Pleural Hypercarbia After Lung Surgery Is Associated With Persistent Alveolopleural Fistulae

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BACKGROUND: Persistent air leak (PAL) > 5 days due to alveolopleural fistulae is a leading cause of morbidity following surgical resection. Elevated CO₂ levels reportedly inhibit alveolar epithelial cell proliferation and impair wound healing in vitro. Because the injured lung surface is in direct communication with the pleural cavity, we investigated whether the pleural gaseous milieu affected lung healing.

METHODS: Oxygen and CO₂ levels in pleural gas were determined prospectively in consecutive patients (N = 116) undergoing lung resection by using an infrared spectroscopy-based analyzer. Poisson and logistic regression analyses were used to determine the relationship between time to resolution of air leaks and pleural oxygen and CO₂. In addition, patients with pleural CO₂ concentrations ≥ 6% on postoperative day 1 (n = 20) were alternatively treated with supplemental oxygen and extrapleural suction to reduce the pleural CO₂ levels.

RESULTS: Poisson analyses revealed that every 1% increase in CO₂ was associated with a delay in resolution of air leak by 9 h (95% CI, 7.1 to 10.8; *P* < .001). Linear regression showed that every 1% increase in CO₂ increased the odds of PAL by 10-fold (95% CI, 2.2 to 47.8; *P* = .003). In patients with pleural CO₂ ≥ 6%, a reduction in CO₂ promoted resolution of air leak (6.0 ± 1.2 vs 3.4 ± 1.1 days; *P* < .001).

CONCLUSIONS: Pleural hypercarbia seems to be associated with persistent alveolopleural fistulae following lung resection. Analysis of pleural gases could allow for better chest tube management following lung resection. Patients with intrapleural hypercarbia seem to benefit from supplemental oxygen and suction, whereas patients who do not have hypercarbia can be maintained on water seal drainage.

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KEY WORDS: lung; lung injury; thoracic surgery

ABBREVIATIONS: INT = intervention; PAL = prolonged air leak; ST = standard treatment

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Despite ongoing technical advances in surgical technique, the occurrence of a prolonged air leak (PAL) following pulmonary resection remains a frequent complication.¹⁻³ The National Emphysema Treatment Trial found that PAL occurred in 50% of patients following lung volume reduction surgery.⁴ In patients without advanced emphysema, the occurrence of PAL is 18% to 26%.^{2,3} However, higher rates of 45% to 58% have also been reported.^{1,2} PAL and associated comorbidities remain one of the most important contributors of mortality following lung surgery.^{2,5} Furthermore, PAL leads to more than \$150 million in additional health-care costs annually in the United States.^{6,7} Several risk factors have been associated with PAL, including low postresection FEV₁, upper lobe lobectomy,^{2,8} incomplete fissures,⁹ emphysema,¹⁰ low diffusion capacity, and pleural

adhesions.⁴ However, the cellular mechanisms that contribute to PAL are unknown.

Alveolar epithelial cells (particularly type II pneumocytes, which have the ability to differentiate into type I pneumocytes) play an important role in the response to lung injury and in lung repair.^{11,12} We have previously shown that hypercarbia impairs alveolar epithelial cell proliferation.^{13,14} Similarly, hypoxia has been reported to suppress wound healing in various tissues, including the lung.¹⁵⁻¹⁸ Because the surface of the injured lung is immediately adjacent to the pleural cavity, we reasoned that the intrapleural gaseous milieu could influence lung healing and resolution of air leaks. Specifically, we hypothesized that intrapleural hypercarbia would be associated with prolonged PAL.

Materials and Methods

Patient Population

This study was approved by the Institutional Review Board at Northwestern University (STU00088120). Consecutive patients undergoing anatomic or nonanatomic lung resection were included in the study after being extubated at completion of the procedure in the operating room. Informed consent was obtained from all patients in the study. Chest tubes were placed on -20 cm water suction following surgery and converted to water seal drainage on the morning of postoperative day 1, as previously described.^{19,20} Exclusion criteria included hemodynamic instability during the postoperative period requiring transfer back to the ICU or reintubation prior to resolution of the air leak, inability to place the chest tube on water seal drainage on postoperative day 1, patients undergoing pneumonectomy, or inability to remove supplemental oxygen from patients at the time of analysis due to a drop in oxygen saturation < 88%.

Visual Inspection for Air Leak

Patients were asked to cough five times followed by five deep breaths to remove any trapped air in the drainage column. This sequence was conducted twice, and if bubbles were observed to pass through the water column during the second sequence, visual inspection was considered positive for an air leak. Duration of air leak was defined as the number of days from surgery to cessation of the air leak.

Pleural Gas Analysis

Gas analysis was performed by connecting a Datex gas analyzer (GE Healthcare Inc) to the sampling port of the chest drainage system (Oasis; Atrium Medical Corp). Any fluid in the chest tubing was passively drained by gravity into the chest drainage system. The sampling port was then held in a nondependent position to allow air (but not fluid) into the gas analyzer. All measurements were performed on postoperative day 1 after the chest tubes were on water seal drainage and patients were breathing room air. Patients receiving supplemental oxygen were taken off this and breathed room air for at least 15 minutes prior to sampling for gas analysis. If oxygen saturation measured by pulse oximetry dropped to < 88% upon removal of supplemental oxygen, the patient was

excluded from the study. Values of CO₂ and oxygen were recorded after sampling for 1 minute.

Intervention to Reduce Pleural CO₂

Under conditions of normal ventilation, the alveolar Pco₂ is between 35 and 45 mm Hg (4.9%-6.3% in patients at sea level), which is similar to the mixed venous Pco₂. This defines the predicted "normal" range of Pco₂ in the presence of a bronchopleural fistula between 0.04% (atmospheric) and 6.3% (alveolar). Patients with intrapleural CO₂ levels > 6% on postoperative day 1 were assigned to standard treatment (ST) or intervention (INT) groups. Patient number 1 and every odd-numbered patient were assigned to the ST group; patient number 2 and every even-numbered patient were included in the INT group. Patients in the ST group underwent water seal drainage and were weaned off supplemental oxygen to keep the oxygen saturation > 88%. Patients in the INT group were underwent pleural suction and were given supplemental oxygen by nasal cannula at a flow rate titrated to decrease the measured pleural CO₂ concentration to < 5% and to increase the pleural oxygen concentration to > 21%. The end point of the study was time to resolution of air leak by visual inspection, as described earlier.

Statistical Analyses

Statistical analyses were performed by using SAS version 9.3 (SAS Institute, Inc), Microsoft Excel 2011 (Microsoft Corporation), and GraphPad Prism, version 6 (GraphPad Software, Inc). Statistical significance was declared at the two-sided 5% alpha level without adjustments for multiplicity. Variables with a continuous distribution (eg, age, leak size and duration, oxygen and CO₂ levels) are summarized by using means ± SDs. Group comparisons were based on analysis of variance when > 2 groups were involved; otherwise, a two-sample Student *t* test with unequal variances or the Wilcoxon rank sum test was used. Variables with discrete distribution are presented by using counts and percentages and compared across groups by using the χ^2 test or exact binomial methods. Correlation between intrapleural airleak duration and pleural oxygen and CO₂ percent levels were measured by using Pearson correlation coefficient. Poisson regression was used to study the relationship between the time until the air leak was undetectable and baseline covariate information such as age, sex, type of surgery (lobar vs sublobar lung resection), pleural oxygen, and CO₂ levels.

A logistic regression model was used to relate the amount of time until an air leak was undetectable (≥ 6 days vs ≤ 5 days) to age, pleural oxygen, and CO₂ percent levels. ORs and corresponding 95% CIs

were calculated. This model has been internally validated by using leave-one-out cross-validation based on the area under the receiver operating-characteristic curve.

Results

Clinical Profile of Study Subjects

Intrapleural oxygen and CO₂ were analyzed on postoperative day 1 in patients undergoing lung resection (N = 116). Table 1 presents the clinical profile of the study patients. Mean age was 55.1 ± 12.0 years, and 59% were women. Anatomic lobectomy was performed in 55 patients (47%), and the other patients underwent sublobar or wedge resection. For patients with lobar resection, the predicted postresection FEV₁ was $> 40\%$. The mean $\pm$ SD size of the air leak on postoperative day 1 was 1.1 ± 1.3 chambers, and the mean duration for the resolution of air leak was 2.6 ± 2.6 days. The mean pleural CO₂ and oxygen levels were $3.3 \pm 1.9\%$ and $16.5 \pm 1.6\%$, respectively.

Intrapleural Hypercarbia Is Associated With PAL

Patients were divided into three groups: (1) no air leak on postoperative day 1 (n = 60), (2) air leak on postoperative day 1 that resolved by day 5 (n = 44), and (3) PAL lasting > 5 days (n = 12), as defined by the Society of Thoracic Surgeons.²¹ The baseline clinical profiles of these three groups were similar (Table 1).

As expected, the group with no air leaks had low CO₂ levels ($2.0 \pm 0.7\%$). However, the PAL group had significantly increased CO₂ levels compared with the group experiencing air leaks on postoperative day 1 that resolved by day 5 ($6.9 \pm 0.8\%$ vs $4.0 \pm 1.3\%$; $P < .001$) (Fig 1A). The duration of air leak and pleural CO₂ concentration were positively correlated (Pearson $r = 0.78$; $P < .0001$), whereas air leak duration and pleural oxygen concentration were negatively correlated (Pearson $r = -0.32$; $P = .0004$) (Fig 1B).

Poisson regression analysis revealed that every 1-unit increase in CO₂ percent level was associated with lack of resolution of the pleural leak of approximately 9 h (95% CI, 7.1 to 10.8; $P < .001$) (Fig 2). Every 1-unit increase in oxygen percent level was associated with a trend toward resolution of the pleural leak by approximately 2 h (95% CI, -0.2 to 3.3 ; $P = .09$). The logistic regression model revealed that a 1-unit increase in CO₂ percent levels was associated with 10 times greater odds of experiencing a time of ≥ 6 days until the air leak was undetectable (95% CI, 2.2 to 47.8; $P = .003$) (Fig 3). As in the Poisson model, logistic regression indicated a trend toward lower rates of persistent air leak of ≥ 6 days in patients with higher pleural oxygen

TABLE 1 Clinical Profile of Study Patients

Characteristic	All (N = 116)	NAL (n = 60)	AL (n = 44)	PAL (n = 12)	P
Age, y	55.1 ± 12.0	53.6 ± 14.3	55.7 ± 10.4	58.6 ± 6.5	.3
Race					.5
AA	35 (30.2)	21 (35)	10 (22.7)	4 (33.3)	
White	75 (64.7)	36 (60)	31 (70.4)	8 (66.7)	
Others	6 (5.1)	3 (5)	3 (6.8)	0	
Sex					.8
Male	48 (41.4)	25 (41.7)	16 (36.6)	7 (58.3)	
Female	68 (58.6)	35 (58.3)	28 (63.4)	5 (41.7)	
Resection					.2
Lobar	55 (47.4)	25 (41.7)	23 (52.3)	7 (58.3)	
Sublobar	61 (52.6)	35 (58.3)	21 (47.7)	5 (41.7)	
Leak size, chambers ^a	1.1 ± 1.3	0	2.1 ± 0.9	2.3 ± 1.3	.1
Pleural CO ₂ , %	3.3 ± 1.9	2.0 ± 0.7	4.0 ± 1.3	6.9 ± 0.8	$< .001$
Pleural O ₂ , %	16.5 ± 1.6	16.8 ± 1.7	16.4 ± 1.4	15.7 ± 1.2	.001
Duration of leak, d	2.6 ± 2.6	1.0 ± 0	3.0 ± 0.9	9.2 ± 2.8	$< .0001$

Data are presented as mean $\pm$ SD or no. (%). AA = African American; AL = air leak (present on day 1 but resolved by day 5); NAL = no air leak present on day 1; O₂ = oxygen; PAL = prolonged air leak (air leak present > 5 days).

^aChambers are the size of the air leak demonstrated on cough. The Oasis system has 5 chambers, which directly correlate with size of leak.

Figure 1 – A, B Correlation of intrapleural (A) CO₂ and (B) O₂ with duration of air leak. Gas analysis was performed on postoperative day 1. O₂ = oxygen.

levels (OR, 0.33 for each 1-unit increase [95% CI, 0.1 to 1.2]; $P = .096$). Age was not a factor in the duration of air leak.

Intrapleural Hypercarbia Can Result From Alveolar Hypoventilation

Because alveolar and intrapleural gas are in communication at the site of lung injury due to a breach in the visceral pleura, we reasoned that intrapleural hypercarbia might be a consequence of increased alveolar CO₂ resulting from hypoventilation. The end-tidal CO₂ and intrapleural CO₂ were measured in patients with obvious air leak immediately following lung resection while still on mechanical ventilation. As expected, lower minute ventilation was associated with increased end-tidal CO₂. The intrapleural CO₂ was always lower but tracked closely with end-tidal CO₂. The increase in end-tidal CO₂ was associated with an increase in intrapleural CO₂ ($2.9\% \pm 0.4\%$ to $6.9\% \pm 0.6\%$ [$P = .01$ and $P = .02$, respectively]) (Fig 4A). The intrapleural oxygen levels did not change ($24.7\% \pm 1.2\%$ vs $25.7\% \pm 0.6\%$; $P = .2$).

Increasing FiO₂ to 100% at fixed minute ventilation led to an increase in intrapleural oxygen with no significant change in CO₂ levels (Fig 4B).

Decreasing Intrapleural CO₂ Shortens Pleural Leak

As discussed earlier, higher intrapleural CO₂ levels were associated with a prolonged pleural leak. However, under normal conditions, the maximum partial pressure of alveolar CO₂ would be approximately 45 mm Hg. This level is equivalent to approximately 6% CO₂, at 600 ft above sea level for Chicago, Illinois, where the average barometric pressure is about 745 mm Hg. Because alveolar and intrapleural air should be in equilibrium, we reasoned that in normocapnic patients, the maximum intrapleural CO₂ should be about 6%. Therefore, we investigated whether reduction of CO₂ in patients with pleural CO₂ levels > 6% (which suggests alveolar hypercapnia) would decrease the time of pleural leak.

Twenty patients with intrapleural CO₂ levels > 6% were alternately assigned to undergo INT directed toward reducing the pleural CO₂ levels or managed according to ST. The INT options to reduce intrapleural CO₂ levels included extrapleural suction up to -40 cm water and supplemental oxygen up to 8 L/min and were administered until the resolution of the leak. The INT procedure led to a reduction in pleural CO₂ from 6.6 ± 0.7 to 3.1 ± 0.5 ($P < .001$) and an increase in pleural oxygen from $15.4\% \pm 2.0\%$ to $27.1\% \pm 3.2\%$ ($P < .001$) (Table 2). There was no difference in air leak size on postoperative day 1 between the two groups (ST vs INT: 2.0 ± 0.9 vs 2.2 ± 0.9 chambers; $P = .7$). Furthermore, there was no significant difference between ST and INT in terms of their initial CO₂ levels (ST vs INT: 6.8 ± 0.9 vs 6.6 ± 1.2 ; $P = .4$) and oxygen levels (ST vs INT: 15.1 ± 1.7 vs 15.4 ± 1.9 ; $P = .6$). However, decreasing the pleural CO₂ levels decreased the duration of the pleural leak (INT vs ST: 3.4 ± 1.1 vs 6.0 ± 1.2 days; $P < .001$) (Fig 5).

Discussion

The pathogenesis of persistent alveolar-pleural leak is unclear and is associated with significant morbidity and mortality.^{2,5} In the present study, we observed that intrapleural hypercarbia might contribute to the persistence of alveolar-pleural leak. The negative effects of hypercarbia on lung injury response have been reported.^{14,22,23} Both proliferation and migration of alveolar epithelial type II cells are important for healing of lung injury.²⁴ Hypercarbia upregulates microRNA-183, which suppresses the mitochondrial enzyme isocitrate dehydrogenase 2 and inhibits oxygen consumption and adenosine triphosphate production.¹⁴

Figure 2 – Histograms of CO₂ and O₂ percent levels by number of days until air leak was undetectable (≤ 5 vs ≥ 6 days). Max = maximum; Min = minimum. See Figure 1 legend for expansion of other abbreviation.

Hypercarbia can also prevent macrophage phagocytosis of pathogens and cellular debris,^{13,25,26} which might further impair alveolar epithelial healing.

As discussed in the Materials and Methods section, the predicted “normal” range of PCO₂ in the presence of a bronchopleural fistula is between 0.04% (atmospheric) and 6.3% (alveolar). Achievement of CO₂ levels higher than this predicted range, as we observed, suggests alveolar hypoventilation, severe shunt, ischemia, or local production of CO₂. The latter might occur as the result of inflammatory cell recruitment to the site of injury or as the result of local tissue hypoxia occurring

and generation of CO₂ from anaerobic metabolism. We found that the supplemental oxygen therapy and extrapleural suction reduced pleural CO₂ levels and increased pleural oxygen levels. The decrease in CO₂ associated with supplemental oxygen was likely related to increased air flow across the alveolo-pleural fistula: we found that room air delivered through the nasal cannula at the same flow rate achieved equivalent reductions in pleural CO₂. This finding is somewhat surprising because it suggests that increased flow across an alveolo-pleural fistula does not slow wound closure, or if it does, this slowing is more than offset by beneficial changes in the gaseous microenvironment of the wound.

Figure 3 – ROC curve from logistic regression model with outcome “days until leak is undetectable ≥ 6 days” predictors were age, O₂, and CO₂. Model summaries are presented by using ORs, corresponding 95% CIs, and P values. ROC = receiver operating characteristic; ROC1 = ROC curve based on leave-one-out cross-validation. See Figure 1 legend for expansion of other abbreviation.

Our data suggest that hypercarbia plays an important role in the persistent of alveolo-pleural fistulae and might help explain the increased risk of this complication in patients undergoing upper lobectomy compared with lower lobectomy.^{2,8} Following upper lobectomy, the lower lobe bronchus migrates upward, making a steeper angle between the main bronchus and the lower lobe bronchus.^{27,28} Moreover, after right upper lobectomy, the longer and narrower middle lobe bronchus must pass inferior and medial to the

Figure 4 – A, B Intrapleural gas milieu correlates with alveolar gas composition. A, At constant FIO₂ of 30%, IPCO₂ closely approximated ETCO₂ and is shown on the left y-axis. IPO₂ did not change significantly and is shown on the right y-axis. B, At constant minute ventilation, an increase in FIO₂ led to an increase in IPO₂ (right y-axis). The IPCO₂ exhibited a decreasing trend with increased FIO₂, but it was not statistically significant (P = .09). SE bars are illustrated. ETCO₂ = end-tidal CO₂; IPCO₂ = intrapleural CO₂; IPO₂ = intrapleural oxygen. See Figure 1 legend for expansion of other abbreviation.

interlobar pulmonary artery before turning 180 degrees to ascend to the apex of the hemithorax. This action would provide more airflow resistance, leading to decreased regional ventilation and higher alveolar CO₂.

TABLE 2] Characteristics of Patients Undergoing Management With Standard Practices or Interventions Directed at Reducing Pleural CO₂

Characteristic	Standard Practice	Intervention	P Value
Size of air leak	2.0 ± 0.9	2.2 ± 0.9	NS
Pleural CO ₂	6.8 ± 0.9	6.6 ± 1.2	NS
Pleural O ₂	15.1 ± 1.7	15.4 ± 1.9	NS
Postintervention pleural CO ₂	NA	3.1 ± 0.5	
Postintervention pleural O ₂	NA	27.1 ± 3.3	

Data are presented as mean ± SD. NA = not applicable; NS = not significant. See Table 1 legend for expansion of other abbreviation.

Figure 5 – Decrease in pleural CO₂ is associated with a decreased duration of air leak following lung resection.

In contrast, in a lower lobectomy, the upper lobe bronchus moves downward, potentially reducing the angle between the upper lobe bronchus and main bronchus and thereby improving ventilation to the upper lobe.²⁹

We suggest that measuring pleural CO₂ and oxygen might help with chest tube management in patients after lobectomy. Patients with intrapleural hypercarbia should benefit from suction and supplemental oxygen, whereas other patients can be maintained on water seal drainage. This method might also help reconcile the conflicting reports about the use of suction or water seal for management of patients with an alveolo-pleural fistula.³⁰ Patients with chronic alveolar hypoventilation (eg, those with emphysema) might be predisposed to developing high intrapleural CO₂ levels and prolonged air leaks, and they may also benefit from suction. Our results suggest

a potential mechanism for the benefits reported with interventions such as incentive spirometry and/or physiotherapy that improve minute ventilation in the postoperative period on reduced rates of prolonged air leaks. Inclusion of pleural gas analysis in future trials of these therapies will help to define the relative importance of pleural CO₂ and oxygen levels on clinical outcomes in patients after lobectomy.

It is worth noting that our findings are not applicable to patients who were mechanically ventilated because these patients were excluded from the regression analysis. It should also be acknowledged that the extrapleural suction that was used in the INT group adds a confounder because it can have effects other than decreasing pleural CO₂. However, extrapleural suction is generally associated with prolonged air leaks and delayed lung healing.³⁰ In addition, the size of the initial air leak might play a role in the development of PAL. Although our data did not find such an association, the data are limited by the fact that very few patients had large air leaks.

Conclusions

We provide evidence that intrapleural hypercarbia seems to be associated with delayed resolution of alveolo-pleural fistulae in patients undergoing lobectomy. Reducing pleural CO₂ levels was associated with faster resolution of air leaks. Further randomized trials are warranted to validate these observations and determine the clinical benefits to patients with prolonged pleural leaks after thoracic surgery.

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