ANESTHESIOLOGY

Intraoperative Ventilation/Perfusion Mismatch and Postoperative Pulmonary Complications after Major Noncardiac Surgery: A Prospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Intraoperative physiologic parameters implicated in the development of postoperative pulmonary complications have not been well elucidated
- Ventilation/perfusion mismatch is implicated, but direct measurement is complex and difficult to do in noncardiac surgery
- Automatic lung parameter estimation is an alternative technique to the more complex multiple inert gas elimination technique

What This Article Tells Us That Is New

- Using automatic lung parameter estimation, the authors assessed ventilation/perfusion matching at three time periods in intubated patients undergoing noncardiac surgery at high or intermediate risk for postoperative pulmonary complications
- After multivariable adjustment, high ventilation/perfusion ratio just before extubation was independently associated with postoperative pulmonary complications within 7 days of surgery

ABSTRACT

Background: Postoperative pulmonary complications can increase hospital length of stay, postoperative morbidity, and mortality. Although many factors can increase the risk of postoperative pulmonary complications, it is not known whether intraoperative ventilation/perfusion (V/Q) mismatch can be associated with an increased risk of postoperative pulmonary complications after major noncardiac surgery.

Methods: This study enrolled patients undergoing general anesthesia for noncardiac surgery and evaluated intraoperative V/Q distribution using the automatic lung parameter estimator technique. The assessment was done after anesthesia induction, after 1 h from surgery start, and at the end of surgery. Demographic and procedural information were collected, and intraoperative ventilatory and hemodynamic parameters were measured at each timepoint. Patients were followed up for 7 days after surgery and assessed daily for postoperative pulmonary complication occurrence.

Results: The study enrolled 101 patients with a median age of 71 [62 to 77] years, a body mass index of 25 [22.4 to 27.9] kg/m^2, and a preoperative Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score of 41 [34 to 47]. Of these patients, 29 (29%) developed postoperative pulmonary complications, mainly acute respiratory failure (23%) and pleural effusion (11%). Patients with and without postoperative pulmonary complications did not differ in levels of shunt at T1 (postoperative pulmonary complications: 22.4% [10.4 to 35.9%] *vs.* no postoperative pulmonary complications:19.3% [9.4 to 24.1%]; P = 0.18) or during the protocol, whereas significantly different levels of high V/Q ratio were found during surgery (postoperative pulmonary complications: 13 [11 to 15] mmHg *vs.* no postoperative pulmonary complications: 10 [8 to 13.5] mmHg; P = 0.007) and before extubation (postoperative pulmonary complications: 13 [11 to 14] mmHg *vs.* no postoperative pulmonary complications: 10 [8 to 12] mmHg; P = 0.006). After adjusting for age, ARISCAT, body mass index, smoking, fluid balance, anesthesia type, laparoscopic procedure and surgery duration, high V/Q ratio before extubation was independently associated with the development of postoperative pulmonary complications (odds ratio, 1.147; 95% CI, 1.021 to 1.289; P = 0.02). The sensitivity analysis showed an E-value of 1.35 (CI, 1.11).

Conclusions: In patients with intermediate or high risk of postoperative pulmonary complications undergoing major noncardiac surgery, intraoperative V/Q mismatch is associated with the development of postoperative pulmonary complications. Increased high V/Q ratio before extubation is independently associated with the occurrence of postoperative pulmonary complications in the first 7 days after surgery.

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Postoperative pulmonary complications are common in patients undergoing major noncardiac surgery, in particular during the first week after intervention, and can prolong hospital length of stay, increase perioperative morbidity and mortality.[1] Despite several preoperative factors having been demonstrated to increase the risk of developing postoperative pulmonary complications, the connection between these risk factors and the pathophysiology of complications is still largely unclear.

General anesthesia and invasive mechanical ventilation are associated with several changes in lung function and important variations of ventilation/perfusion (V/Q) matching.[2,3] The functional residual capacity reduction can cause regional hypoventilation (which determines low V/Q) or lung collapse (which causes shunt). Both mechanisms have detrimental effects on intraoperative gas exchange and can increase the risk of hypoxemia and pneumonia in the postoperative period.

Shunt and low V/Q ratio, which are expressions of ventilatory derangement, are not the only possible V/Q alterations determined by mechanical ventilation and general anesthesia. Intraoperative V/Q may be altered also for relative hypoperfusion, which causes high V/Q ratio (*i.e.*, relative ventilation excess over perfusion) and dead space (ventilated but not perfused units). These alterations are generally associated not with hypoxemia but with decreased carbon dioxide removal and can be caused by lung overdistention, which determines the compression of alveolar capillaries and defective perfusion. All these phenomena are interconnected and may be under-recognized in the perioperative phase.

Intraoperative V/Q mismatch could potentially be linked to the development of postoperative pulmonary complications, but a comprehensive evaluation of the association between intraoperative V/Q mismatch and postoperative pulmonary complications has not been previously performed, mainly due to technical limitations. The reference technique for V/Q mismatch assessment, the multiple inert gas elimination technique,[4] is not easily performed at the bedside and has not therefore been used to investigate patient's centered outcome, such as postoperative pulmonary complications.

The automatic lung parameter estimation (ALPE) technique[5] allows noninvasive assessment of V/Q mismatch at the bedside in patients undergoing invasive mechanical ventilation. The ALPE technique, based on a mathematical multicompartmental interpretation of V/Q matching, evaluates respiratory gas response to fraction of inspired oxygen (F_{IO_2}) changes. The ALPE has been shown to agree with the multiple inert gas elimination technique[5] and has been applied to several contexts[6–9] such as different surgical techniques,[10] one-lung ventilation,[7] or change in position during laparoscopic surgery.[9]

We therefore conducted this prospective cohort study to evaluate whether patients developing postoperative pulmonary complications in the first 7 days after major surgery have an impaired intraoperative V/Q mismatch. Considering the evidence about the increase of shunt after anesthesia induction[11] and the uncertainties about the behavior of the other V/Q categories, our hypothesis was that patients developing postoperative pulmonary complicationshad higher values of shunt after anesthesia induction as compared to patients not developing postoperative pulmonary complications. Secondary endpoints were to evaluate the association with postoperative pulmonary complications of the entire spectrum of V/Q imbalance, namely shunt, low V/Q, high V/Q and dead space, in patients developing or not developing postoperative pulmonary complications and to assess their variation during the entire course of surgery.

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Materials and Methods

This is a prospective, monocentric, cohort study conducted from May 2019 to June 2021 in the emergency department of the Azienda Ospedaliera–Universitaria of Ferrara (Ferrara, Italy). The study was approved by the local ethical committee (approved on March 20, 2019, CE-AVEC 195/2019/Oss/AOUFe), and each patient provided informed consent to participate. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to ensure the reporting of this study (Clinicaltrial.gov NCT05454917). A data analysis and statistical plan was written and posted on a publicly accessible server (Clinical Trials.gov) before the data were accessed.

Patient Population

We screened for inclusion patients undergoing general anesthesia for planned major noncardiac surgery.[12] The inclusion criteria were as follows: age from 18 to 90 yr old; informed consent to participate; clinical indication for invasive arterial pressure monitoring; and major surgery requiring general anesthesia and endotracheal intubation with expected duration of surgery more than 2 h. The exclusion criteria were emergency surgery, severe chronic pulmonary disease (stage > 2 as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD); Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. Available at: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed July 24, 2024.), refusal to participate in the study, and lung surgery requiring one-lung ventilation. To reduce the bias related to the cardiac output (CO) calculation, we did not enroll patients planned for emergency surgery or presenting hemodynamic instability before surgery.

Intraoperative Monitoring and Anesthesia Protocol

Patients fulfilling the enrollment criteria were asked for informed consent. All included patients were monitored according to the current guidelines.[13] For anesthesia induction, the patients were preoxygenated with oxygen enrichment air (F_{IO_2}, 80%) using a face mask for 3 min. Anesthesia was induced intravenously using 2 mg kg^{-1} propofol and 150 to 250 μg of fentanyl, while muscle relaxation was obtained with 0.6 mg kg^{-1} rocuronium. Tracheal intubation was achieved with a cuffed endotracheal tube (size 7 to 8 depending on the patient's size). All patients were connected to the same ventilator type (Drager Perseus, Drager, Germany), and anesthesia was maintained using either halogenated (Sevoflurane) or total intravenous anesthesia with propofol, according to the preferences of the treating physician. The protocol did not interfere with the anesthesia choice for anesthesia maintenance.

Intraoperative mechanical ventilation was set as follows: volume-controlled ventilation, with a tidal volume set to achieve 6 to 8 ml/kg/ideal body weight, respiratory rate adjusted to maintain an arterial Pa_{CO_2} between 40 and 60 mmHg. Positive end-expiratory pressure (PEEP) was set initially to 5 cm H_2O and increased if oxygen saturation measured by pulse oximetry (Sp_{O_2}) was less than 92%, according to the treating physician.[14] F_{IO_2} was set initially at 0.5 and adjusted to achieve an oxygen saturation measured by pulse oximetry to maintain an Sp_{O_2} greater than 92%. Before extubation, the eventual residual activity of muscle relaxant was tested using the train-of-four technique, and any residual muscle relaxant activity was antagonized.

Study Protocol

The study included a physiologic evaluation of mechanical ventilation parameters and V/Q mismatch at three predefined timepoints: after endotracheal intubation (timepoint 1 [T1]), during surgery (after 1 h from the skin incision; timepoint 2 [T2]), and at the end of the surgery (timepoint 3 [T3]). Details of the study protocol are reported in figures 1 and 2.

At T1, after patient intubation and arterial line placement, PEEP was reduced from 5 to 0 cm H_2O, and V/Q was measured using ALPE as soon as a steady state was found. Steady state is reached in maximum 2 min. ALPE

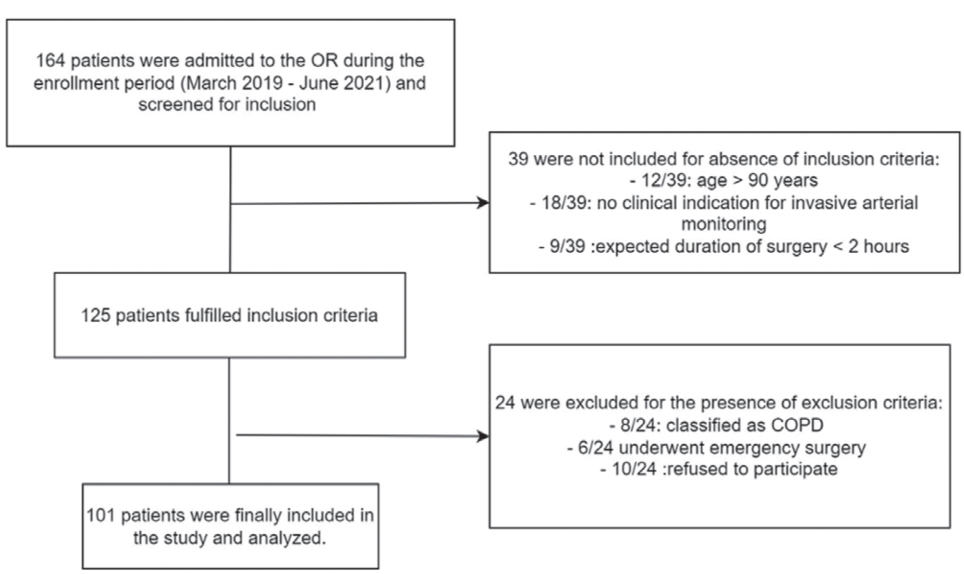

Fig. 1. Flow diagram of the study protocol. The flowchart shows patient screening, enrollment, and follow-up during the study period. COPD, chronic obstructive pulmonary disease; OR, operating room.

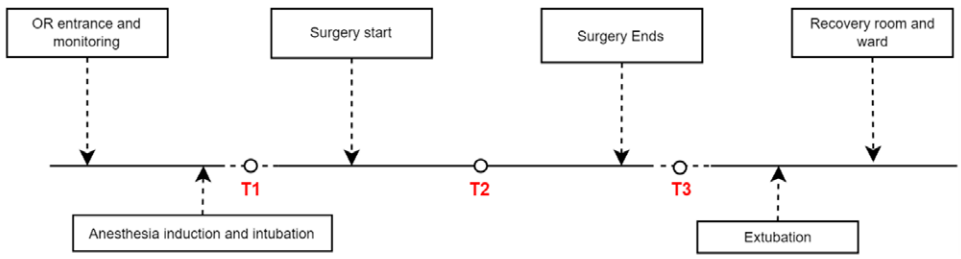

Fig. 2. Flowchart of the study protocol showing the three predefined timepoints (T1, T2, and T3) of measurements. Measurements included the ventilation/perfusion (V/Q) matching, a blood gas analysis, and the collection of mechanical ventilation measurements and of vital parameters. Positive end-expiratory pressure (PEEP) was reduced to 0 for the T1 and T3 measurements, until a steady state is reached (*dashed line*). Clinical PEEP (see text for additional details) was then applied for most of the duration of anesthesia and for the entire duration of surgery. T1 was performed after endotracheal intubation; T2 was performed 1 h after the start of surgery; and T3 was performed at the end of surgery. OR, operating room.

automatically indicates the reach of a steady state analyzing continuously oxygen uptake and carbon dioxide production. This evaluation was performed to (1) assess the impact of anesthesia induction on V/Q mismatch independently from the application of PEEP and (2) to reproduce the study protocol by Hedenstierna *et al.*[2,15,16] and compare therefore our findings with previous data. After T1 measurements, PEEP was set at the previous levels (greater than or equal to 5 cm H_2O), according to the intraoperative mechanical ventilation protocol (see "Intraoperative Monitoring and Anesthesia Protocol"). Measurements during surgery (T2) were collected at the clinical PEEP value after 1 h from the start of surgery (skin incision).

Measurements at T3 started after the end of surgery. During this timepoint, the V/Q matching was tested at the same level of T1 to compare the two steps and to evaluate the eventual impact of surgery and intraoperative anesthesia management on V/Q matching. The measurement was taken at steady state, as in T1. After T3 measurement and before extubation, PEEP was set again at greater than or equal to 5 cm H_2O, as per intraoperative mechanical ventilation protocol.

In addition to V/Q data, at every timepoint we collected the following data: invasive systolic arterial pressure, invasive mean arterial pressure, heart rate, respiratory rate (RR), Spo_2, EtCO2, peak pressure (Ppeak), plateau pressure (Pplat), tidal volume (VT), and total PEEP (PEEPtot). To exclude the presence of intrinsic PEEP, the flow signal was visually inspected to assure the absence of residual flow at end-expiration. Driving pressure (DP) was calculated as Pplat – PEEPtot. Mechanical power (MP) was calculated as: MP = 0.098 · RR · VT · [PEEP + DP] using the surrogate formula, as previously suggested by Chiumello *et al.*[17]

Ventilation/Perfusion Mismatch Measurement

Ventilation/perfusion mismatch was measured using the Beacon ALPE,[5,6] an integrated function of the Beacon Caresystem (Mermaid Care A/S, Denmark). The ALPE estimates V/Q mismatch in mechanically ventilated patients by evaluating the relationship between end-tidal oxygen and oxygenation (arterial oxygen saturation and Spo_2) and the relationship between end-tidal carbon dioxide and $Paco_2$.

To evaluate V/Q matching, the ALPE system instructs the user to modify Fio_2 in three or four steps. At each Fio_2 level, the ALPE system identifies steady state and measures ventilation, Spo_2, oxygen consumption, carbon dioxide production, and inspiratory and expiratory end-tidal fractions of oxygen and carbon dioxide. These measurements are taken automatically by inserting a sampling tube in the respiratory circuit for measurement of flow, oxygen, and carbon dioxide and by placing the pulse oximeter on a finger.

In addition, the system estimates the acid–base and oxygenation status including arterial $Paco_2$, taking into account the results of an arterial blood gas sample. These parameters are then used to identify the fractions of ventilation and perfusion in a three-compartment model of the lung, including two ventilated and perfused compartments and a further perfused-only compartment, describing pulmonary shunt.[6,18] The model takes into account some extrapulmonary factors including acid–base status, hemoglobin concentration, the nonlinearity of hemoglobin oxygen binding, cardiac output, and the measured oxygen consumption and carbon dioxide production. Further details on the ALPE technique can be found in previous reports.[7]

In addition to the ALPE estimates, the Alveolar dead space to tidal volume fraction (VD/VT) was calculated assessing the ratio between $PetCO_2$ and $Paco_2$, as in[19]:

$$\frac{\mathrm{VD}}{\mathrm{VT}} = \frac{\mathrm{PaCO_2} - \mathrm{PetCO_2}}{\mathrm{PaCO_2}} \times 100 \qquad (1)$$

Because the ALPE requires data from an arterial blood gas analysis, an arterial blood sample was collected before every ALPE calculation.

Postoperative Pulmonary Complication Monitoring and Definitions

Postoperative pulmonary complications were evaluated during the 7 days after surgery, and their definition and nomenclature were in accordance with previous studies[20–22] and with the European Perioperative Clinical Outcome taskforce definition.[23] The following postoperative pulmonary complications were evaluated: (1) respiratory failure (defined as partial pressure of alveolar oxygen [PaO_2] < 60 mmHg on room air, a PaO_2:FiO_2 ratio less than 300 mmHg or arterial oxyhemoglobin saturation measured with pulse oximetry less than 90% and requiring oxygen therapy), (2) pleural effusion, (3) atelectasis, (4) pneumothorax, (5) bronchospasm, (6) aspiration pneumonitis, and (7) pneumonia. The complete definitions of the postoperative pulmonary complications can be found in the digital supplement (see the supplemental digital material, https://links.lww.com/ALN/D581). Screening for postoperative pulmonary complications was performed every day during the morning round using a complete respiratory evaluation, starting from 24 h after surgery end until day 7 after surgery or until hospital discharge.

Primary and Secondary Endpoints

The primary endpoint of the study was the difference in shunt measured after induction in patients who developed postoperative pulmonary complications after surgery and patients that did not. Secondary endpoints were differences and time course of shunt, low V/Q, high V/Q, and VD/VT in patients developing or not developing postoperative pulmonary complications.

Statistical Analysis

Quantitative data were checked for normality and analyzed using parametric or nonparametric tests accordingly. Continuous variables are expressed as means ± SD or median [interquartile range] according to data distribution. Categorical variables are expressed as count (percentage).

Differences among independent groups (with or without postoperative pulmonary complications) were tested using the independent *t* test or the independent sample Mann–Whitney U test with Holm–Bonferroni correction for multiple comparisons, as appropriate, although the differences in frequencies among categorical variables were tested using the Fisher's exact test. The correlation among variables was tested using the Pearson correlation test or the Spearman (Rs) correlation test, according to the distribution of variables.

To assess the effect of time on the kinetics of V/Q matching over time, a two-way ANOVA for repeated measures was conducted with postoperative pulmonary complication group as between fixed effect and time as within fixed effect. The Holm–Sidak's multiple comparisons test was used for *post hoc* analysis to compare T2 and T3 with T1 within the respective groups.

To test the influence of smoking on high V/Q, a two-way ANOVA for repeated measures was conducted with smoking status (actual smoker *vs.* nonsmoker or former smoker) group as between fixed effect and time as within fixed effect. The Holm–Sidak's multiple comparisons test was used for *post hoc* analysis to compare groups at each timepoint.

A directed acyclic graph[24] was created (fig. 3) to illustrate the relationship between exposure (surgery), outcome (pulmonary postoperative complications), and the variables used in the model. Analysis of the data was done using the dagitty package (version 0.3-1).[25]

A logistic regression analysis was performed to analyze the relationship between shunt after induction and high V/Q before extubation on the probability of developing postoperative pulmonary complications. The model was adjusted for possible confounders (age, body mass index, ARISCAT, cumulative fluid, surgery duration, laparoscopy, type of anesthetics for maintenance, and smoking). The selection of variables was based on predefined expert consensus among the investigators, except for smoking, which was added to the model during the revision process.

Finally, to evaluate the crude risk of developing postoperative pulmonary complications during the first week after surgery, we categorized the population in two groups based on the median value of high V/Q before extubation (group 1, high V/Q above median; group 2, high V/Q below median; median value = 11 mmHg). The unadjusted cumulative risk of postoperative pulmonary complications in the two groups was therefore compared using the log rank test for trend.

All *P* values provided are intended for two-tailed tests, and the *P* values less than 0.05 were considered significant. The mean missing data in the overall database was 1.4% and can be described as missing completely at random.[26] No missing data were present in the data set for the variables of interest (V/Q data). Consequently, because no variable had proportion of missing data greater than 5%, the missing data were ignored for the current calculations.

Sensitivity Analyses for Potential Unmeasured Confounding. We used the E-value[26] in a *post hoc* analysis to estimate the magnitude of an unmeasured confounding variable that would reduce an observed relative risk to 1.0 and to reduce the upper or lower confidence limit to 1.0. For example, an E-value of 2.0 means that there would need to be an unmeasured variable that was associated with both the exposure and the outcome with a relative risk of 2.0, both after adjusting for other confounding variables already included in the analyses. The approximate E-value was obtained from odds ratio and hazard ratio as suggested by VanderWeele *et al.*[26]

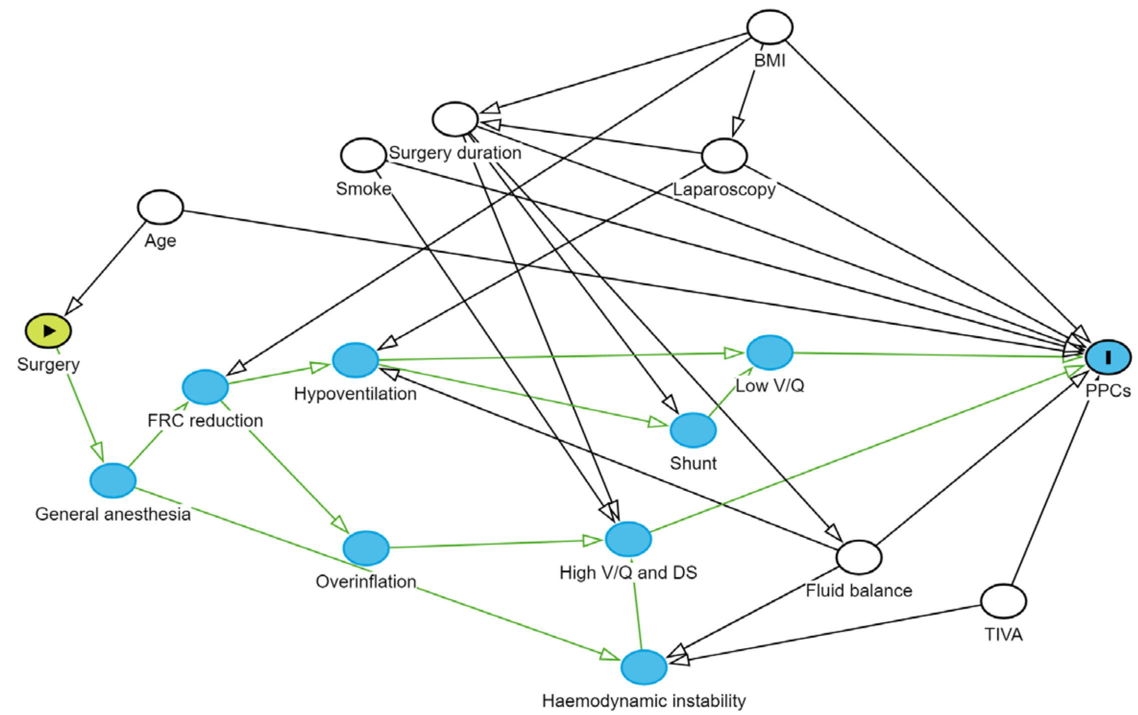

Fig. 3. Directed acyclic graph showing the causal relationship between exposure (surgery), outcome (postoperative pulmonary complications [PPC]). A directed acyclic graph showing the causal relationship between exposure (surgery), outcome (PPCs), and the covariates used in the model. The *green path* illustrates the causal path. *White variables* are adjusted factors. No bias path was found in the model. Analysis of the data was done using the dagitty package (version 0.3-1).[25] DS, dead space; FRC, functional residual capacity; TIVA, total intra-venous anesthesia; V/Q, ventilation/perfusion.

Sample Size Calculation. Sample size was calculated based on the data on pulmonary shunt by Spadaro *et al.*[10] in a population of patients undergoing major surgery in the same hospital. Considering a shunt level of 12 ± 7% and hypothesizing 30% of patients experiencing postoperative pulmonary complications and a relative clinically relevant increase in shunt of 50% in those with postoperative pulmonary complications, we found that 90 patients were sufficient to evaluate differences between groups (effect size 0.8) with a power of 0.95 and an α error of 0.05. Considering a dropout of 12%, we found a minimum sample size of 101 patients. Statistical analysis was performed with using SPSS Statistics for Windows, version 20.0 (IBM, USA) and Prism 8 (GraphPad Software, LCC).

Results

Patients and Surgery Characteristics

We screened for inclusion 164 patients from March 2019 to June 2021. Of the 125 patients who fulfilled inclusion criteria, 24 were excluded due to the presence of exclusion criteria (8 were classified as having severe chronic obstructive pulmonary disease, 6 underwent emergency surgery, and 10 refused to participate). A total of 101 patients were confirmed eligible, provided consent to participate, and were finally enrolled. No patients were lost during follow-up (fig. 1).

Patients' characteristics are reported in table 1. The median age was 71 [62 to 77] years old, the median body mass index was 25 [22.4 to 27.9] kg/m^2, and 43 of 101 (43%) were females. The patients were mainly classified as having American Society of Anesthesiologists status III (72.2%), and 70.2% of them had a previous cardiovascular disease, primarily hypertension. Of the total 101 patients, 27 (27%) were smokers. Anesthesia choice and surgery type was similar between the two groups (table 1).

Intraoperative Hemodynamics and Lung Mechanics

The data on intraoperative hemodynamics and lung mechanics are reported in table 2. We did not find differences among groups in the percentage of laparoscopic surgery (postoperative pulmonary complications, 38%; no postoperative pulmonary complications, 37.5%; $P = 0.968$) and intraoperative use of vasopressors (postoperative pulmonary complications, 31%; no postoperative pulmonary complications, 25%; $P = 0.535$).

Patients with PPCs had significantly longer anesthesia duration (postoperative pulmonary complications, 305 [245 to 400] minutes; no postoperative pulmonary complications,

Table 1. Demographic, Baseline Characteristics, and Hospital Outcomes for the Study Population

	PPCs			
Characteristics	**No (72 of 101)**	**Yes (29 of 101)**	**All Patients (101)**	***P* Value**
Age, yr	71 [62–77]	70 [64–80]	71 [62–77]	0.98
Body mass index, kg/m^2	24.8 [21.6–27.2]	25.7 [24.1–28.7]	25 [22.4–27.9]	0.08
Metabolic equivalents	6 [5–7]	6 [5–6]	6 [5–6]	0.15
Modified Medical Council Questionnaire score	1 [0–1]	1 [0–1]	1 [0–1]	0.10
New York Heart Association score	0 [0–1]	0 [0–1]	0 [0–1]	0.96
Assess Respiratory Risk in Surgical Patients in Catalonia score	41 [34–41]	41 [38–52]	41 [34–47]	0.30
Hospital length of stay, days	5 [3–7]	7 [6–7]	6 [4–7]	0.001
Sex				
Female	30 (41.6%)	13 (44.8%)	43 (42.6%)	0.83
Male	42 (58.4%)	16 (55.2%)	58 (57.4%)	0.83
ASA Physical Status				
I	1 (1.4%)	0 (0%)	1 (1%)	0.68
II	19 (26.4%)	5 (17.2%)	24 (23.8%)	
III	50 (69.4%)	23 (79.4%)	73 (72.2%)	
IV	2 (2.8%)	1 (3.4%)	3 (3%)	
Cardiovascular diseases				
Yes	50 (69.4%)	21 (72.4%)	71 (70.2%)	0.81
Hypertension	49 (68%)	17 (59%)	66 (65%)	
Atrial fibrillation	8 (11%)	7 (24%)	15 (15%)	
Coronary disease	7 (10%)	2 (7%)	9 (9%)	
Cardiac failure	0	1 (3%)	1 (1%)	
Respiratory diseases				
Yes	9 (12.6%)	6 (20.6%)	15 (14.8%)	0.36
COPD/asthma	3 (4%)	2 (7%)	5 (5%)	
Lung emphysema	1 (1%)	4 (14%)	5 (5%)	
Obstructive sleep apnea	4 (5%)	2 (7%)	6 (6%)	
Other	2 (3%)	0	2 (2%)	
Smoking				
No	25 (35.2%)	10 (34.4%)	35 (35%)	0.82
Former	28 (39.4%)	10 (34.4%)	38 (38%)	
Yes	18 (25.4%)	9 (31%)	27 (27%)	
Packs/yr	20 [9–52]	33 [26–47]	30 [12–46]	0.28
Surgical procedure, n (% of the group)				
Intestinal resection	41 (56.9%)	15 (51.7%)	56 (55.4%)	0.20
Gynecological surgery	1 (1.4%)	2 (6.9%)	3 (3%)	
Aortic aneurism repair	10 (13.9%)	5 (17.2%)	15 (14.9%)	
Carotid endarterectomy	10 (13.9%)	1 (3.4%)	11 (10.9%)	
Adrenalectomy	2 (2.8%)	2 (6.9%)	4 (4%)	
Splenectomy	1 (1.4%)	0	1 (1%)	
Liver surgery	4 (5.6%)	4 (13.8%)	8 (7.9%)	
Pancreatic surgery	3 (4.2%)	0	3 (3%)	
Total intravenous anesthesia, n (%)	11 (15%)	5 (17%)	16 (15.8%)	0.77

The values are either the median [interquartile range] or the frequency (%). The *P* values are from independent samples Mann–Whitney U test or Fisher's exact test, as appropriate.
ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

260 [205 to 327.5] minutes; $P = 0.02$) and higher cumulative fluid balance during surgery (postoperative pulmonary complications, 2,450 [2,000 to 3,300] ml; no postoperative pulmonary complications1,825 [1,275 to 2,750] ml; $P = 0.02$). When normalizing the cumulative fluid balance for the anesthesia duration, the difference was no longer statistically significant (postoperative pulmonary complications, 8.7 ml/min; no postoperative pulmonary complications, 7.5 ml/min; $P = 0.11$).

The maximum amount of PEEP used was 5 [5 to 6] cm H_2O and 6 [5 to 7] cm H_2O ($P = 0.007$), respectively, in the no postoperative pulmonary complicationsand postoperative pulmonary complicationsgroups. A lower Pa_{O_2}/F_{IO_2} ratio (postoperative pulmonary complications, 287 [208 to 391] mmHg; no postoperative pulmonary complications, 387 [292.5 to 465] mmHg; $P = 0.014$) and a higher driving pressure (postoperative pulmonary complications, 12 [8 to 13.5] cm H_2O; no postoperative pulmonary complications, 9 [7 to 10.5] cm H_2O; $P = 0.011$) and tidal volume were found after anesthesia induction. Nevertheless, none of these parameters were significantly different during surgery (T2) and before extubation (T3). No other differences were found between groups in hemodynamic or in other respiratory parameters (supplementary table S4, https://links.lww.com/ALN/D581).

Table 2. Intraoperative Data in the Two Populations during General Anesthesia

	After Anesthesia Induction (T1)			During Surgery (T2)			Before Extubation (T3)		
PPCs	No (72)	Yes (29)	*P* Value	No (72)	Yes (29)	*P* Value	No (72)	Yes (29)	*P* Value
Heart rate, beats/min	62 [55–70]	62 [57–72]	0.39	61 [54–70]	61 [55–71.5]	0.80	63 [55–71]	64 [54–73]	0.94
Systolic arterial pressure, mmHg	100 [87–120]	100 [87–120]	0.89	103 [93–126]	110 [99–122]	0.47	109.5 [98–127]	106 [98–121]	0.54
Mean arterial pressure, mmHg	69 [61.5–80]	70 [63–83]	0.54	73.5 [66–85.5]	82 [73–88]	0.12	78 [69.5–89]	75 [66–91]	0.72
Tidal volume, $ml \cdot kg^{-1} \cdot$ ideal body $weight^{-1}$	6.7 ± 0.9	7.15 ± 0.7	0.012*	6.9 ± 0.9	7.17 ± 0.5	0.09	6.97 ± 0.9	7.24 ± 0.6	0.14
Respiratory system compliance, ml cm H_2O^{-1}	49.4 [37.7–61.7]	40 [31.8–57.1]	0.72	51.3 [38.5–63.7]	43.8 [34.6–56.7]	0.55	43 [32.3–54.7]	42.2 [34.3–52.4]	0.93
Driving pressure, cm H_2O	9 [7–10.5]	12 [8–13.5]	0.011*	8.5 [7–12]	9 [8–13]	0.44	10 [8–14]	10 [8–14]	0.81
PAO_2/FIO_2, mmHg	387 [292.5–465]	287 [208–391]	0.014*	386.5 [301–451.5]	309 [246–400]	0.06	374 [310.5–457.5]	328 [264–381]	0.08
Mechanical power, $J \cdot min^{-1}$	5.12 [4.49–6.49]	5.94 [4.5–6.83]	0.36	8.65 [6.73–10.75]	9.19 [7.53–11.24]	0.33	6.14 [4.91–7.68]	5.82 [4.89–7.5]	0.31

The table shows data on hemodynamic and respiratory system mechanics collected in the tree predefined timepoints. The *P* values are provided for group comparison. The *P* values are from independent-sample Mann–Whitney U tests.

*Significantly different after multiple comparison correction using the Holm–Bonferroni correction.

FIO_2, fraction of inspired oxygen; PAO_2, partial pressure of alveolar oxygen; PPC, postoperative pulmonary complication.

Intraoperative Ventilation/Perfusion Mismatch

Data on V/Q mismatch in the two groups during surgery are reported in figure 4. Patients with postoperative pulmonary complications did not have significantly higher shunt in T1 (postoperative pulmonary complications, 22.4% [10.4 to 35.9%]; no postoperative pulmonary complications, 19.3% [9.45 to 24.15%]; $P = 0.18$) during surgery (T2) or before extubation (T3).

Patients with postoperative pulmonary complications showed significantly higher levels of high V/Q during surgery (postoperative pulmonary complications, 13 [11 to 15] mmHg; no postoperative pulmonary complications, 10 [8 to 13.5] mmHg; $P = 0.007$) and before extubation (postoperative pulmonary complications, 13 [11 to 14] mmHg; no postoperative pulmonary complications, 10 [8 to 12] mmHg; $P = 0.006$). No difference was found between the groups in low V/Q , but a significant correlation was present between delta shunt and delta low V/Q between T1 and T2 (supplemental fig. S1, https://links.lww.com/ALN/D581; Rs = 0.5; $P < 0.001$). When evaluating the impact of smoking on intraoperative V/Q matching, we found that smokers had significantly higher high V/Q at all measured timepoint (supplemental fig. S3, https://links.lww.com/ALN/D581). Finally, time had significant impact on shunt, high V/Q , and VD/VT with an overall decrease in the levels of shunt in the postoperative pulmonary complications group between T1 and T3 and an increase in high V/Q and VD/VT (supplemental table S3, https://links.lww.com/ALN/D581).

Postoperative Data

Data on hemodynamic and respiratory features after extubation are reported in supplemental table S4 (https://links.lww.com/ALN/D581). Patients who developed postoperative pulmonary complications needed higher supplemental oxygen before discharge to the surgical ward (postoperative pulmonary complications, 32% [21 to 40%]; no postoperative pulmonary complications, 21% [21 to 28%],;$P = 0.008$) and had significantly lower SpO_2/FIO_2 ratios (postoperative pulmonary complications, 281 [247 to 350]; no postoperative pulmonary complications, 343 [278 to 358]; $P = 0.027$). All the other data collected in the recovery room were similar among groups with no significant difference.

Of the total 101 patients, 29 (29%) developed postoperative pulmonary complications (supplemental table S1, https://links.lww.com/ALN/D581). The most common complication was respiratory failure, defined as PAO_2 less than 60 mmHg on room air, a $PAO_2:FIO_2$ ratio less than 300 mmHg, or arterial oxyhemoglobin saturation measured with pulse oximetry less than 90% and requiring oxygen therapy (23% of patients), followed by pleural effusion (11%), atelectasis (6%), and pneumonia (4%), whereas no patient developed pneumothorax, bronchospasm, or aspiration pneumonia (supplemental table S1, https://links.lww.com/ALN/D581). No patient required reintubation. Patients with postoperative pulmonary complications had a significantly longer hospital length of stay as compared to patients with no postoperative pulmonary complications after surgery (table 1).

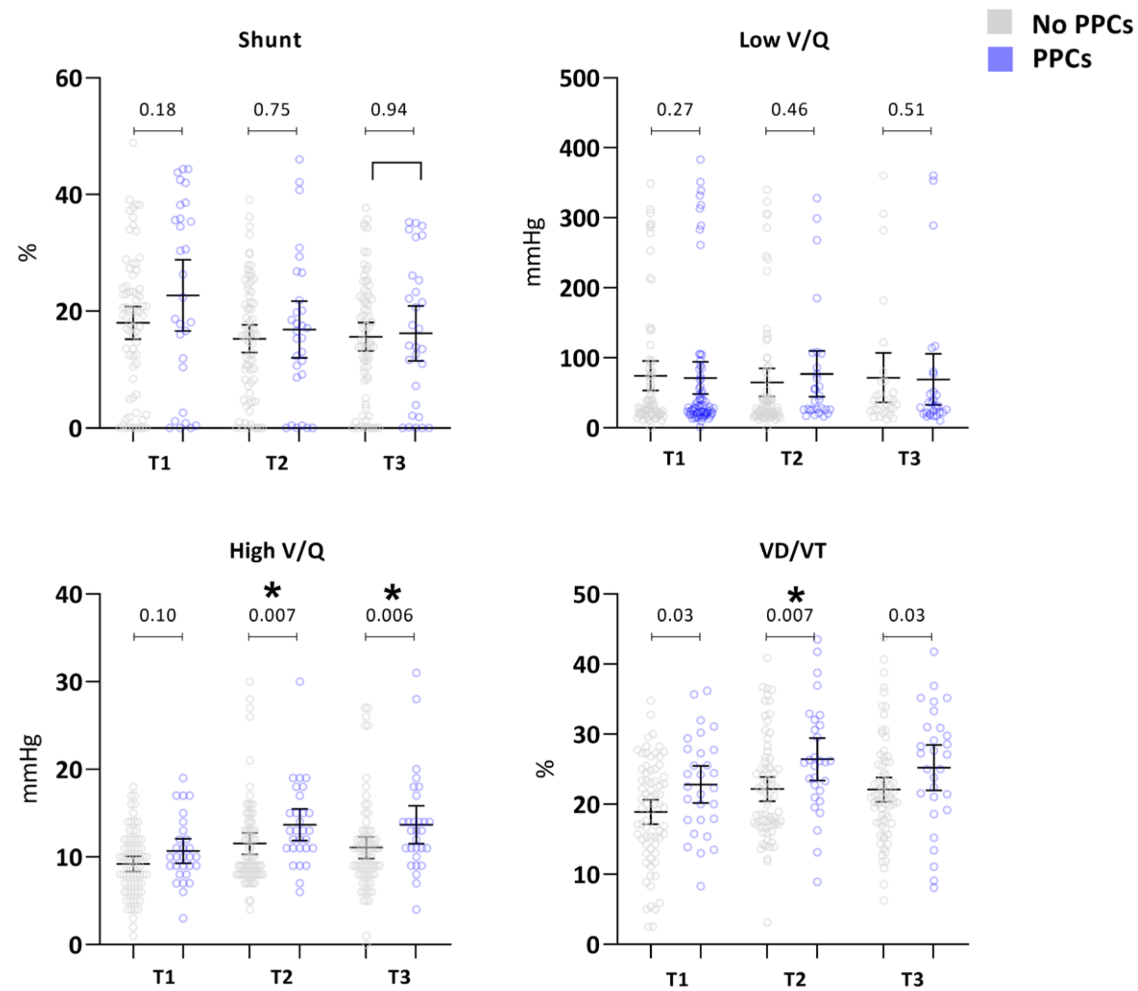

Fig. 4. Ventilation/perfusion (V/Q) mismatch during surgery in the two groups based on the occurrence of pulmonary postoperative complications (PPCs). The figure shows individual values and means (95% CI) for shunt, low V/Q, and high V/Q in the three different timepoints. (T1 is after anesthesia induction, T2 is during surgery, and T3 is before extubation) in the two groups (with [*blue dots*] or without [*gray dots*] PPCs). Patients with PPCs had significantly higher high V/Q during surgery and before extubation. The *P* values are reported for the Mann–Whitney U test. *, significantly different considering a correction for multiple comparisons (Holm–Bonferroni significance level). VD/VT, dead space to tidal volume ratio.

Logistic Regression of Postoperative Pulmonary Complications Using Preoperative and Intraoperative Factors

The logistic regression analysis results are shown in table 3. In the multivariable model, shunt in T1 was not significantly associated with postoperative pulmonary complications (odds ratio, 1.025 [0.987 to 1.065]; P = 0.19), whereas high V/Q before extubation (T3) was significantly associated with the occurrence of postoperative pulmonary complications within 7 days from surgery (odds ratio, 1.147 [1.021 to 1.289]; P = 0.02; E-value, 1.35 [CI, 1.11]). When dichotomizing the population on the median value of high V/Q in T3 (11 mmHg; fig. 4), being in the group with higher high V/Q before extubation doubled the risk of postoperative pulmonary complications (hazard ratio, 2.15; 95% CI, 1.023 to 4.530; P = 0.03; E-value, 2.78 [CI, 1.14]; fig. 5).

Discussion

In this study, we found that intraoperative V/Q matching is altered in patients who develop postoperative pulmonary complications, mainly represented by postoperative respiratory failure, in the first 7 days after major noncardiac surgery. Specifically, our main findings were the following:

(1) Patients who develop postoperative pulmonary complications showed significantly higher levels of high V/Q ratio both during surgery and before extubation.

Table 3. Logistic Regression Model for Occurrence of Pulmonary Postoperative Complications within 7 Days from Surgery

	Univariate Analysis			Multivariable Analysis		
Variable	Crude Odds Ratio	95% CI	*P* Value	Adjusted Odds Ratio	95% CI	*P* Value
Age, yr	0.99	0.96–1.04	0.98	0.984	0.933–1.037	0.54
Body mass index, kg/m^2	1.117	1.009–1.235	0.03	1.156	1.011–1.321	0.03
Assess Respiratory Risk in Surgical Patients in Catalonia score	1.030	0.985–1.078	0.19	1.036	0.973–1.102	0.27
Surgery duration, min	1.006	1.001–1.011	0.01	1.002	0.996–1.009	0.53
Smoking	1.325	0.512–3.430	0.56	1.192	0.358–3.970	0.77
Cumulative fluid balance, ml/min	1.010	0.935–1.091	0.80	1.011	0.981–1.042	0.47
Laparoscopy	0.982	0.404–2.388	0.97	2.165	0.560–8.377	0.99
Total intravenous anesthesia	1.155	0.363–3.677	0.81	0.549	0.110–2.751	0.47
Shunt (T1)	1.027	0.994–1.062	0.11	1.022	0.984–1.061	0.25
High ventilation/perfusion (T3) ratio	1.086	1.005–1.173	0.04	1.147	1.021–1.289	0.02

The dependent variable was the occurrence of pulmonary postoperative complications within 7 days after surgery.

(2) Patients who developed postoperative pulmonary complications had higher driving pressure and lower PaO_2/FiO_2 ratio after anesthesia induction, indicating a higher tendency to derecruitment after intubation. This difference, nevertheless, disappears during surgery. Shunt level did not differ between groups in all timepoints but decreased during surgery in the postoperative pulmonary complications group.

(3) After correcting for confounders, high V/Q ratio before extubation was the only intraoperative V/Q parameter significantly associated with an increased risk of postoperative pulmonary complications.

Many preoperative features have been considered as risk factors for postoperative pulmonary complications, but although the baseline risk can be determined by preoperative conditions[27,28] and/or genetics,[29] the additional impact of intraoperative lung ventilation, perfusion, or of their matching, is usually neglected. Recently, driving pressure[30] and mechanical power[31] have been associated with the development of postoperative pulmonary complications, but these parameters focus only on the mechanical side of damage, not considering lung perfusion. In this context, intraoperative V/Q matching may add important information on mechanisms that can promote the development of postoperative pulmonary complications and can be useful to increase the predictive ability of current models.

In our study, patients developing postoperative pulmonary complications had a higher driving pressure and a lower PaO_2/FiO_2 ratio after anesthesia induction, which is consistent with a higher decrease in functional residual capacity and with the development of atelectasis.[32] Although shunt was higher after induction, this difference was not statistically significant and was not present either during anesthesia, probably because (1) atelectasis were partially reverted by mechanical ventilation and by the use of PEEP, and (2) shunt was partially reduced by the protective mechanism of hypoxic vasoconstriction. The increased lung collapse and shunt after anesthesia induction can therefore be considered transient, and no differences were seen thereafter.

Interestingly, the postoperative pulmonary complications group showed significantly higher levels of high V/Q ratio both during surgery and before extubation. High V/Q represents regions in which there is an imbalance between ventilation and perfusion with a relative excess of ventilation.[2] High V/Q may be exacerbated by regional overdistension, because higher transmural pressures may squeeze alveolar vessels and reduce local perfusion.[33] Alveolar overinflation (as *barotrauma*) is one of the components of ventilator-induced lung injury[34] and can therefore contribute to lung inflammation and postoperative impairment. In this context, high V/Q may therefore be a functional marker of regional overinflation.

Many recent trials highlighted the important role of high V/Q ratio as a marker of lung damage and predictor of mortality in acute respiratory distress syndrome,[8,35,36] but only a few trials have assessed this in the context of postoperative pulmonary complications,[37] where classically atelectasis (and therefore shunt) have been considered to be the main actors in postoperative lung disfunction.[38]

Although atelectasis can increase shunt fraction, determine intraoperative hypoxemia, and potentially increase the risk of postoperative pneumonia, their link with postoperative pulmonary complications is not definitely proved. Indeed, in the recent *post hoc* analysis of the ENIGMA II trial,[39] although a lower incidence of atelectasis was found in the group treated with nitrous oxide, the pneumonia rates among groups was comparable.

Hedenstierna *et al.*, by evaluating the effect of age[16] and body mass index[15] on intraoperative V/Q in a mixed patients population, found that age and body mass index were not

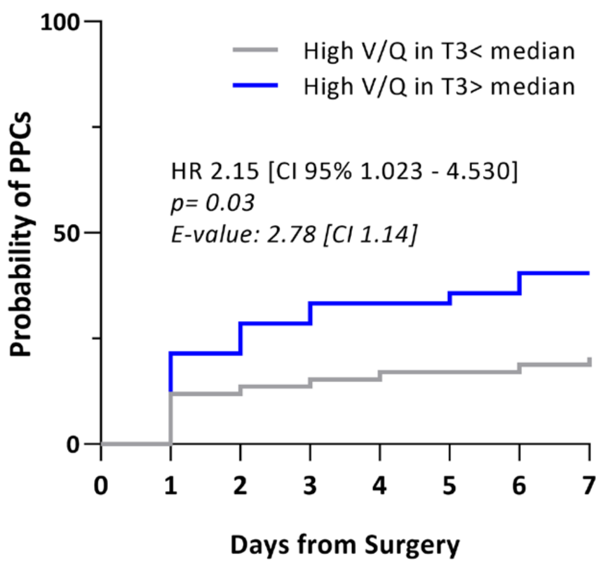

Fig. 5. Probability of pulmonary postoperative complications (PPCs) in two groups based on high ventilation/perfusion (V/Q) matching before extubation. Cumulative probability of PPCs in different groups of high V/Q measured before extubation (*gray line*, patients less than median; *blue line*, patients greater than median). Patients with a higher high V/Q before extubation are at higher risk for pulmonary postoperative complications (hazard ratio [HR] 2.15 [1.023 to 4.530]; $P = 0.03$). A sensitivity analysis was performed *post hoc* to account for unmeasured confounding factors (E-value). The analysis showed that a strong unmeasured factor would be needed for the association not to be causal.

associated with shunt. This is particularly important considering that both age[28,40] and obesity[41] have been found to increase the risk of postoperative pulmonary complications.

Shunt cannot be, therefore, the only factor responsible for lung impairment after surgery. This concept is furtherly strengthened by our results and can increase the focus on other important pathophysiological mechanisms responsible for postoperative lung disfunction. Moreover, shunt can be partially reverted by the mechanisms of hypoxic vasoconstriction, meaning that the shunt fraction may potentially decrease during time with no effect on atelectasis. Therefore, since (1) atelectasis are not the sole actors in the pathophysiology of postoperative pulmonary complications and (2) shunt may not be a good surrogate for atelectasis (hypoxic vasoconstriction phenomenon), it is clear that intraoperative shunt might not be a good intraoperative marker for potential postoperative lung impairment. This was confirmed by our data, because shunt was not significantly different among the two groups after induction and during surgery and was not significantly associated with postoperative pulmonary complications after adjusting for confounders.

High V/Q ratio, which is a direct consequence of overinflation, can indirectly also be a marker of lung collapse, because the same tidal volume will be distributed to a smaller available parenchyma. This has previously been shown in animal models of acute respiratory distress syndrome[42] but could be potentially applicable also to alveolar collapse during general anesthesia.

Interestingly, our data showed that high V/Q was significantly higher without significant differences in driving pressure during or at the end of surgery. Because lung compliance may differ from patient to patient according to their clinical history and characteristics, the use of driving pressure as a surrogate for lung overdistension may be inaccurate. For patients with high chest wall elastance (obese) or high lung compliance (emphysema), respiratory driving pressure may be inappropriately high or low.[43] Evaluating high V/Q may allow evaluation of the functional impairment of the lung, independently from the patient's lung mechanical baseline status.

Another possible cause of high V/Q increase may be structural lung damage and emphysema. We did not include in our study patients with severe chronic pulmonary disease, but we found that smokers had higher high V/Q levels throughout the entire protocol (supplemental fig. S3, https://links.lww.com/ALN/D581). Previous experimental evidence[44] showed that smoking can alter V/Q both by chronic structural damage (*i.e.*, emphysema) and by reversible inflammation. We did not find clear mechanical signs of emphysema, such as lung compliance increase in patients with postoperative pulmonary complications. Nevertheless, the inflammation related to smoking may partially explain the increase of high V/Q ratio in this category of patients, without apparent macroscopical mechanical features. When smoking was added to the logistic regression model, the strength of association between high V/Q ratio and postoperative pulmonary complications increased, with a consequent increase of the E-value, meaning that smoking may be an additional confounder and is not able to completely explain the association between high V/Q ratio and postoperative pulmonary complications.

In our study, we highlighted a new possible pathophysiological mechanism contributing to postoperative lung impairment and a potential intraoperative marker for postoperative pulmonary complications risk. The clinical management of patients with higher V/Q ratio may include reducing regional overinflation by optimizing driving pressure and/or PEEP or by increasing regional perfusion. Whether the best therapeutic option for high V/Q is manipulating ventilation and/or perfusion depends on the defect responsible for the unbalance (hyperventilation of hypoperfusion) and from the clinical meaning of high V/Q ratio.

Indeed, we do not know at this stage whether high V/Q can be considered a marker of lung damage[45] or whether it represents a possible mechanism of damage *per se*. In both cases, the clinical advantage of measuring high V/Q ratio is clear, because from one side it may increase the ability to predict patients at higher risk of postoperative pulmonary complications, whereas from the other side it may address clinical interventions (*i.e.*, PEEP adjustment, volume titration, intravascular volume assessment), which may reduce lung damage. Our results indicate the importance of balancing risks and benefits of both ends of the V/Q scale, preventing atelectasis to reduce postoperative shunt but also being aware of the potential risks of high V/Q ratio.

Our study has several strengths. First, we evaluated both intraoperative V/Q mismatch and postoperative pulmonary complications in a large cohort of patients. The evaluation of V/Q was done not only after anesthesia induction but also during surgery and at the end of surgery, to assess the effective impact of MV and surgery on lung mechanics. Second, the use of preoperative and intraoperative risk factors for postoperative pulmonary complications allowed a regression model to eliminate possible confounding factors. The age range of enrolled patients is wide, as is the distribution of their baseline characteristics. Finally, the baseline population had a moderate to high risk of developing postoperative pulmonary complications, according to the ARISCAT score. Nevertheless, no difference was found between the two groups, underlining the insufficiency of preoperative parameters to correctly stratify patient risk of developing postoperative pulmonary complications.

Our study also has some limitations. First, the difference in V/Q matching may be related to problems affecting both ventilation and/or perfusion. Because the overall hemodynamic profile of the two groups was comparable, the differences can be related to regional ventilation and/or perfusion problems. Future studies with alternative techniques (*i.e.*, electrical impedance tomography) are needed to understand whether the increase of high V/Q ratio in patients at higher risk of postoperative pulmonary complications are caused by problems of regional ventilation or perfusion. Second, this study is not designed to elucidate the effects of volatile or intravenous anesthesia on shunt. Further study should explore this hypothesis. Third, we did not evaluate patients' recruitability using recruitment-to-inflation ratio[46] or airway opening pressure.[47] Fourth, the ALPE technique is not widely available; further studies should explore whether a simplified surrogate of high V/Q ratio may be used to improve postoperative pulmonary complications prediction. Fifth, we enrolled patients at intermediate or high risk of postoperative pulmonary complications according to their ARISCAT score and undergoing major noncardiac surgery for more than 2 h. Further studies are required to understand whether these results are generalizable to patients with lower preoperative risk and/or undergoing other surgeries (*e.g.*, thoracic surgery, cardiac surgery). Sixth, the sensitivity analysis for high V/Q ratio in the multivariable regression showed an E-value of 1.35. Therefore, a possible unmeasured confounder with an odds ratio on both outcome and predictor of 1.35 (CI, 1.11) could fully explain the association between predictor and outcome. Finally, we only evaluated postoperative pulmonary complications in the first 7 days after surgery and therefore do not have data about longer-term outcomes.

Conclusions

Patients with worst intraoperative V/Q matching are more likely to develop postoperative pulmonary complications after major noncardiac surgery. Although shunt improved over time after anesthesia induction, it was not different among groups. Higher V/Q ratio before extubation is independently associated with postoperative pulmonary complication in the first 7 days after surgery.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Additional tables (tables S1–S4) and figures (S1–S3), https://links.lww.com/ALN/D581

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