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Hyperoxemia post thoracic surgery – Does it matter?

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ABSTRACT

Introduction: Post-operative oxygen therapy is used to prevent hypoxemia and surgical site infection. However, with improvements of anesthesia techniques, post-operative hypoxemia incidence is declining and the benefits of oxygen on surgical site infection have been questioned. Moreover, hyperoxemia might have adverse effects on the pulmonary and cardiovascular systems. We hypothesized hyperoxemia post thoracic surgery is associated with post-operative pulmonary and cardiovascular complications.

Methods: Consecutive lung resection patients were included in this post-hoc analysis. Post-operative pulmonary and cardiovascular complications were prospectively assessed during the first 30 post-operative days, or hospital stay. Arterial blood gases were analyzed at 1, 6 and 12 h after surgery. Hyperoxemia was defined as arterial partial pressure of oxygen (PaO_2)>100 mmHg. Patients with hyperoxemia duration in at least two adjacent time points were considered as hyperoxemic. Student t-test, Mann-Whitney *U* test and two-tailed Fisher exact test were used for group comparison. *P* values < 0.05 were considered statistically significant.

Results: Three hundred sixty-three consecutive patients were included in this post-hoc analysis. Two hundred five patients (57%), were considered hyperoxemic and included in the hyperoxemia group. Patients in the hyperoxemia group had significantly higher PaO_2 at 1, 6 and 12 h after surgery ($p < 0.05$). Otherwise, there was no significant difference in age, sex, comorbidities, pulmonary function tests parameters, lung surgery procedure, incidence of post-operative pulmonary and cardiovascular complications, intensive care unit and hospital length of stay and 30-day mortality.

Conclusion: Hyperoxemia after lung resection surgery is common and not associated with post-operative complications or 30-day mortality.

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1. Introduction

Post-operative oxygen supplementation has been used for many years to prevent hypoxemia [1] and recommended to reduce surgical site infection [2]. However, the incidence of post-operative hypoxemia has been declining over the past several decades [3] and the role of routine oxygen supplementation in the reduction of surgical site infection has become controversial and in current practice is not widely practiced [4].

Hyperoxemia may have adverse effects on the respiratory system including absorption atelectasis, worsening of ventilation-perfusion matching, reduction of mucociliary clearance and oxidative stress to the lung [5–8]. Hyperoxemia may also have adverse effects on the cardiovascular system including reduced cardiac output and increased vascular resistance [9].

A possible mechanism of hyperoxemia-associated organ damage is the production of reactive oxygen species (ROS) [10]. Production of ROS is especially pronounced during ischemia/reperfusion injury and/or hypoxia/re-oxygenation [11] conditions which are frequently observed with lung resection surgery and one lung ventilation [12] suggesting these patients may be more susceptible to adverse effects of hyperoxemia.

We hypothesized post-operative hyperoxemia is common and associated with adverse post-operative complications in patients undergoing lung resection. Accordingly, the aim of this study was to evaluate post-operative arterial blood gases and pulmonary and cardiovascular complications in patients after lung resection surgery.

2. Methods

Subject selection. Patients from our two studies (ClinicalTrials.gov NCT03498352 and NCT04826575) were included in this secondary analysis study. Inclusion criteria for all patients were ability to undergo cardiopulmonary exercise testing and age $\geq$18 years. Patients with contraindication for lung resection surgery were excluded. Subjects were recruited in two centers from May 2017 through September 2022. All participants provided written informed consent. Studies were approved by both centers Ethics Committees (St. Anne's University Hospital in Brno: reference No. 19 J S/2017; reference No. 2G/2018; reference No. 03G/2021 and by the local Ethics Committee of the University Hospital Brno: reference No. 150617/EK; No. 14–100620/EK).

Arterial blood gases. Arterial blood gases were obtained 1, 6 and 12 h after surgery for research purposes of the NCT03498352 and NCT04826575 studies. Analysis was done at the bedside and results were immediately available to the clinical management team. Inspired oxygen fraction (FiO_2) was estimated based on the form of oxygen therapy (nasal cannula or face mask) and oxygen flow similar to a previous study on non-intubated adults in the intensive care unit [13]. Hyperoxemia was defined as the use of oxygen with arterial partial pressure of oxygen (PaO_2)>100 mmHg, similar to previous studies [11,14]. Patients with hyperoxemia observed from at least two consecutive time points were considered hyperoxemic and included in the hyperoxemia group. Hypoxemia was defined as PaO_2 <60 mmHg [15].

Pulmonary function tests. All included patients underwent pulmonary function tests within two weeks before the surgery. Measurements were done as recommended [16] and described in detail in our previous study [17]. In brief, measured parameters included diffusing lung capacity for carbon monoxide (DL_{CO}), forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), expressed as a percentage of predicted value.

Post-operative pulmonary complications. Post-operative pulmonary complications were assessed from the first 30 post-operative days or from the hospital stay. Complications were defined as in previous studies [17–21] and described in detail in the study of Brat et al. [17]. In brief, complications included respiratory failure requiring mechanical ventilation (both invasive and non-invasive), adult respiratory distress syndrome, pneumonia, atelectasis and tracheostomy.

Post-operative cardiovascular complications. Post-operative cardiovascular complications were assessed from the first 30 post-operative days or from the hospital stay. Complications were defined as in previous studies [22,23] and described in detail in the study of Mazur et al. [22]. In brief, complications included hypotension, newly developed arrhythmias, pulmonary edema, heart failure, myocardial infarction/minimal myocardial lesion, pulmonary embolism, stroke and cardiopulmonary resuscitation.

Mortality. Intensive care unit (ICU) length of stay (LOS), hospital LOS and mortality within the 30 post-operative days were monitored and recorded.

Anesthesia. Anesthesia was done irrespective of both study protocols. In general, all of the patients underwent surgery under general anesthesia (intravenous induction, inhalation maintenance). Patients undergoing open thoracotomy also had thoracic epidural catheter inserted for post-operative analgesia. All subjects were intubated with double-lumen tubes. During the surgery, protective ventilation was used as recommended [24]. Including tidal volume of 4–6 ml/kg, plateau pressure up to maximum of 30 cm H_2O, positive end-expiratory pressure of 5 H_2O (up to 10 cm H_2O during one lung ventilation), breathing frequency to maintain normocapnia (or permissive hypercapnia of 45–60 mmHg during one lung ventilation) and FiO_2 to maintain O_2 saturation of 88–94%. Neuromuscular blockade was routinely monitored and patients extubated when their train-of-four ratio was >0.9.

Post-operative physiotherapy. Based on our local protocols, all patients underwent standard chest physiotherapy including airway clearance techniques and early mobilization on a daily basis with the help of a physiotherapist.

Statistics. Sample size of 363, mean under H_0 of 14% (expected incidence of post-operative complications in the control group [25]), minimum detectable effect of 10% (clinically significant increase of post-operative complications) and alpha of 5% were used for the post-hoc power analysis yielding the power of 80%. The Shapiro-Wilk test was used to evaluate normality. Student t-test (for data with normal distribution), Mann-Whitney *U* test (for data without normal distribution) and two-tailed Fisher exact test were used for group comparison (hyperoxemia vs. control group). Friedman's ANOVA was used to test for arterial blood gas differences among the three time-points. Data are summarized as mean $\pm$ SD (for data with normal distribution) or median (IQR) (for data without

normal distribution); *P* values < 0.05 were considered statistically significant. Statistica software 12.0 (StatSoft Inc., Prague, Czech Republic) was used for the analysis.

3. Results

Three hundred sixty-three consecutive patients were included in this post-hoc analysis. Basic characteristics are shown in Table 1. Most of the patients were men who underwent lobectomy via open thoracotomy (Table 1). Arterial blood gas analysis at 1, 6 and 12 h is shown in Table 2. Overall, PaO_2, PaO_2/FiO_2, O_2 saturation and pH significantly increased and FiO_2 and arterial partial pressure of carbon dioxide ($PaCO_2$) significantly decreased in the first 12 h in the ICU.

Of 363 patients, 280 (77%) experienced at least one episode of hyperoxemia during the first 12 h (comparison shown in Supplement Table 1). In two hundred five patients (57%), an observed hyperoxemia episode did not trigger FiO_2 reduction. These patients remained hyperoxic for at least two consecutive time points and were included in the hyperoxemia group.

Patients in the hyperoxemia group had significantly higher PaO_2 and PaO_2/FiO_2 for all three time points (Table 3). There were no significant differences in age, sex, comorbidities (*S*-MPM), pulmonary function tests parameters and lung surgery procedure (Table 4). BMI was slightly higher in the control group. The two groups did not differ in ICU or hospital LOS, ICU readmissions and 30-day mortality (Table 4).

On comparison of the two study groups, there was no significant difference in the number of patients with pulmonary [hyperoxemia n = 23 (11%) vs. control group n = 28 (18%); p = 0.09] or cardiovascular complications [hyperoxemia n = 45 (22%) vs. control group n = 28 (18%); p = 0.36]. Comparison of each different pulmonary and cardiovascular complication is shown in Table 5. No significant differences were observed, only hypoxemia was more frequent in the control group.

In 51 (14%) patients, the mean PaO_2 during the first 12 h in the ICU was $\geq$150 mmHg. These patients did not differ in the number of post-operative pulmonary complications [hyperoxemia n = 4 (8%) vs. control group n = 47 (15%); p = 0.20], cardiovascular complications [hyperoxemia n = 10 (20%) vs. control group n = 63 (20%); p = 1.00] and 30-day mortality [hyperoxemia n = 1 (2%) vs. control group n = 6 (2%); p = 1.00].

4. Discussion

The major findings of this post-hoc analysis were that hyperoxemia in patients after thoracic surgery is common, mild, often neglected and not associated with increased risk for post-operative pulmonary or cardiovascular complications or mortality.

In our cohort, the incidence of hyperoxemia was high (77% at least once; 57% at least twice) during the first 12 h. Hyperoxemia incidence in our study is difficult to compare with previous studies focusing on post-operative period as in the Karalapillai et al. study [26] a different hyperoxemia definition was used (>150 mmHg instead of the commonly used >100 mmHg [11,14]) while in the Ehrenfeld et al. study [27], PaO_2 and FiO_2 were not reported.

In more than half of hyperoxemic patients, PaO_2 results did not trigger oxygen therapy reduction by the managing physician. This liberal strategy is common [26], performed as part of hypoxemia prevention and considered low risk [28]. However, this may not be true for different patient subgroups with distinct O_2 requirements [11], especially patients after hypoxia/re-oxygenation (e.g., lung resection surgery and one lung ventilation [12]) who may be more prone to adverse effects of hyperoxemia [11].

In our cohort, the overall incidence of post-operative pulmonary (14%) and cardiovascular complications (20%) was similar to previously reported studies [25,29]. Importantly, neither pulmonary nor cardiovascular post-operative complications were significantly associated with the presence of hyperoxemia.

Table 1
Basic characteristics (n = 363).

Age (years)	66 (58–71)
BMI (kg/m^2)	27 (24–31)
Male No. (%)	205 (57)
S-MPM	6 (4–6)
FEV_1 (% predicted)	91 ± 20
FVC (% predicted)	94 (83–105)
FEV_1/FVC (% predicted)	80 (73–86)
DL_{CO} (% predicted)	82 ± 22
Lobectomy No. (%)	180 (50)
Bilobectomy No. (%)	11 (3)
Wedge resection No. (%)	163 (45)
Pneumonectomy No. (%)	9 (2)
Open thoracotomy No. (%)	195 (54)
ICU LOS (days)	3 (2–5)
Hospital LOS (days)	7 (5–9)

BMI = body mass index; DL_{CO} = diffusing lung capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; ICU = intensive care unit; LOS = length of stay; *S*-MPM=Surgical Mortality Probability Model.

Table 2
Arterial Blood Gases during the first 12 h in the ICU (n = 363).

Parameter	1 h	6 h	12 h	*P*
PaO_2 (mmHg)	106 (83–141)	110 (86–141)	109 (84–137)	0.02
FiO_2	0.30 (0.30–0.40)	0.30 (0.30–0.35)	0.30 (0.30–0.30)	<0.01
PaO_2/FiO_2	315 (242–430)	355 (276–455)	365 (288–461)	<0.01
O_2 saturation	98 (96–99)	98 (97–99)	98 (97–99)	<0.01
$PaCO_2$ (mmHg)	43 (40–47)	39 (36–42)	40 (37–44)	<0.01
pH	7.36 (7.33–7.38)	7.40 (7.38–7.43)	7.41 (7.39–7.44)	<0.01

FiO_2 = inspired oxygen fraction; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2 = arterial partial pressure of oxygen.

Table 3
Arterial blood gases comparison.

Parameter	Hyperoxemia (n = 205)	Control group (n = 158)	*P*
1 h after surgery			
PaO_2 (mmHg)	125 (102–150)	84 (71–101)	<0.01
FiO_2	0.30 (0.30–0.40)	0.30 (0.30–0.40)	0.06
PaO_2/FiO_2	369 (304–469)	255 (116–769)	<0.01
O_2 saturation (%)	99 (97–99)	96 (94–98)	<0.01
$PaCO_2$ (mmHg)	44 (40–46)	43 (41–47)	0.11
pH	7.36 (7.33–7.38)	7.35 (7.32–7.38)	0.10
6 h after surgery			
PaO_2 (mmHg)	131 (110–155)	85 (74–97)	<0.01
FiO_2	0.30 (0.30–0.35)	0.30 (0.30–0.35)	0.09
PaO_2/FiO_2	405 (341–484)	282 (143–711)	<0.01
O_2 saturation (%)	99 (98–99)	97 (95–98)	<0.01
$PaCO_2$ (mmHg)	39 (35–42)	39 (36–43)	0.39
pH	7.40 (7.38–7.43)	7.40 (7.37–7.42)	0.11
12 h after surgery			
PaO_2 (mmHg)	125 (109–153)	86 (74–101)	<0.01
FiO_2	0.30 (0.30–0.30)	0.30 (0.25–0.30)	<0.01
PaO_2/FiO_2	410 (345–498)	300 (145–810)	<0.01
O_2 saturation (%)	99 (98–99)	97 (95–98)	<0.01
$PaCO_2$ (mmHg)	39 (36–43)	41 (38–44)	0.03
pH	7.41 (7.39–7.44)	7.40 (7.38–7.44)	0.10

FiO_2 = inspired oxygen fraction; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2 = arterial partial pressure of oxygen.

Table 4
Comparison of hyperoxemia and control group.

Parameter	Hyperoxemia (n = 205)	Control group (n = 158)	*P*
Age (years)	66 (58–72)	66 (58–71)	0.83
BMI (kg/m^2)	27 (23–30)	28 (25–33)	<0.01
Male No. (%)	115 (56)	90 (57)	0.92
S-MPM	6 (4–6)	6 (4–6)	0.75
FEV_1 (% predicted)	91 ± 20	90 ± 19	0.91
FVC (% predicted)	92 (83–104)	94 (82–107)	0.32
FEV_1/FVC (% predicted)	81 (74–86)	79 (71–86)	0.24
DL_{CO} (% predicted)	81 ± 21	84 ± 23	0.26
Surgery			
Lobectomy No. (%)	101 (49)	79 (50)	0.92
Bilobectomy No. (%)	5 (2)	6 (4)	0.54
Wedge resection No. (%)	97 (47)	69 (44)	0.52
Pneumonectomy No. (%)	4 (2)	5 (3)	0.51
Open thoracotomy No. (%)	113 (55)	82 (52)	0.6
Outcome			
ICU LOS (days)	3 (2–5)	3 (2–5)	0.78
Hospital LOS (days)	7 (5–9)	7 (5–9)	0.92
ICU readmission	3 (1)	6 (4)	0.19
30-day mortality	6 (3)	1 (1)	0.14

BMI = body mass index; DL_{CO} = diffusing lung capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; ICU = intensive care unit; LOS = length of stay; *S*-MPM=Surgical Mortality Probability Model.

Table 5
Post-operative complications comparison.

	Hyperoxemia (n = 205)	Control group (n = 158)	*P*
Pulmonary complications			
Pneumonia No. (%)	19 (9)	23 (15)	0.14
Atelectasis No. (%)	6 (3)	7 (4)	0.57
Respiratory failure No. (%)	7 (3)	5 (3)	1.00
ARDS No. (%)	3 (2)	0	0.26
Tracheostomy No. (%)	2 (1)	1 (1)	1.00
Hypoxemia No. (%)	5 (2)	11 (7)	0.04
Cardiovascular complications			
Lung edema No (%)	2 (1)	0	0.51
Pulmonary embolism No (%)	2 (1)	2 (1)	1.00
Arrhythmia No (%)	26 (13)	19 (12)	0.87
Hypotension No (%)	25 (12)	16 (10)	0.62
Heart failure No (%)	2 (1)	0	0.51
Acute myocardial infarction No (%)	0	1 (1)	0.44
Cardiopulmonary resuscitation No (%)	2 (1)	1 (1)	1.00
Ischemic stroke No (%)	2 (1)	0	0.51

ARDS = Adult respiratory distress syndrome.

Previous studies have shown hyperoxemia might have multiple adverse physiological pulmonary and cardiovascular effects including absorption atelectasis, worsening of the ventilation-perfusion matching, reduction of mucociliary clearance, oxidative stress to the lung, increased vascular resistance (including the coronary arteries), and decreased cardiac output [5–9].

In prior surgical cohort studies, observations have been discrepant. In agreement with our study, no association of hyperoxemia (intraoperative + 2 h after surgery) and post-operative pulmonary complications was found in a large randomized clinical trial by Meyhoff et al. [30]. In contrast, hyperoxemia was found to be associated with major post-operative pulmonary complications and 30-day mortality in a large retrospective analysis [28]. The reason for these apparent discrepancies might be relatively mild hyperoxemia in our lung resection surgery patients. Although hyperoxic, the inspired oxygen fraction in our hyperoxemia group was low and similar to "low oxygen" groups in previous trials [28,30–33] comparing high (0.80) vs. low oxygen (0.30–0.35) therapy. Indeed, a dose-dependent effect of hyperoxemia on major respiratory complications and 30-day mortality has been shown by Saehr-Rye et al. [28].

The PaO_2/FiO_2 ratio was significantly higher in the hyperoxemia group suggesting better lung capacity to oxygenate blood [34]. This may also explain the significantly higher PaO_2 in the hyperoxemia group despite relatively mild differences in FiO_2 between both groups. No difference in the incidence of post-operative complications between both groups suggests the better lung capacity to oxygenate blood together with unnecessary oxygen therapy did not cause post-operative complications development. However, it may have also prevented it.

In our cohort, there was no significant difference in 30-day mortality between the study groups. In surgical patients, hyperoxemia has been shown associated with increased 30-day [28] and long-term mortality [35]. Despite these reports, doubt remains regarding the hyperoxemia – mortality relation [30].

In our study, the incidence of post-operative hypoxemia was low (4%), but significantly higher in the control group. However, the hypoxemia was mild as mean O_2 saturations of these patients were 87 ± 6% at 1hr; 90 ± 2% at 6 h s and 89 ± 4% at 12 h s. Moreover, 14 (88%) of 16 patients were diagnosed with chronic obstructive pulmonary disease, where lower O_2 saturation (above 88%) is usually tolerated [36] suggesting lower O_2 saturation may have been intentional in these patients.

Our study may have clinical implications. To date, an association of hyperoxemia and poor outcome has not been shown in the post-operative period [1]. Therefore, an optimal oxygen target is not known [1]. In our study we have shown mild hyperoxemia seems harmless (no association with poor outcome), but also unnecessary (no association with favorable outcome). This supports the previous suggestion that FiO_2 should be titrated to maintain normoxemia in the post-operative period [1,11]. Further studies, preferably randomized controlled trials, are necessary to determine the optimal oxygen target for the post-operative period.

This study has several limitations. First, arterial blood gases were monitored only during the first 12 h in the ICU. Intraoperative arterial blood gases as well as detailed data about anesthesia and immediate post-operative care were not part of both study protocols and thus not recorded. However, we report complete blood gas analyses at 1, 6 and 12 h post ICU admission together with inspired oxygen fraction which was not done in previous studies [26,27]. Moreover, our patients in the hyperoxemia group remained hyperoxemic for at least 5 h, which is longer than in the previous studies where hyperoxemia was used during surgery [28,30–33] and maximum of 2 h post-operatively [30,35]. Second, data on surgical site infection were not collected and therefore not included in this post-hoc analysis. Hyperoxemia as a method to reduce surgical site infection has been recommended [2]. However, this recommendation has been questioned and no benefit of hyperoxia has been found in several studies [1,28,30,37]. Surgical site infection is associated with increased hospital LOS [38] and no such difference was observed in our study groups. Third, this was an observational study and thereby we cannot comment on causality.

In conclusion, in patients after lung resection surgery, short-term, mild hyperoxemia is common. Importantly, no adverse outcomes associated with mild hyperoxemia were observed in this study. Moreover, no significant differences in mortality rates, or in the incidence of cardiovascular or pulmonary complications were found in patients with and without hyperoxemia.

Author contribution statement

Kristian Brat; Zdenek Chovanec; Ivan Cundrle: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ladislav Mitas; Vladimir Sramek; Lyle Olson: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Additional information

Supplementary content related to this article has been published online at [URL].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17606.

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