment. No individual patient data will be transferred between the involved institutions during this project.

3.4 Exposures

Chemical and mechanical power will be calculated in hourly intervals during intraoperative ventilation. Time−weighted average chemical and mechanical power will be calculated as the area under the driving pressure and mechanical power time curve divided by the number of hours of exposure for quantifying cumulative exposure.

3.4.1 Primary Exposure

Chemical power calculated according to Lilien et al. [Lilien et al. 2023]:

Step 1: Estimation of local superoxide (O_2^-) production ($Pulm_{ROS}$) from lung oxygen consumption as a function of F_IO_2

$$Pulm_{ROS} = 1.7 * 10^{-5} + ((FiO2 - 0.21) \times 1.63 * 10^{-4}) \ (\mathrm{mol/min})$$

Step 2: Calculate chemical power (CP) from step 1 based on the first electron affinity of oxygen (141 kJ/mol).

$$\mathrm{CP} = 141000 \times Pulm_{ROS} \ (\mathrm{J/min})$$

3.4.2 Secondary Exposure

Since plateau pressure was not recorded in every patient, dynamic driving pressure will be calculated as peak pressure – PEEP and dynamic mechanical power will be calculated according to the following formula:

$$MP = 0.098 * Vt * RR * (Ppeak - 0.5 * \Delta Pinsp)$$

3.5 Outcome

3.5.1 Primary Outcome

Collapsed composite outcome of postoperative pulmonary complications (PPCs) during the first seven postoperative days according to the definitions of the underlying studies presented in table 1.

Table 1. Definitions of postoperative pulmonary complications.

	PROVHILO	**iPROVE**	**PROBESE**
Mild respiratory failure	PaO2 < 60 mmHg or SpO2 < 90% breathing at least 10 minutes of room air but responding to supplemental oxygen of 2 L/minute	SpO2 < 92% with FiO2 of 0.21 or SpO2 < 95% with FiO2 of 0.50	PaO2 < 60 mmHg or SpO2 < 90% breathing at least 10 minutes of room air but responding to supplemental oxygen of 2 L/minute
Severe respiratory failure	PaO2 < 60 mmHg or SpO2 < 90% breathing ≥ 10 minutes of room air but responding only to supplemental oxygen > 2 L/minute or need for noninvasive or invasive mechanical ventilation	Increased FiO2, increased requirement for CPAP, or the need for noninvasive or invasive ventilation	PaO2< 60 mmHg or SpO2 < 90% breathing ≥ 10 minutes of room air but responding only to supplemental oxygen > 2 L/minute or need for noninvasive or invasive mechanical ventilation
ARDS	AECC criteria*	Berlin criteria**	Berlin criteria**
Pulmonary infection	Need of antibiotics and at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest X-ray when clinically indicated, tympanic temperature >38.3°C, WBC count >12,000/µl in the absence of other infectious focus	Presence of a new pulmonary infiltrate and/or progression of previous pulmonary infiltrates on a chest radiograph plus at least two of the following criteria: (a) leukocytosis with > 12,000 WBC/mm3 or leukopenia with < 4000 WBC/mm3, (b) fever > 38.5°C or hypothermia < 36°C, and (c) increased secretions with purulent sputum and a positive bronchial aspirate	Presence of a new pulmonary infiltrate and/or progression of previous pulmonary infiltrates on a chest radiograph plus at least two of the following criteria: (a) leukocytosis with > 12,000 WBC/mm3 or leukopenia with < 4000 WBC/mm3, (b) fever > 38.5°C or hypothermia < 36°C, and (c) increased secretions with purulent sputum and a positive bronchial aspirate
Pleural effusion	Chest radiography with the presence of costophrenic angle blunting, displacement of adjacent anatomical structures, and blunting of the hemidiaphragmatic silhouette in the supine position	Chest radiography with the presence of costophrenic angle blunting, displacement of adjacent anatomical structures, and blunting of the hemidiaphragmatic silhouette in the supine position	Chest radiography with the presence of costophrenic angle blunting, displacement of adjacent anatomical structures, and blunting of the hemidiaphragmatic silhouette in the supine position
Atelectasis	Chest radiography with lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non-atelectatic lung	Combination of SpO2 ≤ 96% during the air test and chest radiography with lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non-atelectatic lung	Chest radiography with lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non-atelectatic lung
Pneumothorax	Chest radiography with air in the pleural space with no vascular bed surrounding the visceral pleura	Chest radiography with air in the pleural space with no vascular bed surrounding the visceral pleura	Chest radiography with air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Presence of expiratory wheezing treated with bronchodilator	Presence of expiratory wheezing treated with bronchodilator	Presence of expiratory wheezing

ARDS: Acute Respiratory Distress Syndrome; SIRS: systemic inflammatory response syndrome; AECC: American–European consensus conference; WBC: White blood cells; PaO2: Arterial oxygen pressure: SpO2: peripheral oxygen saturation; FiO2: inspired oxygen fraction.
*Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med 1994;20:225–232.
**Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526–2533.

3.6 Statistical Analysis

3.6.1 Descriptive statistics

The following variables will be descriptively presented, and additionally grouped by low, moderate, marked, and substantial chemical power (<25%, 25-50%, 50-75%, and 75-100% quantile of mechanical power), and considered as potential confounders (*) for the inferential statistics. Mean (standard deviation), median (interquartile range), frequency (percentage) will be reported based on variable type

and distribution.

Demographics

- Age *
- Sex *
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) *
- ASA physical status *
- Trial *

Respiratory risk factors

- ARISCAT score *
- Preoperative SpO2 *
- Respiratory infection within the past month *
- Anemia *

Coexisting conditions

- Heart failure *
- Chronic obstructive pulmonary disease *
- Cancer *

Surgery characteristics

- Preoperative hemoglobin (g/dL) *
- Type of surgery (abdominal versus non-abdominal) *
- Specific procedure
- Surgical approach (laparoscopic versus non-laparoscopic) *
- Year of surgery *
- Emergency or elective procedure *
- Duration of surgery *

Intraoperative mechanical ventilation parameters

- Tidal volume (Vt)
- Respiratory rate (RR)
- Peak pressure (Pinsp)
- Driving pressure (ΔPinsp)
- Inspiratory oxygen fraction (FiO2)
- Positive end-expiratory pressure (PEEP) *
- Exposures: chemical power and mechanical power
- Ventilation mode (VCV vs. PCV)

3.6.2 Inferential statistics

Primary aim:

We will summarize intraoperative chemical and mechanical power by calculating time-weighted averages for each patient. The influence of the intraoperatively applied time-weighted average chemical and mechanical power on composite postoperative pulmonary complications will be evaluated by multivariable logistic regression – estimating the odds ratios related to the effect of 1 unit increase in chemical or mechanical power. The regression model will be calculated with and without the above-mentioned confounders. We will consider the exclusion of a potential confounder if its inclusion results in a change in the regression coefficients (beta) for both exposures of less than 10%.

Secondary aim 1:

The relationship between varying levels of chemical / mechanical power and postoperative pulmonary complications will be analysed via multivariable logistic regression including cubic splines with up to five knots of chemical and mechanical power. We will further evaluate whether chemical and mechanical power have an upper threshold of harm, whereafter the odds for PPCs increase substantially by means of threshold regression. We will consider a 5% change in slope as clinically relevant, although there is no established minimal clinically important difference for PPCs, and this definition remains arbitrary.

Secondary aim 2:

We will evaluate the interaction between chemical power and mechanical power by implementing an interaction term for the intraoperatively applied time-weighted average mechanical power in the multivariable regression model performed to evaluate the primary aim. Additionally, we will analyse the effect of chemical and mechanical power on PPCs for 5 subsets of the study population stratified by chemical or mechanical power for each of the following patterns: 1) increasing chemical power and matched mechanical power, 2) matched chemical power and increasing mechanical power, 3) increasing chemical power and decreasing mechanical power, and 4) increasing chemical power and increasing mechanical power. Data will also be graphically presented with a 3D surface plot showing chemical and mechanical power on the x- and z-axes and the percentage of PPCs on the y-axis. Therefore, the population will be divided into equally sized groups including an certain fraction of patients of the ranges of both exposures.

3.6.3 Tables and figures (planned)

Table 1: Patient characteristics

Demographics, respiratory risk factors, coexisting conditions, and surgery characteristics will be descriptively presented, grouped by low, moderate, marked, and substantial chemical power (<25%, 25-50%, 50-75%, and 75-100% quantile of mechanical power).

Table 2: Intraoperative mechanical ventilation parameters (alternatively as figure)

Intraoperative mechanical ventilation parameters will be descriptively presented, grouped by low, moderate, marked, and substantial chemical power (<25%, 25-50%, 50-75%, and 75-100% quantile of mechanical power)

Figure 1: CONSORT diagram

Figure 2: Ranges of chemical, mechanical, and mechanochemical power quartiles

Barplots showing the ranges of time-weighted averages of chemical, mechanical, and mechanochemical power for patients with low (first quartile: <25%), moderate (second quartile: 25-50%), marked (third quartile: 50-75%), and substantial (fourth quartile: 75-100%) power.

Figure 3 a/b (take-away-figure): Chemical and mechanical versus the risk of PPCs.

Smoothed spline regression curves with the odds ratios for each spline presenting the risk for PPCs over the observed ranges of chemical (a), and mechanical power (b).

Figure 4 a/b/c: Stratified analysis of chemical and mechanical power on PPCs

Bar plots on top: a) increasing chemical power and matched mechanical power, b) matched chemical power and increasing mechanical power, c) increasing chemical power and decreasing mechanical power, and d) increasing chemical power and increasing mechanical power. Error bars on bottom: corresponding relative risks of PPC, calculated for each subsample; error bars represent the 95% confidence interval.

Figure 5 (alternative take-away-figure): Chemical and mechanical versus the risk of PPCs

A 3D surface plot with chemical and mechanical power on the x- and z-axes and the percentage of PPCs on the y-axis. The population will be divided into equally sized groups including an applicable fraction of patients of the ranges of both exposures.

3.6.4 Sample size considerations

We do not perform a formal power calculation; instead, the available number of patients in the pooled dataset serves as the sample size.

3.6.5 Limitations

We are aware of several limitations of our analyzes. (1) Although the database was derived from trials, our study is observational, meaning we may detect associations but not establish causality. (2) Due to a widespread use of lung-protective mechanical ventilation exposure to higher ranges of mechanical power is presumably rare. (3) The use of supplemental oxygen (FiO2) is potentially highly confounded by underlying pulmonary risk and patients' intraoperative responses to surgery and mechanical ventilation. (4) The underlying trials used slightly different definitions of postoperative pulmonary complications, adding further variability and potential bias to the results.

4. REFERENCES

1. Kallet RH, Matthay MA: Hyperoxic Acute Lung Injury. Respir Care 2013; 58:123–41
2. Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, Vidal Melo MF, Gätke MR, Walsh JL, Ladha KS, Grabitz SD, Nikolov MI, Kurth T, Rasmussen LS, Eikermann M: High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. Br J Anaesth 2017; 119:140–9
3. McIlroy DR, Shotwell MS, Lopez MG, Vaughn MT, Olsen JS, Hennessy C, Wanderer JP, Semler MS, Rice TW, Kheterpal S, Billings FT, Multicenter Perioperative Outcomes Group: Oxygen administration during surgery and postoperative organ injury: observational cohort study. BMJ 2022; 379:e070941
4. Cohen B, Ruetzler K, Kurz A, Leung S, Rivas E, Ezell J, Mao G, Sessler DI, Turan A: Intra-operative high inspired oxygen fraction does not increase the risk of postoperative respiratory complications: Alternating intervention clinical trial. Eur J Anaesthesiol 2019; 36:320–6
5. Mackintosh N, Gertsch MC, Hopf HW, Pace NL, White J, Morris R, Morrissey C, Wilding V,

Herway S: High intraoperative inspired oxygen does not increase postoperative supplemental oxygen requirements. Anesthesiology 2012; 117:271–9

6. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Høgdall C, Lundvall L, Svendsen P-E, Mollerup H, Lunn TH, Simonsen I, Martinsen KR, Pulawska T, Bundgaard L, Bugge L, Hansen EG, Riber C, Gocht-Jensen P, Walker LR, Bendtsen A, Johansson G, Skovgaard N, Heltø K, Poukinski A, Korshin A, Walli A, Bulut M, Carlsson PS, Rodt SA, Lundbech LB, Rask H, et al.: Effect of High Perioperative Oxygen Fraction on Surgical Site Infection and Pulmonary Complications After Abdominal Surgery. JAMA 2009; 302:1543
7. Li XF, Jiang D, Jiang YL, Yu H, Zhang MQ, Jiang JL, He LL, Yu H: Comparison of low and high inspiratory oxygen fraction added to lung-protective ventilation on postoperative pulmonary complications after abdominal surgery: A randomized controlled trial. J Clin Anesth 2020; 67
8. Park MH, Jung K, Sim WS, Kim DK, Chung IS, Choi JW, Lee EJ, Lee NY, Kim JA: Perioperative high inspired oxygen fraction induces atelectasis in patients undergoing abdominal surgery: A randomized controlled trial. J Clin Anesth 2021; 72
9. Suzuki S, Mihara Y, Hikasa Y, Okahara S, Ishihara T, Shintani A, Morimatsu H, Sato A, Kusume S, Hidaka H, Yatsuzuka H, Okawa M, Takatori M, Saeki S, Samuta T, Tokioka H, Kurasako T, Maeda M, Takeuchi M, Hirasaki A, Kitaura M, Kajiki H, Kobayashi O, Katayama H, Nakatsuka H, Mizobuchi S, Sugimoto S, Yokoyama M, Kusudo K, Shiraishi K, et al.: Current ventilator and oxygen management during general anesthesia: A multicenter, cross-sectional observational study. Anesthesiology 2018; 129:67–76
10. Wetterslev J, Meyhoff CS, Jørgensen LN, Gluud C, Lindschou J, Rasmussen LS: The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. Cochrane Database of Systematic Reviews 2015; 2016
11. Ferrando C, Aldecoa C, Unzueta C, Belda FJ, Librero J, Tusman G, Suárez-Sipmann F, Peiró S, Pozo N, Brunelli A, Garutti I, Gallego C, Rodríguez A, García JI, Díaz-Cambronero O, Balust J, Redondo FJ, la Matta M de, Gallego-Ligorit L, Hernández J, Martínez P, Pérez A, Leal S, Alday E, Monedero P, González R, Mazzirani G, Aguilar G, López-Baamonde M, Felipe M, et al.: Effects of oxygen on post-surgical infections during an individualised perioperative open-lung ventilatory strategy: a randomised controlled trial. Br J Anaesth 2020; 124:110–20
12. Stuby J, Kaserer A, Ott S, Ruetzler K, Rössler J: Perioperative hyperoxia—More harmful than beneficial? Anaesthesiologie 2023 doi:10.1007/s00101-023-01274-4
13. Weenink RP, Jonge SW de, Hulst RA van, Wingelaar TT, Ooij P-JAM van, Immink R V, Preckel B, Hollmann MW: Perioperative Hyperoxyphobia: Justified or Not? Benefits and Harms of Hyperoxia during Surgery. J Clin Med 2020; 9:642
14. Volk T, Peters J, Sessler DI: The WHO recommendation for 80% perioperative oxygen is poorly justified 2017; 66:pp 227–9
15. Weiss R, Prien T, Fischer L, Aken H Van, Zarbock A: “O2 can do” – harm you! Kommentar zur aktuellen WHO-Empfehlung zur Wundinfektionsprävention. Anästh Intensivmed 2017; 58:211–9

16. Beitler JR, Malhotra A, Thompson BT: Ventilator-induced Lung Injury. Clin Chest Med 2016; 37:633–46

17. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, Cammaroto A, Brioni M, Montaruli C, Nikolla K, Guanziroli M, Dondossola D, Gatti S, Valerio V, Vergani GL, Pugni P, Cadringher P, Gagliano N, Gattinoni L: Mechanical power and development of ventilator-induced lung injury. Anesthesiology 2016; 124:1100–8

18. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E, Chiumello D, Quintel M: Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016; 42:1567–75

19. Scharffenberg M, Wittenstein J, Ran X, Zhang Y, Braune A, Theilen R, Maiello L, Benzi G, Bluth T, Kiss T, Pelosi P, Rocco PRM, Schultz MJ, Kotzerke J, Gama de Abreu M, Huhle R: Mechanical Power Correlates With Lung Inflammation Assessed by Positron-Emission Tomography in Experimental Acute Lung Injury in Pigs. Front Physiol 2021; 12

20. Schuijt MTU, Hol L, Nijbroek SG, Ahuja S, Meenen D van, Mazzinari G, Hemmes S, Bluth T, Ball L, Gama–de Abreu M, Pelosi P, Schultz MJ, Serpa Neto A: Associations of dynamic driving pressure and mechanical power with postoperative pulmonary complications–posthoc analysis of two randomised clinical trials in open abdominal surgery. EClinicalMedicine 2022; 47:101397

21. Zhang Z, Zheng B, Liu N, Ge H, Hong Y: Mechanical power normalized to predicted body weight as a predictor of mortality in patients with acute respiratory distress syndrome. Intensive Care Med 2019; 45:856–64

22. Zhu Y, Peng W, Zhen S, Jiang X: Mechanical power normalized to predicted body weight is associated with mortality in critically ill patients: a cohort study. BMC Anesthesiol 2021; 21

23. Lilien TA, Meenen DMP van, Schultz MJ, Bos LDJ, Bem RA: Hyperoxia-Induced Lung Injury in Acute Respiratory Distress Syndrome: What is its Relative Impact? American Journal of Physiology-Lung Cellular and Molecular Physiology 2023 doi:10.1152/ajplung.00443.2022

24. Li L-F, Liao S-K, Ko Y-S, Lee C-H, Quinn DA: Hyperoxia increases ventilator-induced lung injury via mitogen-activated protein kinases: a prospective, controlled animal experiment. Crit Care 2007; 11:R25

25. Quinn DA, Moufarrej RK, Volokhov A, Hales CA: Interactions of lung stretch, hyperoxia, and MIP-2 production in ventilator-induced lung injury. J Appl Physiol (1985) 2002; 93:517–25

26. Bailey TC, Martin EL, Zhao L, Veldhuizen RAW: High oxygen concentrations predispose mouse lungs to the deleterious effects of high stretch ventilation. J Appl Physiol (1985) 2003; 94:975–82

27. Sinclair SE, Altemeier WA, Matute-Bello G, Chi EY: Augmented lung injury due to interaction between hyperoxia and mechanical ventilation. Crit Care Med 2004; 32:2496–501

28. Makena PS, Gorantla VK, Ghosh MC, Bezawada L, Balazs L, Luellen C, Parthasarathi K, Waters CM, Sinclair SE: Lung injury caused by high tidal volume mechanical ventilation and hyperoxia is dependent on oxidant-mediated c-Jun NH2-terminal kinase activation. J Appl Physiol (1985)

2011; 111:1467–76

29. Makena PS, Luellen CL, Balazs L, Ghosh MC, Parthasarathi K, Waters CM, Sinclair SE: Preexposure to hyperoxia causes increased lung injury and epithelial apoptosis in mice ventilated with high tidal volumes. Am J Physiol Lung Cell Mol Physiol 2010; 299:L711-9

30. Liu Y-Y, Liao S-K, Huang C-C, Tsai Y-H, Quinn DA, Li L-F: Role for nuclear factor-kappaB in augmented lung injury because of interaction between hyperoxia and high stretch ventilation. Transl Res 2009; 154:228–40

31. Li L-F, Liao S-K, Ko Y-S, Lee C-H, Quinn DA: Hyperoxia increases ventilator-induced lung injury via mitogen-activated protein kinases: a prospective, controlled animal experiment. Crit Care 2007; 11:R25

32. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, Fu R, Azad T, Chao TE, Berry WR, Gawande AA: Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. The Lancet 2015; 385:S11