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Original Article

Individual and combined effects of chemical and mechanical power on postoperative pulmonary complications: a secondary analysis of the REPEAT study

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Summary

Introduction Intra-operative supplemental oxygen and mechanical ventilation expose the lungs to potentially injurious energy. This can be quantified as `chemical power´ and `mechanical power´, respectively. In this study, we sought to determine if intra-operative chemical and mechanical power, individually and/or in combination, are associated with postoperative pulmonary complications.

Methods Using an individual patient data analysis of three randomised clinical trials of intra-operative ventilation, we summarised intra-operative chemical and mechanical power using time-weighted averages. We evaluated the association between intra-operative chemical and mechanical power and a collapsed composite of postoperative pulmonary complications using multivariable logistic regression to estimate the odds ratios related to the effect of 1 $J.min^{-1}$ increase in chemical or mechanical power with adjustment for demographic and intra-operative characteristics. We also included an interaction term to assess for potential synergistic effects of chemical and mechanical power on postoperative pulmonary complications.

Results Of 3837 patients recruited to three individual trials, 2492 with full datasets were included in the analysis. Intra-operative time-weighted average (SD) chemical power was 10.2 (3.9) $J.min^{-1}$ and mechanical power was 10.5 (4.4) $J.min^{-1}$. An increase of 1 $J.min^{-1}$ in chemical power was associated with 8% higher odds of postoperative pulmonary complications (OR 1.08, 95%CI 1.05–1.10, $p < 0.001$), while the same increase in mechanical power raised odds by 5% (OR 1.05, 95%CI 1.02–1.08, $p = 0.003$). We did not find evidence of a significant interaction between chemical and mechanical power ($p = 0.40$), suggestive of an additive rather than synergistic effect on postoperative pulmonary complications.

Discussion Both chemical and mechanical power are independently associated with postoperative pulmonary complications. Further work is required to determine causality.

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Plain Language Summary may be found on PubMed and in the Supporting Information.

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Introduction

Intra-operative ventilation transfers energy from the ventilator to lung tissue, which can be quantified as `mechanical power´ [1, 2]. Elevated intra-operative mechanical power levels may harm the lungs and are associated with worse patient outcomes [3, 4]. Interventions that seek to reduce mechanical power are under consideration for patients who require intra-operative ventilation [5]. However, less is known about the use of supplemental oxygen during intra-operative ventilation, quantified as `chemical power´ [6]. The chemical power concept was introduced recently as a quantitative measure of the biochemical stress induced by hyperoxia and translates oxygen exposure (fraction of inspired oxygen, F_IO_2) into a power metric with units of joules per minute ($J.min^{-1}$). This involves estimation of pulmonary oxygen consumption; calculation of oxygen fraction converted into reactive oxygen species; and multiplication of the rate of reactive oxygen species production by the energy released per mole of superoxide formation [6].

Exposure to high chemical power is linked with postoperative pulmonary complications (PPCs); multiorgan injury; and mortality [7, 8]. The simplest way to reduce chemical power is to reduce F_IO_2 to the lowest safe level, including the use of recruitment manoeuvres and/or titration of positive end-expiratory pressure (PEEP). Despite potential dangers of high intrapulmonary oxygen levels, high fractions of oxygen continue to be utilised during intra-operative ventilation [9]. Clinical guidelines continue to recommend higher intra-operative oxygen fractions [10, 11], justified by perceived safety margins for airway complications and limited evidence for a reduction in postoperative wound infections [12, 13]. Preclinical studies suggest that the combined effect of chemical and mechanical power may amplify the risk of pulmonary injury synergistically [14, 15], but the clinical relevance of this observation is uncertain.

Our aim was to evaluate how intra-operative chemical and mechanical power, individually and in combination, influence the incidence of PPCs. We conducted a secondary analysis on the Re–Evaluation of the effects of high PEEP During General AnesThesia for surgery (REPEAT) database [16, 17]. This resource integrates individual patient data from three randomised clinical trials that evaluated the impact of intra-operative ventilation with high PEEP on the incidence of PPCs. We hypothesised that both chemical and mechanical power are individually associated with PPCs, with a synergistic interaction.

Methods

This is a secondary analysis of individual patient data from three randomised controlled trials that investigated the effect of low vs. high PEEP on PPCs: PROVHILO [18]; iPROVE [19]; and PROBESE [20]. The original trials were approved by a central institutional review board and all patients provided informed consent. Additional institutional review board approval or individual patient consent was required to access this pooled database. Our report adheres to the STROBE guideline.

For this secondary analysis, we did not include patients with missing data on the variables of interest (complete case analysis); duration of surgery < 2 h; and intra-operative mechanical power > 30 $J.min^{-1}$. We extracted patient and surgery baseline characteristics: age; sex; height; weight; BMI; ASA physical status; ARISCAT score [21]; pre-operative SpO_2; respiratory infection; pre-operative anaemia; history of heart failure; chronic obstructive pulmonary disease (COPD); active cancer; pre-operative haemoglobin levels; surgical approach (open vs. laparoscopic); emergency procedure; duration of surgery; and surgical specialty. The following intra-operative ventilatory variables were available and extracted in hourly intervals: tidal volume; respiratory rate; maximum airway pressure; PEEP; dynamic driving pressure; and F_IO_2. Patients were followed up for 7 days after surgery to detect PPCs in the original trials, as defined in online Supporting Information Table S1.

The two co-primary exposures were defined as the time-weighted average of intra-operative chemical and mechanical power. Chemical power was calculated using the following equations [6]: $Pulm_{ROS} = 1.7 \times 10^{-5} + ((F_IO_2 - 0.21) \times 1.63 \times 10^{-4})$ ($mol.min^{-1}$); chemical power = $141{,}000 \times Pulm_{ROS}$ ($J.min^{-1}$), where $Pulm_{ROS}$ is the local superoxide production in $mol.min^{-1}$. Dynamic driving pressure (ΔP) was used for mechanical power calculations, since plateau pressure was not available for all patients. Dynamic driving pressure was calculated with maximum airway pressure (P_{max}) using the following equation: $\Delta P = P_{max}$ - PEEP (cmH_2O), where P_{max} and PEEP are expressed in cmH_2O. Mechanical power was calculated using the following equation: mechanical power = $0.098 \times$ tidal volume $\times$ respiratory rate $\times (P_{max} - 0.5 \times \Delta P)$ ($J.min^{-1}$), where tidal volume in litres, respiratory rate in $breaths.min^{-1}$, P_{max} is maximum airway pressure in cmH_2O and ΔP is dynamic driving pressure in cmH_2O as described above.

The primary study endpoint was a composite of PPCs during the first seven postoperative days according to the definitions of the original trials presented in online Supporting Information Table S1. No

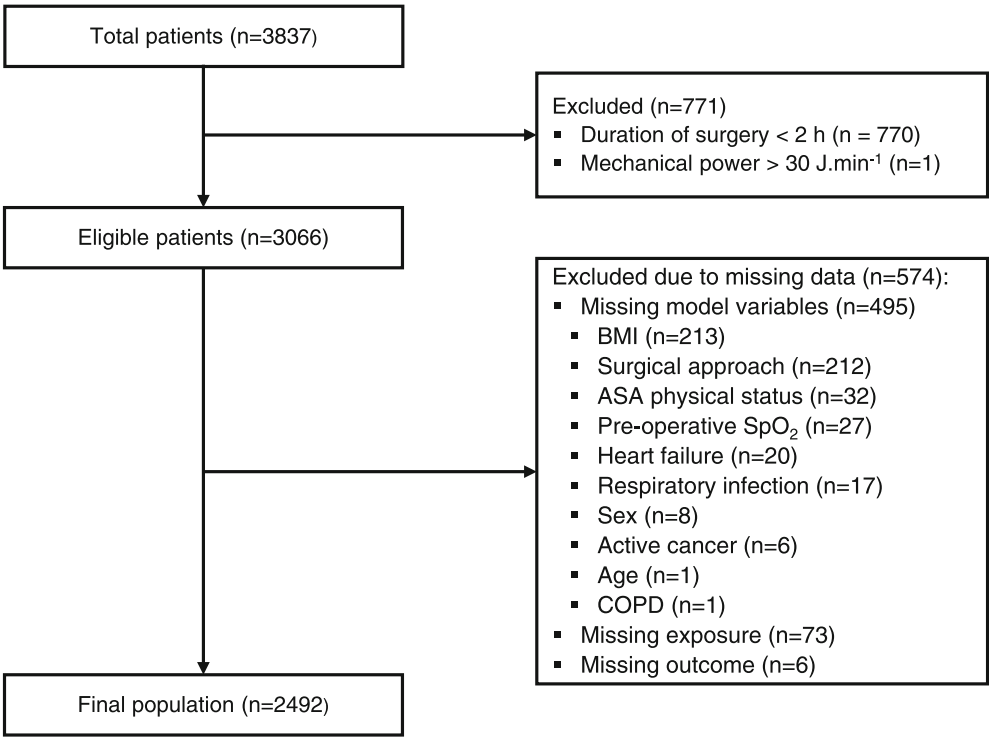

Figure 1 Study flow chart. COPD, chronic obstructive pulmonary disease; SpO_2, peripheral oxygen saturation.

formal power calculation was performed; instead, we used all available patients with complete data from the pooled dataset. For descriptive purposes only, the population was divided at the median of chemical power to create a `high chemical power group´ and a `low chemical power group´ and the absolute standardised difference was calculated to assess baseline balance. Inferential statistics were performed with continuous values of chemical and mechanical power.

Chemical and mechanical power were calculated hourly. We summarised intra-operative chemical and mechanical power by calculating time-weighted averages as the area under the chemical and mechanical power time curves divided by the number of hours of exposure for quantifying cumulative exposure for each patient. The association between intra-operatively applied time-weighted average chemical and mechanical power on a collapsed composite of PPCs was evaluated by multivariable logistic regression, estimating the odds ratios related to the effect of 1 $J.min^{-1}$ increase in chemical or mechanical power. Potential confounders were defined a priori and included as covariates in the multivariable model. To assess a potential interaction between chemical and mechanical power, we repeated the model with an interaction term for chemical and mechanical power.

We performed sensitivity analyses to explore our results. This included analyses restricted to patients with available plateau pressure; patients in whom F_IO_2 was likely set by default to 0.4, 0.5 or 0.8, i.e. without titration to the individual patient's oxygenation requirements; removal of exclusion criteria to include all patients in the database; and with adjustment for potential effects between individual trials. All analyses were performed based on an overall significance level of 0.05, using R (version 4.4.1, R Studio, Vienna, Austria).

Results

Of 3837 patients in the pooled database, 2492 were included in this analysis (Fig. 1). The main reasons for exclusion were duration of surgery < 2 h; missing BMI; and missing information on surgical approach. The mean (SD) patient age was 57 (15) y, 1300 (52%) were female and 1258 (50%) underwent colorectal or bariatric surgery (Table 1).

The time-weighted averages of chemical and mechanical power were mean (SD) 10.2 (3.9) $J.min^{-1}$ and 10.5 (4.4) $J.min^{-1}$, respectively (Table 2). Patients who were administered higher chemical power were older; more often male; had a lower median BMI; and a lower median ARISCAT score (Table 1). The time-weighted average mechanical power was similar in patients with low and high

Table 1 Baseline characteristics for all included patients and for patients with below and above median chemical power. Values are mean (SD) or number (proportion).

	Overall n = 2492	**Chemical power < 9 J.min^{-1} n = 1532**	**Chemical power > 9 J.min^{-1} n = 960**	**SMD**
Age; y	57 (15)	55 (15)	62 (14)	0.496
Sex; female	1300 (52%)	882 (58%)	418 (44%)	0.283
Height; cm	170 (9.4)	170 (9.4)	170 (9.3)	0.099
Weight; kg	94 (31)	100 (30)	84 (29)	0.569
BMI	34 (10)	36 (10)	30 (9.6)	0.586
ASA physical status				0.077
1	144 (6%)	96 (6%)	48 (5%)	
2	1255 (50%)	783 (51%)	472 (49%)	
3	1069 (43%)	639 (42%)	430 (45%)	
4	24 (1%)	14 (1%)	10 (1%)	
ARISCAT score	38 (9.2)	40 (8.1)	36 (10)	0.468
Pre-operative SpO_2;%	97 (2.0)	97 (1.9)	97 (2.1)	0.148
Respiratory infection	113 (5%)	67 (4%)	46 (5%)	0.020
Pre-operative anaemia	679 (27%)	337 (22%)	342 (36%)	0.304
Heart failure	201 (8%)	151 (10%)	50 (5%)	0.177
COPD	161 (6%)	110 (7%)	51 (5%)	0.077
Active cancer	1181 (47%)	511 (33%)	670 (70%)	0.783
Pre-operative haemoglobin; g.dl^{-1}	13 (4.5)	14 (4.9)	13 (3.9)	0.111
Laparoscopic surgery	1138 (46%)	706 (46%)	432 (45%)	0.022
Emergency procedure	34 (1%)	30 (2%)	4 (0%)	0.143
Duration of surgery; min	220 (85)	210 (85)	230 (84)	0.176
Specific procedure				0.704
Abdominal/visceral	1153 (46%)	549 (36%)	604 (63%)	
Bariatric	685 (27%)	569 (37%)	116 (12%)	
Urologic	212 (9%)	132 (9%)	80 (8%)	
Gynaecologic	117 (5%)	71 (5%)	46 (5%)	
Vascular	45 (2%)	28 (2%)	17 (2%)	
Hernia	36 (1%)	27 (2%)	9 (1%)	
Other	244 (10%)	156 (10%)	88 (9%)	
Postoperative pulmonary complications	872 (35%)	444 (29%)	428 (45%)	

ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; COPD, chronic obstructive pulmonary disease; SMD, standardised mean difference; SpO_2, peripheral oxygen saturation.

chemical power. Patients administered high chemical power tended to receive higher tidal volumes but lower respiratory rates (Table 2). Patients who experienced PPCs were more likely to have received higher intra-operative chemical power (online Supporting Information Figure S1).

We observed that a 1 J.min^{-1} increment in chemical power was associated with an 8% increased risk of PPCs (OR 1.08, 95%CI 1.05–1.10, $p < 0.001$). A 1 J.min^{-1} increment in mechanical power was associated with a 5% increased risk of PPCs (OR 1.05, 95%CI 1.02–1.08, $p < 0.003$) (Table 3). The probability of PPCs increased linearly over the range of chemical power (Fig. 2a), whereas the probability of PPCs started to increase after 15 J.min^{-1} of delivered mechanical power (Fig. 2b). Our model-derived risk of PPCs suggests that chemical and mechanical power did not interact ($p = 0.40$, Fig. 3).

These findings were not altered in sensitivity analyses when we limited patients to those who had plateau pressures available (online Supporting Information Tables S2–S4 and Figures S2 and S3); and to patients in whom F_IO_2 was likely set by default to 0.4, 0.5 or 0.8 (i.e. without titration to the individual oxygenation

Table 2 Intra-operative ventilation parameters for all included patients and for patients with below and above median chemical power. Values are mean (SD).

	Overall n = 2492	**Chemical power < 9 J.min^{-1} n = 1532**	**Chemical power > 9 J.min^{-1} n = 960**	**SMD**
Tidal volume; ml	460 (80)	460 (83)	470 (75)	0.208
Tidal volume; ml.kg PBW^{-1}	7.6 (0.8)	7.5 (0.7)	7.8 (0.8)	0.425
Respiratory rate; breaths.min^{-1}	14 (4)	15 (4)	14 (3)	0.224
Maximum airway pressure; cmH_2O	25 (6)	24 (6)	25 (6)	0.110
PEEP; cmH_2O	7.5 (4)	7.6 (5)	7.5 (4)	0.016
Dynamic driving pressure; cmH_2O	17 (6)	17 (6)	18 (6)	0.124
F_IO_2; %	55 (17)	43 (4)	74 (10)	3.875
Chemical power; J.min^{-1}	10 (4)	7 (1)	15 (2)	3.875
Mechanical power; J.min^{-1}	10 (4)	10 (5)	10 (4)	0.011

F_IO_2, fraction of inspiratory oxygen; PBW, predicted bodyweight; PEEP, positive end-expiratory pressure; SMD, standardised mean difference.

Table 3 Multivariable logistic regression model to assess the associations of chemical and mechanical power with postoperative pulmonary complications (n = 2492).

	Odds ratio	**95%CI**	**p value**
Chemical power; J.min^{-1}	1.08	1.05–1.10	< 0.001
Mechanical power; J.min^{-1}	1.05	1.02–1.08	0.003
Age; y	1.02	1.01–1.03	< 0.001
Sex; female	0.95	0.78–1.15	0.600
BMI	1.01	0.99–1.02	0.400
ASA physical status			
1	—	—	
2	1.94	1.22–3.18	0.006
3	2.84	1.77–4.72	< 0.001
4	2.24	0.83–6.09	0.110
Pre-operative SpO_2; %	0.92	0.87–0.96	< 0.001
Respiratory infection	1.54	1.01–2.33	0.042
Pre-operative anaemia	1.05	0.86–1.30	0.600
Heart failure	1.36	0.98–1.88	0.064
COPD	1.12	0.79–1.59	0.500
Active cancer	0.92	0.72–1.16	0.500
Laparoscopic surgery	0.56	0.44–0.72	< 0.001
Emergency procedure	1.86	0.88–3.87	0.100
PEEP; cmH_2O	0.97	0.94–0.99	0.008
Duration of surgery; min	1.01	1.00–1.01	< 0.001

COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure; SpO_2, peripheral oxygen saturation.

requirements) (online Supporting Information Tables S5–7 and Figures S4 and S5). Similarly, findings were not altered when we extended our study population to include all patients in the database (online Supporting Information Tables S8–S10 and Figures S6 and S7) or included the individual trial as an independent variable in the regression analysis (online Supporting Information Table S11).

Discussion

We found that chemical and mechanical power are individually associated with PPCs, but with additive rather than synergistic effects. This is important because both mechanical and chemical power are modifiable via optimisation of intra-operative ventilator settings. Further work is required to determine if these observed associations

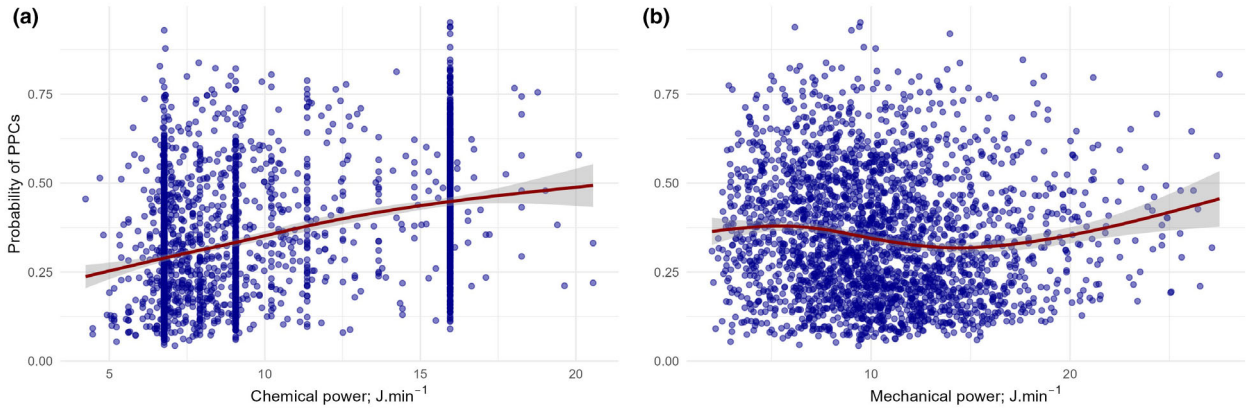

Figure 2 Probability of postoperative pulmonary complications (PPCs) over the ranges of (a) chemical and (b) mechanical power. Blue dots represent the probability of PPCs for each patient (n = 2492) based on the exposure to chemical or mechanical power, estimated using the primary confounder-adjusted logistic regression model (Table 3). Smoothed curves with 95%CIs were added to highlight the trends in the average probability of postoperative pulmonary complications over the ranges of chemical and mechanical power (red lines with grey ranges).

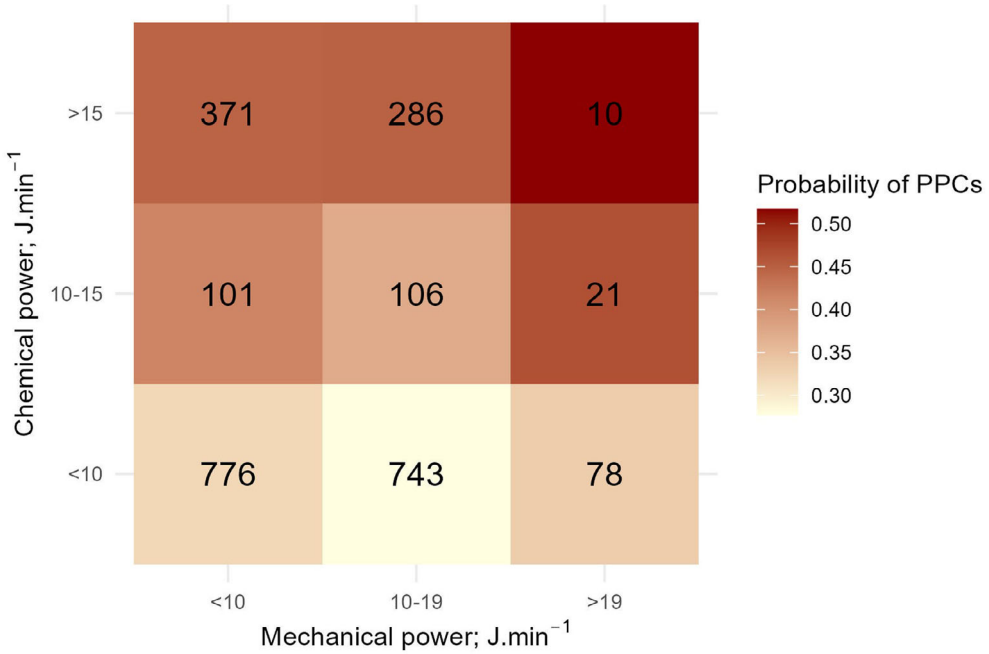

Figure 3 Probability of postoperative pulmonary complications (PPCs) associated with chemical and mechanical power. The population (n = 2492) was divided into 9 (3 × 3) bins of equally sized ranges of chemical and mechanical power (low, moderate, high). For each bin, the average probability of PPCs was estimated using the primary confounder-adjusted logistic regression model (Table 3) and presented on a colour scale from light yellow to dark red as a 3 × 3 field heat map.

are causal or predictive for postoperative lung injury. Given the high biological plausibility of the contribution of chemical and mechanical power to ventilator-induced lung injury, we recommend titration of both parameters to aim for safe, rather than supranormal, respiratory physiological end points.

The evidence of pulmonary harm from high chemical power, or high F_IO_2, used for mechanical ventilation during surgery, is uncertain [7, 8]. Although older randomised trials found no effect of inspired oxygen on the incidence of PPCs [22, 23], more recent studies, with incorporation of lung-protective ventilation, showed an increased risk of postoperative atelectasis and severe PPCs with 80% compared with 30% inspired oxygen [24, 25]. Regarding mechanical power, to date there are no randomised clinical trials that target mechanical power explicitly. Nevertheless,

high mechanical power-induced lung injury has been reported in animal studies [26, 27] and was repeatedly associated with postoperative lung injury [28, 29]. Our findings underline the need for large robust randomised clinical trials on intra-operative chemical and mechanical power minimisation strategies.

Reduction of chemical power may seem straightforward in most patients by avoiding unnecessarily high F_IO_2 levels. However, patients prone to intra-operative atelectasis, such as patients with obesity and patients undergoing laparoscopic procedures, may require recruitment manoeuvres and higher PEEP values to facilitate ventilation with low F_IO_2. In contrast, multiple interventions may reduce mechanical power, and it remains unclear which intervention works best [30, 31]. Recent studies underlined three essential concepts: lowering tidal volumes necessitates higher respiratory rates, potentially outweighing a tidal volume-related reduction in mechanical power [32]; lowering respiratory rate effectively reduces mechanical power [33]; and permissive hypercapnia tolerated to facilitate lung-protective ventilation protects the lungs [34, 35]. Therefore, permissive hypercapnic ventilation through low respiratory rates represents a potential strategy to reduce intra-operative mechanical power, and warrants evaluation in future randomised trials.

Our study has several strengths and limitations. We developed our protocol a priori before conducting our analysis and this strengthens the scientific rigour of our report. A key strength is the use of robust prospectively collected clinical trial data to reduce the risk of undetected errors common in routine clinical documentation. The large sample size allowed us multiple adjustments for well-established factors of pulmonary risk. Regarding limitations, the observational design of our study precludes definitive conclusions about causality. Although we adjusted for numerous potential confounders, the use of supplemental oxygen is likely confounded by underlying pulmonary conditions and individual responses to surgery and ventilation. Several hundred patients were not included due to missing covariate data. However, as missingness is likely random, we considered the risk of selection bias from a complete case analysis to be less significant than potential bias introduced by imputation. We have included a sensitivity analysis with inclusion of all patients in the database to explore this potential effect. The original studies used slightly different definitions of PPCs, introducing potential variability and bias to our results. Finally, our calculation of chemical power utilises F_IO_2 primarily; however, the underlying model also includes pulmonary oxygen consumption, which could be individualised at patient or group level in future studies.

In conclusion, both chemical and mechanical power are independently associated with PPCs. However, while chemical and mechanical power have an additive effect on the risk of PPCs, we did not observe a synergistic effect. Our findings contribute to the growing body of evidence emphasising the need for mechanical ventilation to be as `permissive´ as possible, minimising exposure to mechanical and chemical power.

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The REPEAT analysis was additionally registered at clinicaltrials.gov (NCT03937375) and the study protocol of this study was attached to the entry of the REPEAT analysis. This research project emerged from connecting LMM-W and MJS within the European Society of Anaesthesia and Intensive Care mentorship programme 2023. LMM-W was supported by the Deutsche Forschungsgemeinschaft – 466655093. Data are available upon reasonable request from MJS (marcus.j.schultz@gmail.com). The R statistical code used for this study is publicly available in a github online repository licensed under the GNU General Public Licence v3.0: https://github.com/LukasMuellerWirtz/CPMP-PPC. No other external funding or competing interests declared. Open Access funding enabled and organized by Projekt DEAL.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. REPEAT investigators.

Table S1. Definitions of postoperative pulmonary complications.

Table S2. Patient characteristics (including only patients with available plateau pressures).

Table S3. Intra-operative ventilation parameters (including only patients with available plateau pressures).

Table S4. Multivariable regression model to assess the associations of chemical and mechanical power with postoperative pulmonary complications (including only patients with available plateau pressures).

Table S5. Patient characteristics (including only patients with F_IO_2 of 0.4, 0.5 or 0.8).

Table S6. Intra-operative ventilation parameters (including only patients with F_IO_2 of 0.4, 0.5 or 0.8).

Table S7. Multivariable regression model to assess the associations of chemical and mechanical power with postoperative pulmonary complications (including only patients with F_IO_2 of 0.4, 0.5 or 0.8).

Table S8. Patient characteristics (including all patients).

Table S9. Intra-operative ventilation parameters (including all patients).

Table S10. Multivariable regression model to assess the associations of chemical and mechanical power with postoperative pulmonary complications (including all patients).

Table S11. Multivariable regression model to assess the associations of chemical and mechanical power with postoperative pulmonary complications (adjustment of the primary analysis for trial effects).

Figure S1. Chemical power and the corresponding F_IO_2 in patients with and without postoperative pulmonary complications.

Figure S2. Probability of postoperative pulmonary complications over the ranges of chemical and mechanical power (including only patients with available plateau pressures).

Figure S3. Probability of postoperative pulmonary complications associated with chemical and mechanical power (including only patients with available plateau pressures).

Figure S4. Probability of postoperative pulmonary complications over the ranges of chemical and mechanical power (including only patients with F_IO_2 of 0.4, 0.5 or 0.8).

Figure S5. Probability of postoperative pulmonary complications associated with chemical and mechanical power (including only patients with F_IO_2 of 0.4, 0.5 or 0.8).

Figure S6. Probability of postoperative pulmonary complications over the ranges of chemical and mechanical power (including all patients).

Figure S7. Probability of postoperative pulmonary complications associated with chemical and mechanical power (including all patients).

Plain Language Summary.