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RESEARCH ARTICLE

Intraoperative open lung condition and postoperative pulmonary complications. A secondary analysis of iPROVE and iPROVE-O2 trials

Carlos Ferrando[1,2] | Julian Librero[3] | Gerardo Tusman[4] | Ary Serpa-Neto[5,6,7] | Jesús Villar[2,8,9] | Francisco J. Belda[6] | Eduardo Costa[10,11] | Marcelo B. P. Amato[10] | Fernando Suarez-Sipmann[2,12,13] | the iPROVE Network Group

[1]Department of Anesthesiology and Critical Care, Hospital Clínic, Institut D'investigació August Pi i Sunyer, Barcelona, Spain

[2]CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

[3]Navarrabiomed, Complejo Hospitalario de Navarra, UPNA, REDISSEC (Red de Investigación en Servicios de Salud), La Palma de Cervelló, Spain

[4]Department of Anesthesiology, Hospital Privado de Comunidad, Mar de Plata, Argentina

[5]Australian and New Zealand Intensive Care-Research Centre (ANZIC-RC), Monash University, Melbourne, Vic., Australia

[6]Department of Critical Care Medicine, Hospital Israelita Albert Einstein, Sao Paulo, Brazil

[7]Department of Critical Care, Melbourne Medical School, University of Melbourne, Austin Hospital, Melbourne, Vic., Australia

[8]Multidisciplinary Organ Dysfunction Evaluation Research Network, Research Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain

[9]Keenan Research Center for Biomedical Science at the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

[10]Cardio-Pulmonary Department, Pulmonary Division, Heart Institute (Incor), University of São Paulo, Sao Paulo, Brazil

[11]Research and Education Institute, Hospital Sirio-Libanês, Sao Paulo, Brazil

[12]Department of Surgical Sciences, Hedenstierna Laboratory, Uppsala University Hospital, Uppsala, Sweden

[13]Department of Intensive Care, Hospital Universitario La Princesa, Madrid, Spain

Correspondence
Carlos Ferrando, Department of Anesthesiology and Critical Care, Hospital Clínic i Provincial de Barcelona , C/ Villarroel 170. 08036, Barcelona. Spain.
Email: cafeoranestesia@gmail.com

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Abstract

Background: The preventive role of an intraoperative recruitment maneuver plus open lung approach (RM + OLA) ventilation on postoperative pulmonary complications (PPC) remains unclear. We aimed at investigating whether an intraoperative open lung condition reduces the risk of developing a composite of PPCs.

Methods: Post hoc analysis of two randomized controlled trials including patients undergoing abdominal surgery. Patients were classified according to the intraoperative lung condition as "open" (OL) or "non-open" (NOL) if PaO_2/FIO_2 ratio was ≥ or <400 mmHg, respectively. We used a multivariable logistic regression model that included potential confounders selected with directed acyclic graphs (DAG) using Dagitty software built with variables that were considered clinically relevant based on biological mechanism or evidence from previously published data. PPCs included severe acute respiratory failure, acute respiratory distress syndrome, and pneumonia.

Results: A total of 1480 patients were included in the final analysis, with 718 (49%) classified as OL. The rate of severe PPCs during the first seven postoperative days was 6.0% (7.9% in the NOL and 4.4% in the OL group, $p = .007$). OL was independently

associated with a lower risk for severe PPCs during the first 7 and 30 postoperative days [odds ratio of 0.58 (95% CI 0.34–0.99, $p = .04$) and 0.56 (95% CI 0.34–0.94, $p = .03$), respectively].

Conclusions: An intraoperative open lung condition was associated with a reduced risk of developing severe PPCs in intermediate-to-high risk patients undergoing abdominal surgery.

Trial registration: Registered at clinicaltrials.gov NCT02158923 (iPROVE), NCT02776046 (iPROVE-O2).

KEYWORDS

intraoperative, open lung, positive end-expiratory pressure, postoperative pulmonary complications, recruitment maneuvers

Editorial Comment

Lung gas exchange for oxygen for perioperative patients may be linked to likelihood for later serious postoperative pulmonary complications. From two trials of lung recruitment interventions, this secondary analysis of case oxygenation results showed that better lung gas exchange is associated with lower risk for postoperative pulmonary complications. Less risk for pulmonary complications is also noted for those cases treated with lung recruiting maneuvers.

1 | INTRODUCTION

In the era of lung-protective ventilation, different ventilatory strategies have been proposed to reduce postoperative pulmonary complications (PPCs).[1] The open lung approach (OLA) combines a lung recruitment maneuver (RM), to reopen collapsed alveoli, with the selection of a post-RM positive end-expiratory pressure (PEEP) to prevent their recollapse. It is known that alveolar collapse minimizes regional lung mechanical stress and strain, known triggers of local and systemic inflammatory responses increasing the risk for developing PPCs.[2,3] However, whether OLA reduces the risk of PPCs is unclear as previous comparative trials with conventional ventilation strategies have been inconclusive.[4–7] None of the previous published comparative studies evaluating an OLA have confirmed whether an open lung was reached using a predefined physiological response or imaging assessment. Differences on how the OLA is applied, variable and uncontrolled success in reaching and maintaining an open lung condition, differences in the ventilatory strategies used in controls, and variable definitions of PPCs, may account, at least in part, for this lack of evidence.[4–7]

The prevalence of intraoperative atelectasis has been reported as high as 90%,[8] although recent studies suggest that current prevalence may be significantly lower.[9,10] This could have important implications in the design of pragmatic studies comparing OLA versus a standard "low-PEEP-no-recruitment" strategies that never considered the presence or absence of atelectasis.[4–7] Indeed, all these studies were based on the assumption that most patients develop intra- and postoperative atelectasis, departing from an "ideal" open lung condition, and that an OLA strategy should thus be effective. Now, patients who do not develop atelectasis will maintain an open lung when managed with a standard ventilation strategy or will be submitted to unnecessary RMs when managed with an OLA strategy. By contrast, in patients who do develop atelectasis, the standard ventilation strategy would be a true control but those managed with an OLA may or may not reach an open lung condition depending on the success of the strategy. Both possibilities, but especially the latter, are systematically neglected as trials arbitrarily assume that the desired state (i.e., an open lung condition) is reached just because a certain ventilation protocol was applied.

Therefore, we aimed to demonstrate that an open lung condition associates a decrease risk of developing severe PPCs, irrespective of the ventilatory strategy used. To confirm our hypothesis, we performed this secondary analysis using the datasets of the previously published iPROVE and iPROVE-O2 trials.[6,11]

2 | METHODS

2.1 | Study design and participants

This is a post hoc exploratory analysis of the datasets from the iPROVE (NCT02158923) and iPROVE-O2 (NCT02776046) multicenter randomized controlled clinical trials that enrolled 965 and 718 surgical patients, from January 2, 2015 to May 18, 2016 and from June 6, 2017 to July 19, 2018, respectively.[6,11] Both trials followed the CONsolidated Standards of Reporting Trials (CONSORT).[12] The main study characteristics and ventilatory management are presented in the appendix. Briefly, the iPROVE and iPROVE-O2 trials enrolled adult patients (≥18 years) scheduled for major abdominal surgery (by laparotomy/laparoscopy) with an expected surgical time >2 h, and a body mass index (BMI) <35 kg/m^2. Of note, iPROVE, but not

iPROVE-O2, included patients with intermediate to high risk for PPCs (as defined by the ARISCAT score).[13] Exclusion criteria were pregnant or breastfeeding women, moderate–severe acute respiratory distress syndrome (ARDS), heart failure, intracranial hypertension, mechanical ventilation during the previous 15 days, pneumothorax or giant bullae, chronic obstructive pulmonary disease requiring oxygen or continuous positive airway pressure (CPAP), or those participating in another interventional study.

Ethics: Being a post hoc analysis of two previously published randomized controlled trials, ethical approval was not required for this analysis.[6,11]

2.2 | Randomization and masking

In both trials, intraoperative and post-anesthetic care data were collected by an unmasked investigator; postoperative data in the ward were collected by an investigator masked to randomization. Patients were masked to treatment allocation. In both, patients were randomly assigned to the study arms through the iPROVE website (iprove.incliva.es) with an allocation rate of 1:1:1:1 in the iPROVE and 1:1 in the iPROVE-O2 and stratified according to the study site. Recruitment among hospitals was competitive.

2.3 | Procedures

The complete protocols have been previously published.[6,11] Protocolized monitoring and management, except for the ventilatory management, were identical in the two trials and followed high standard of care practices. All patients received a tidal volume (VT) of 8 ml/kg PBW and plateau pressure (Pplat) was limited to ≤25 cmH_2O. Intraoperatively, two different ventilatory strategies were compared: (i) *OLA*, as defined by a controlled, stepwise RM up to an airway pressure of 40 cmH_2O followed by a decremental PEEP titration trial until the highest respiratory system compliance (Cdyn) was observed (supplementary material). Individualized PEEP was set based on the highest Cdyn level after a new RM.[14] Additional RM and PEEP titration trials were performed only if Cdyn decreased ≥10% and hemoglobin oxygen saturation (SpO_2) decreased to ≤96%, 5 min after reducing FIO_2 to 0.21, both assessed every 40 min. This last maneuver (air test) was performed to detect the presence of shunt ≥10% induced by lung-collapse, as previously described.[15] (ii) *STD (STanDard)*, in which patients received standard intraoperative lung-protective ventilation with a fixed PEEP of 5 cmH_2O, without RMs. Postoperatively, patients received either CPAP or supplemental oxygen (Table S1; Figure S1).[6,11]

For the present analysis, patients were classified as having an open lung (OL) or non-open lung condition (NOL) based on intraoperative arterial blood gases (ABG). OL was defined as a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FIO_2) ≥400 mmHg, as per protocol scheduled ABG analysis 60 min after intubation and at the end of surgery before extubation. The NOL was defined as a PaO_2/FIO_2 <400 mmHg in at least one of these two ABG samples. This oxygenation criterion was based on previous physiological studies that defined a PaO_2/FIO_2 ratio ≥400 mmHg as an open lung condition and on the iso-shunt curves in which a PaO_2/FIO_2 ≥400 with an FIO_2 of ≤0.8 corresponds to a shunt level <10%.[16,17] The driving pressure (DP) was calculated as plateau pressure minus PEEP. For the analysis, we used mean values obtained 60 min after intubation and at the end of surgery before extubation.

2.4 | Outcomes

The primary outcome was to demonstrate that an intraoperative OL reduces the occurrence of severe PPCs [a composite of pulmonary complications including severe acute respiratory failure (ARF), pulmonary infection, acute respiratory distress syndrome (ARDS)] during the first seven postoperative days. Secondary outcomes included the composite of the PPCs reported in the original protocols (atelectasis, mild ARF, severe ARF, pulmonary infection, ARDS, aspiration pneumonitis, bronchospasm, pleural effusion, pulmonary edema, pneumothorax) during the first seven postoperative days, and both composites during the first 30 postoperative days (definitions in Table S2). Pulmonary outcomes were defined according to the Joint Taskforce of the European Society of Anaesthesiology and the European Society of Intensive Care Medicine.[18] Other secondary outcomes included hospital length of stay (LOS) and hospital mortality at 30 days of surgery.

2.5 | Statistical analysis

We compared variables using either Student's *t* test or the Mann–Whitney *U* test for continuous variables, depending on their distribution (Shapiro–Wilk test was used to assess normality). Data are reported as mean (SD) or median (IQR), as appropriate. Qualitative variables were described as frequency (percentages) and compared between groups using Pearson's chi-square test or Fischer's test. First, we studied factors associated with lung condition after surgery, and second, factors associated with PPC (according to measurement time and severity) both by multivariable logistic regression analysis. The multivariable models included the potential confounders selected with directed acyclic graphs (DAG) using Dagitty software available online at http://dagitty.net/development/dags. The DAG was built with variables that were considered clinically relevant based on biological mechanism or evidence from previously published data (Figure S2). Adjusted odds ratios (OR) of variables present in the final model are presented with their 95% confidence intervals (CI). Finally, we conducted a mediation analysis to assess to what extent the open lung condition and driving pressure (indirect effects) mediated the direct effect of randomization in the iPROVE trial, which compared RM + OLA with a low (5 cmH_2O) PEEP strategy. We hypothesized that both, open lung condition and driving pressure,

would show complementary mediation, that is, randomization to the intervention arm would increase the likelihood of attaining an open lung condition and reduced driving pressures, which in turn would be associated with a lower incidence of pulmonary complications. To assess the significance of these indirect effects, we used Preacher and Hayes' bootstrap method.[19] All tests were two-sided and *p* values less than .05 were considered statistically significant. All statistical analyses were performed with R statistical software, version 3.2.0 (available online at http://www.r-project.org/).

3 | RESULTS

From 1684 patients, 204 were excluded due to missing data, mainly ABGs. A total of 1480 patients were included in the final analysis: 1058 received OLA and 422 received STD ventilation. Patient's distribution in the OL or NOL condition was similar (717 vs. 762, respectively). Demographic characteristics of analyzed patients are described in Table S4.

Intraoperatively, although median PEEP was higher in the OL group (10 vs. 8 cmH_2O, $p < .001$), Pplat and DP were significantly lower at 60 min (19 vs. 21 cmH_2O, $p < .001$, and 10 vs. 12 cmH_2O, $p < .001$, respectively) and at the end of surgery (18 vs. 19 cmH_2O, $p < .001$, and 9 vs. 10 cmH_2O, $p < .001$, respectively; Table 2). There were no differences in mean arterial pressure, cardiac output, or volume administration between groups. Although vasoactive drugs were more frequently used in the OL group 431 (61%) versus 404 (54%), $p < .009$, the proportion of patients with epidural-anesthesia-induced vasodilation was higher in this group 410 (57%) versus 368 (48%), $p < .001$ (Table 2), which was directly related to an increase in vasoactive drug use (OR 1.97, 95% CI 1.61–2.39, $p < .001$). The proportion of patients with shunt >10% in the postoperative period was significantly higher in NOL 242 (32%) versus 186 (26%) in OL, $p = .008$, as was the need for protocolized rescue maneuvers, as described in the original protocols (supplement) due to postoperative hypoxemia 83 (12.3%) in NOL versus 46 (6.9%) in OL group, $p < .001$ (Table 2).

3.1 | Outcomes

Among patients receiving OLA, 575 (54%) had a confirmed open lung condition, compared to 143 (33%) of those receiving a STD strategy ($p < .001$) (shown in Figure 1 and Table S3). In the first multivariable regression analysis (where OL is the dependent variable), age, body mass index (BMI), preoperative peripheral oxyhemoglobin saturation (SpO_2), driving pressure, the surgical technique, and the ventilation strategy were independently associated with an OL (Table 1). OLA was associated with a significantly higher probability of achieving an OL [odds ratio (OR) 2.19, 95% CI 1.63–2.95, $p < .001$] (Table 1).

The directed acyclic graph (Figure S2) indicates that the minimal sufficient adjustment sets for estimating the total effect of lung condition or driving pressure on PPC (the outcome) were: American Society of Anesthesiology physical status classification (ASA), BMI, preoperative SpO_2, previous pulmonary infection, surgical technique (laparoscopy/laparotomy), and ventilation strategy (OLA or STD).

In the second multivariable regression analysis (where the exposure variable was "open lung -OL- condition" and PPC was the dependent variable), we found that open lung condition, BMI, surgical technique, and ventilation strategy were independently associated with the development of severe PPCs (Table 3). Among those factors, OL condition was associated with a reduction of severe PPCs at 7th and 30th postoperative days (OR 0.58, 95% CI 0.34–0.99, $p = .04$; and OR 0.56, 95% CI 0.34–0.94, $p = .03$) (Figure 2). This also applied when the composite outcome included all PPCs reported during the first 7 and 30 postoperative days (OR 0.64, 95% CI 0.49–0.84, $p < .01$, and OR 0.63, 95% CI 0.48–0.82, $p < .001$), respectively. Bivariate analysis is shown in Table S5. We also found similar associations when the exposure variable was the driving pressure, although not for severe PPCs (Table S6). The association between the PaO_2/FiO_2 and severe PPCs is shown in Figure S3 and Table S7. The prevalence of severe and total PPCs in the OL and NOL groups is presented in Figure S4.

The mediation analysis, only performed in the iPROVE dataset (Figure 3), reinforced the above results, supporting that, despite the marginal results of the randomized strategy (OLA) in the original publication with total PPCs reduced by 6% and with severe PPCs reduced by 3.3%, OL significantly mediated such effects ($p < .001$ and $p = .002$, respectively), with a mediation proportion of 65% and 57%, respectively. The multivariate mediating effect exhibited odds ratio of 0.48 and 0.44, respectively (95% CI 0.31↔0.66 and 0.24↔0.75, for all PPCs and for severe PPCs, respectively). Driving pressure was also a simultaneous mediator for all PPCs ($p = .01$), mediating 27% of the benefits of randomization, and only 7% of the reduction in severe PPCs (nonsignificant mediation).

Although we found no differences in hospital LOS or in mortality at day 30 between groups (Table S7), patients who developed severe PPCs had an increased risk for mortality at postoperative day 30 (RR 4.87, 95% CI 1.96–12.2, $p < .001$).

4 | DISCUSSION

To our knowledge, this is the first study examining the risk of developing PPCs based on a physiologically defined lung condition—open versus non-open—instead of a ventilatory strategy. The main finding of this study is that patients maintaining an open lung condition, independent of the applied intraoperative ventilatory strategy, had a lower risk for developing severe PPCs. Patients submitted to an OLA were more likely to achieve an open lung condition than those receiving a standard ventilation using low PEEP. Of note, only 55% of patients in the OLA and up to 33% in the conventional strategy reached such a condition during the intraoperative period.

Atelectasis acts as a lung stress-raiser promoting ventilator-induced lung injury, and is thus considered a risk factor for developing PPCs.[20] For instance, lung collapse reduces respiratory system

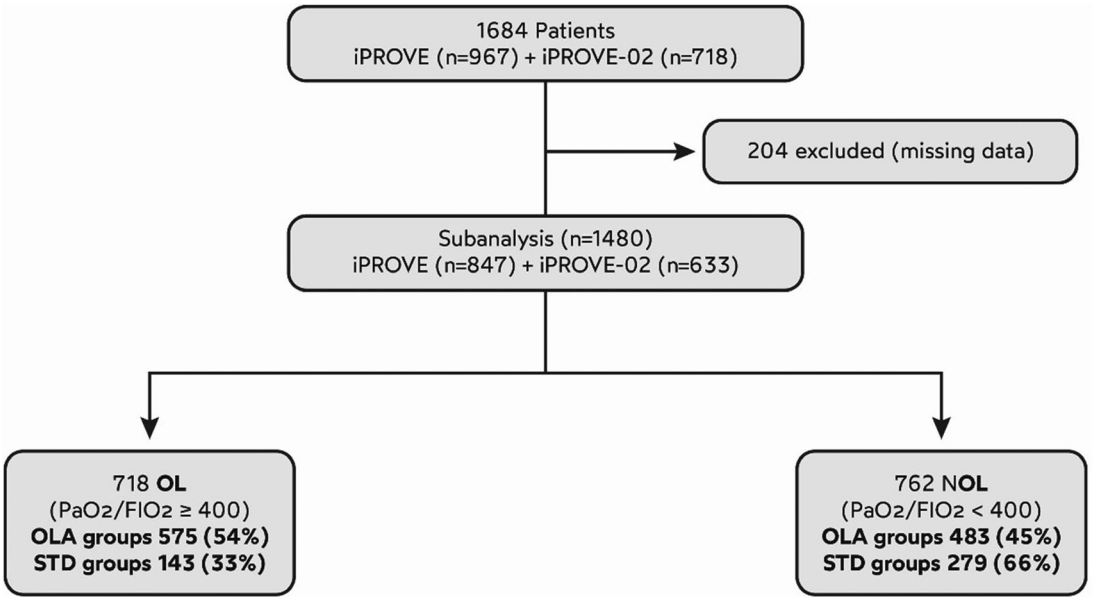


FIGURE 1 Flowchart. NOL, non-open lung; OL, open lung; OLA, open lung approach; RM, recruitment maneuver; STD, standard

TABLE 1 Factors associated with lung condition. Multivariable regression analysis

Variable	Open lung condition
Age	0.98 (0.97–0.99)**
Preoperative SpO_2 > 96%	1.18 (1.10–1.27)***
Previous pulmonary infection	1.07 (0.53–2.14)
Laparotomy	1.44 (1.10–1.89)**
Driving pressure	0.89 (0.85–0.94)***
RM + OLA	2.19 (1.63–2.95)***
BMI > 30	0.54 (0.38–0.77)***

Note: The multivariable model includes the potential confounders selected with the directed acyclic graphs (DAG). It was built with variables that yielded *p* values less than .05 on univariate analysis and/or that were considered to be clinically relevant based on biological mechanism or evidence from previously published data. Laparotomy: type of surgery. The ARISCAT score was not included since the variables that compose it are included. Data are presented as odds ratio (OR), 95% confidence interval.

Driving pressure as plateau pressure minus positive end-expiratory pressure; Open lung condition defined as PaO_2/FIO_2 ≥ 400 mmHg. BMI, body mass index; RM + OLA, recruitment maneuver plus open lung approach; SpO_2, peripherical oxyhemoglobin saturation

*p < .05; **p < .01; ***p < .001.

compliance, which results in an increase in driving pressure,[21–23] an independent predictor for PPCs.[24] In our study, the open lung condition was associated with lower driving and plateau pressures. However, when comparing different open lung strategies aimed at minimizing atelectasis with conventional ventilation strategies, recent clinical trials have provided contradictory results.[3–7] Discrepancies might be related on the one hand to differences in how those strategies were applied and succeeded in reaching an open lung condition, and on the other hand on the selected control ventilatory strategies. In the IMPROVE trial, the use of RMs and PEEP of 6 cmH_2O compared with a control group of zero-PEEP without recruitment maneuvers resulted in a reduction of PPCs in moderate- to high-risk patients undergoing laparotomy.[5] However, the use of an excessive high tidal volume in the control group might have influenced the results. In the PROVHILO and PROBESE studies, a recruitment maneuver strategy associated with an arbitrary PEEP level of 12 cmH_2O was compared with a conventional ventilation using PEEP of 2–4 cmH_2O. Using a more balanced control and identical tidal volumes in both arms, they did not find differences in PPCs.[4,7] In the iPROVE trial, with identical tidal volumes in both arms, the individualized OLA strategy resulted in significant reductions of PPCs when compared to the control arm (5 cmH_2O PEEP).[6] A common feature of these studies is that the open lung condition was never confirmed. Given the different open lung strategies applied and the use of low opening pressures in the IMPROVE,[5] PROVHILO,[4] and PROBESE[7] trials (5–15 cmH_2O below the recommended level obtained in previous physiological studies), it is likely that a significant proportion of patients never reached the intended open lung condition. This is supported by the current analysis where only half of patients submitted to an OLA strategy reached an intraoperative open lung condition. Considering that we used higher opening pressures than in previous studies in combination with an individualized PEEP titration, we speculate that probably ≤50% of patients reached an intraoperative open lung condition in previous trials.

This secondary analysis supports the benefits of maintaining an open lung condition during the intraoperative period and provides new insights to better interpret and understand the findings of previous trials. First, given the significant proportion of patients in the low PEEP groups with an intraoperative open lung condition, the reported high prevalence of anesthesia-induced atelectasis, in the

TABLE 2 Perioperative characteristics

Variable	OL	NOL	*p*-value
PEEP, cmH_2O			
1 h after ventilation start	10 (7–12)	8 (5–10)	<.001
End of surgery	10 (6–12)	8 (5–12)	<.001
Tidal volume, ml			
Baseline	480 (425–540)	500 (440–540)	.024
1 h after ventilation start	480 (425–530)	480 (433–540)	.038
End of surgery	480 (425–530)	490 (440–540)	.010
Plateau Pressure, cmH_2O			
Baseline	15 (13–17)	16 (14–18)	<.001
1 h after ventilation start	19 (16–23)	21 (17–25)	<.001
End of surgery	18 (15–21)	19 (15–22)	.045
Driving pressure, cmH_2O[a]			
Baseline	10 (8–12)	10 (9–13)	<.001
1 h after ventilation start	10 (8–12)	12 (9–12)	<.001
End of surgery	9 (7–10)	10 (8–12)	<.001
PaO_2/FIO_2, mmHg			
Baseline	455 (383–516)	352 (277–432)	<.001
1 h after ventilation start	506 (461–552)	346 (279–390)	<.001
End of surgery	504 (461–553)	350 (282–401)	<.001
$PaCO_2$, mmHg			
Baseline	38.0 (34.8–41.0)	38.0 (35.0–42.0)	.027
1 h after ventilation start	40.0 (36.0–44.0)	41.0 (37.2–45.0)	<.001
End of surgery	40.0 (36.9–43.73)	40.3 (37.0–44.1)	.164
Mean arterial pressure, mmHg			
Baseline	76 (69–86)	78 (70–88)	.029
1 h after ventilation start	80 (70–89)	81 (72–91)	.006
End of surgery	77 (69–77)	78 (70–87)	.004
Cardiac index, $ml/min/m^2$			
Baseline	2.5 (2.2–3.0)	2.4 (2.1–2.9)	.065
1 h after ventilation start	2.7 (2.4–3.2)	2.6 (2.2–3.1)	.008
End of surgery	2.8 (2.5–3.2)	2.7 (2.3–3.2)	.013
Volume of fluids			
Total volume, ml	2000 (1500–2903)	2000 (1500–2780)	.375
Blood loss, ml	250 (150–450)	200 (100–400)	.091
Urine Output, ml	200 (0–360)	200 (0–400)	.119
Vasoactive drugs[b]	431 (61)	404 (54)	.009
Epidural analgesia	410 (57)	368 (48)	<.001
NMB optimization[c]	510 (74)	482 (69)	.048
Temperature, °C[d]	36.0 (35.6–36.4)	36.0 (35.6–36.5)	.355
Prophylaxis of PONV	675 (95)	690 (92)	.006
Duration of ventilation, min	245 (185–320)	240 (180–300)	.163
Duration of surgery, min[e]	208 (150–270)	200 (150–260)	.514
Positive air test, *n* (%)	186 (26)	242 (32)	.008
Postoperative rescue maneuvers, *n* (%)	46 (6.9)	83 (12.3)	<.001

Note: Data are presented as mean (standard deviation) or median (interquartile range) for continuous variables and *n* (%) for categorical variables.

Protocolized postoperative rescue maneuvers were initiated if the patient developed hypoxemia during the first three postoperative hours.

Abbreviations: CPAP, Continuous positive airway pressure; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2/FIO_2, partial pressure of arterial oxygen to inspiratory oxygen fraction ratio; PEEP, Positive end-expiratory pressure; PONV, prophylaxis of postoperative nausea and vomiting; TOF, Train Of Four.

[a]Driving pressure was calculated as plateau pressure minus positive end-expiratory pressure.

[b]Vasoactive drugs: patients who received vasopressors and/or inotropes.

[c]NMB optimization: patient in which the neuromuscular blockade was monitored and/or reversed when considered by the attending physician before extubation.

[d]Temperature recorded at end of surgery.

[e]Time between skin incision and closure of the incision.

TABLE 3 Factors associated with PPCs. Multivariable regression analysis

Variable	Severe PPC (7 days)	All PPC (7 days)	Severe PPC (30 days)	All PPC (30 days)
Open lung condition	0.58 (0.34–0.99)*	0.64 (0.49–0.84)**	0.56 (0.34–0.94)*	0.63 (0.48–0.82)***
Preoperative SpO_2 < 97%	0.97 (0.86–1.10)	0.89 (0.84–0.96)***	0.99 (0.88–1.11)	0.89 (0.83–0.95)***
Previous pulmonary infection	0.87 0.20–3.80)	1.64 (0.83–3.22)	0.80 (0.18–3.47)	1.74 (0.89–3.40)
Laparotomy	2.00 (1.18–3.38)**	1.73 1.33–2.24)***	2.02 (1.22–3.35)**	1.74 (1.34–2.25)***
RM + OLA	0.57 (0.35–0.94)*	0.40 (0.31–0.52)***	0.67 (0.41–1.09)	0.43 (0.33–0.56)***
BMI > 30	1.74 (0.98–3.07)	1.38 (0.99–1.91)	1.82 (1.05–3.14)*	1.41 (1.02–1.96)*
ASA	2.90 (0.68–12.42)	1.82 (0.96–3.43)	3.03 (0.71–12.98)	1.92 (1.02–3.61)*

Note: The multivariable model includes the potential confounders selected with the directed acyclic graphs (DAG). It was built with variables that yielded *p* values less than .05 on univariate analysis and/or that were considered to be clinically relevant based on biological mechanism or evidence from previously published data. Data are presented as odds ratio (OR), 95% confidence interval.

Open lung condition defined as $PaO_2/FIO_2 \geq 400$ mmHg.

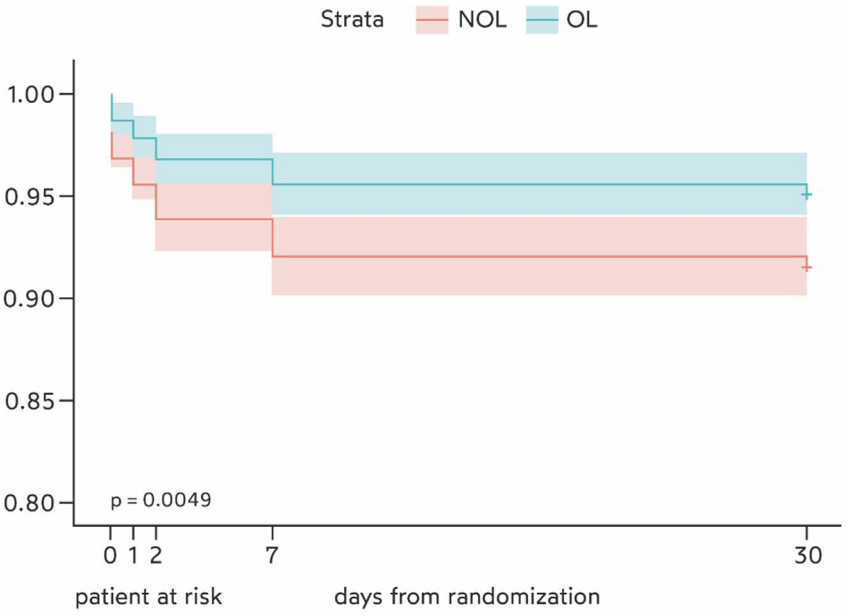
Abbreviations: ASA, American Society of Anesthesiologist risk score; BMI, body mass index; RM + OLA, recruitment maneuver plus open lung approach; SpO_2, peripherical oxyhemoglobin saturation.

*$p < .05$; **$p < .01$; ***$p < .001$.

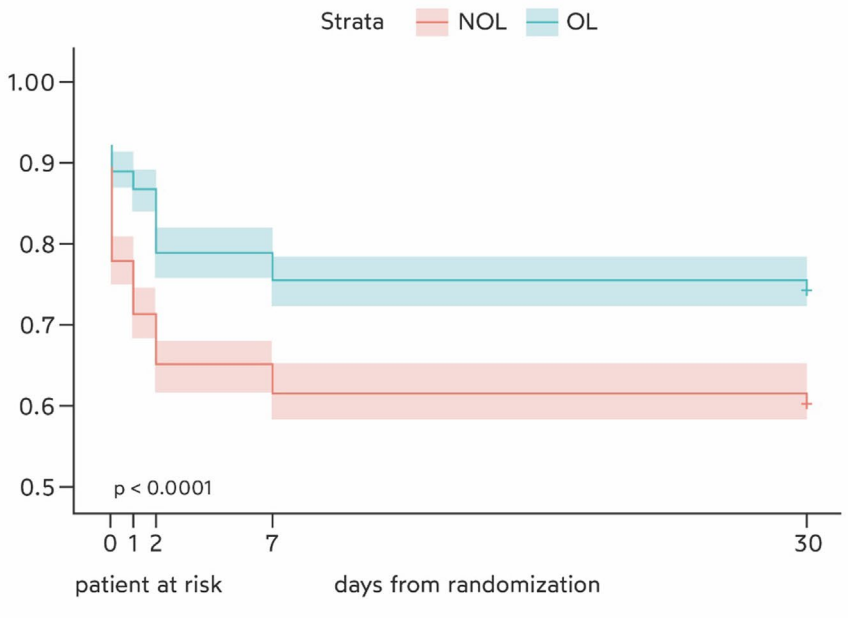
light of current management practices, may need to be reevaluated. Second, assessment of the presence of atelectasis may be important not only to select the best intraoperative ventilation strategy but also for an appropriate selection and enrollment of patients in comparative studies. In this respect, the air test, used in iPROVE and iPROVE-O2 trials, can become a simple, fast, and easy available option to detect anesthesia-induced atelectasis with high sensitivity and specificity.[15] The air test could identify patients that may benefit (or not) from an OLA strategy by discriminating between an open and a non-open condition. This would help to objectively and individually assess the opening and closing pressures of the lung,[10,25] an important step to standardize an OLA strategy. Third, the benefits of an intraoperative open lung condition do not necessarily extend to the postoperative period. We found that, even though the proportion of patients with a postoperative positive air test ($SpO_2 \leq 96\%$ on room air) was higher in the non-open lung group, 25% of patients with a confirmed intraoperative open lung lost this condition postoperatively as confirmed by a positive air test. This finding may be related to the use of a high FIO_2 during the extubation period to prevent hypoxemia during the awakening phase. Given the relation between an open lung condition and the reduction of PPCs found in the current analysis, raises the question whether those patients loosing the open lung condition in the early postoperative period could particularly benefit from noninvasive respiratory support.

Our findings, while supporting consensus recommendations on intraoperative lung-protective ventilation,[26] challenge the rationale and interpretation of study designs using fixed, protocol-driven ventilation strategies in non-selected patients. Furthermore, they question the universal use of such strategies in routine practice as they do not guarantee lung protection and could even be detrimental in some circumstances. For instance, an OLA strategy would only benefit patients who develop atelectasis and should therefore be limited to them. If any benefit is expected from an OLA strategy, careful individualization of opening pressures and post-recruitment PEEP should be attempted and an open lung condition confirmed. In patients without perioperative alveolar collapse, ventilatory management should also be individualized, targeting the lowest PEEP that maintains an open lung condition. Our findings may provide the basis for enrichment strategies to improve the design of future intraoperative ventilation trials, where the priority should be the achievement of a meaningful physiological response instead of a pragmatic fixed ventilation protocol. The mediation analysis adds two important insights. First, the strong odds ratio (~0.44) shows that a maneuver with higher efficacy, applied in an enriched population where all patients had confirmed atelectasis, could markedly reduce total PPCs or severe PPCs. Second, this analysis suggests that a maneuver guided by a change in the mediator(s) could be a potential solution to individualize ventilation and improve its efficacy. One could titrate higher pressures and/or repeated RMs for those at higher risk (high BMI or laparoscopic patients), to achieve an open lung condition and low driving pressures at the end of surgery. In the original trial by Ferrando et al.,[6] the OLA had an odds ratio for open lung condition of only 2.93 at the end of surgery. To ensure efficacy in >90% of patients, a larger odds ratio (OR ≥ 20) would be required. That could be tested in small preliminary studies.

The presented study has several important limitations. First, since this analysis was not prespecified in the original design of the iPROVE and iPROVE-O2 trials, it must be considered an exploratory analysis. However, both original studies and the current analysis are based on the hypothesis that an open lung condition improves the outcomes analyzed. The difference, as discussed above, is that in the original studies, the lung condition was assumed, and now the results are analyzed based on the lung condition not the ventilation strategy. Therefore, this analysis can be considered to be based on "a priori hypothesis," minimizing the risk of incurring in HARKing. Second, we acknowledge the important inherent limitations of defining an open lung condition based solely on oxygenation criteria. Recruitment and open lung are difficult to assess by other means than computed tomography imaging. In addition, both residual and unmeasured confounding that may affect intraoperative oxygenation independently of shunt induced by lung collapse are likely by the nature of the study design, even after careful covariate



NOL	755	731	721	709	695
OL	711	702	696	688	680



NOL	755	589	540	491	467
OL	711	634	617	561	537

FIGURE 2 Number of patients at risk of complications. Top panel presents patients free of severe postoperative pulmonary complications. OL was associated with a reduction of the risk of severe PPCs with an OR (0.58; 95% CI: 0.34–0.99 $p = .04$ and .56; 95% CI 0.34–0.94 $p < .03$) at the postoperative days 7th and 30th, respectively. Bottom panel shows patients free of postoperative pulmonary complications. OL was associated with a reduction of the risk of PPCs with an OR (0.64; 95% CI: 0.49–0.84. $p < .01$ and .63; 95% CI 0.48–0.82. $p < .001$) at the postoperative days 7th and 30th, respectively. CI, confidence interval; NOL, non-open lung condition; OL, open lung condition; OR, odds ratio; PPCs, postoperative pulmonary complications

adjustment. Nevertheless, oxygenation is a frequently used variable that is particularly useful in the presence of normal lungs such as the ones included in this analysis in which shunt is mostly related to atelectasis. This relationship has been recently confirmed by using the air test in the postoperative period.[15] However, being a clinical study, we used an FIO_2 of 0.8 or 0.3 instead of the usual 1.0 to define an open lung condition. Thus, it is plausible that some patients with open lung were misclassified as non-open lung, since the PaO_2/FIO_2

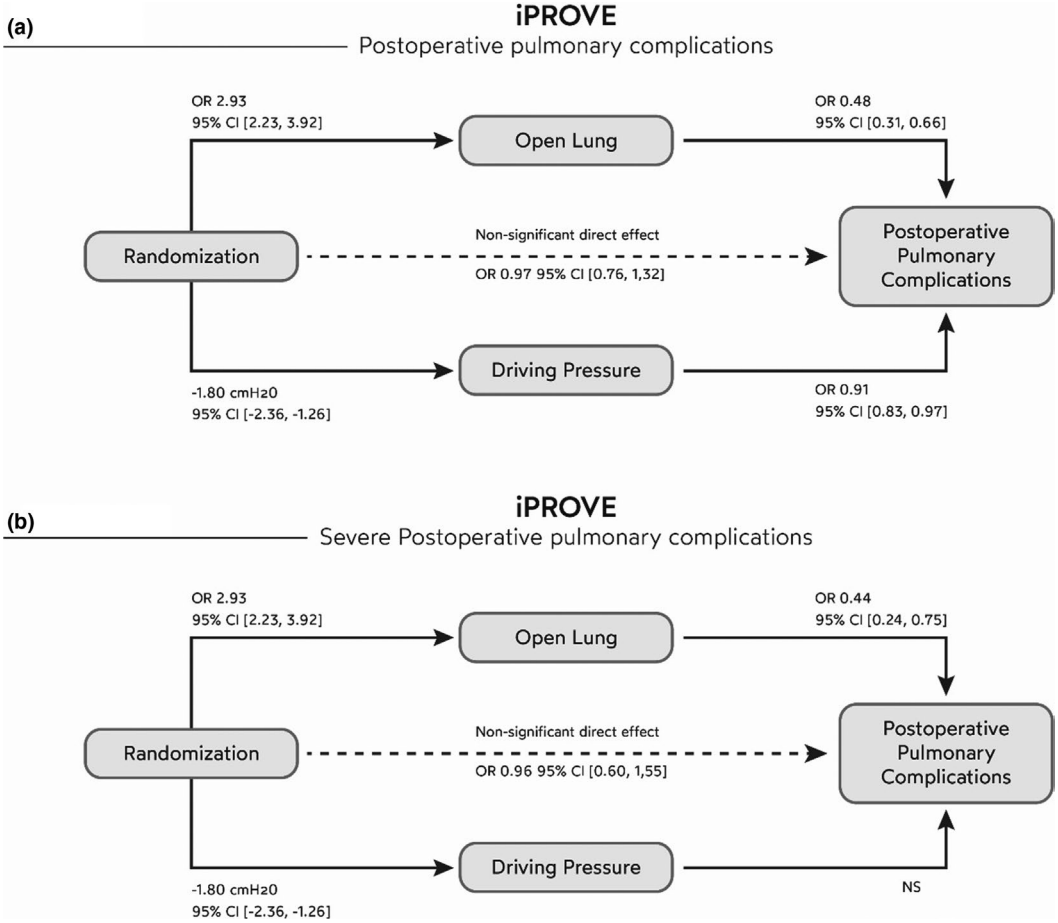


FIGURE 3 Mediational model showing the contribution of driving pressure and open lung condition to the development of: a) postoperative pulmonary complications and b) severe postoperative pulmonary complications. Solid arrows in the path diagram represent significant association between variables, with left to right direction representing an independent to dependent relationship. The dashed arrows represent non-significant effects. A multivariable linear regression model was used to calculate the coefficients expressing the influence of randomization on driving pressure (ΔP), and a logistic regression model to calculate the effect of randomization on open lung condition. The coefficients are shown in the middle of the arrows linking *randomization* to potential mediators, indicating that randomization caused a significant change of −1.80 cmH_2O in ΔP and increased the chance of an open lung condition by 193% (i.e., promoting ~3 times higher chances of an open lung condition). We then calculated the adjusted influence of the potential mediators on postoperative pulmonary complications, after adjusting for study and type of surgery (laparoscopic vs. open). The net relative risks of the two potential mediators on mortality (shown in the middle of the arrows linking mediators to postoperative pulmonary complications) are multiplied by the mean influence of randomization on potential mediators. Note that open lung condition and ΔP, when taken together, explain away the effect of randomization

ratio is not linear.[13] However, we reanalyzed the data using a less stringent cutoff value ($PaO_2/FIO_2 \geq 350$), obtaining the same association between an OL and a reduced risk of suffering severe PPCs (Figure S5; Tables S8–S10). Third, the patient population included (abdominal surgery with an intermediate to high risk of suffering PPCs) does not allow us to extrapolate our findings to other surgical populations. Only two studies could be included in this analysis because intraoperative ABGs were not obtained in all other randomized trials.[4,5,7]

In conclusion, in this analysis of two large trials comparing two lung-protective ventilation strategies in patients submitted to elective abdominal surgery, we found that an open lung condition and not the ventilation strategy per se was associated with a reduced risk of developing PPCs. These findings may have important implications for improving the intraoperative ventilatory management and in the design of future comparative studies.

AUTHORS' CONTRIBUTIONS

CF and JL had full access to all data and are responsible for the integrity and the accuracy of the data analysis. Study design: CF, JL, GT, ASN, JV, FJB, EC, MBPA, FSS. Acquistion data: iPROVE Network investigators. Interpretation of data: CF, JL, GT, ASN, JV, FJB, EC, MBPA, FSS. Drafting of the manuscript: CF, JL, GT, ASN, JV, FJB, EC, MBPA, FSS. Critical revision of the manuscript: CF, JL, GT, ASN, JV, FJB, EC, MBPA, FSS and the iPROVE Network investigators.

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iPROVE Network investigators (Supplement Data S1). The authors declare no conflict of interest.

ORCID

Carlos Ferrando https://orcid.org/0000-0002-1907-5323

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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