CHEST

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 CO_2 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 CO_2 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 CO_2. In addition, patients with pleural CO_2 concentrations ≥ 6% on postoperative day 1 (n = 20) were alternatively treated with supplemental oxygen and extrapleural suction to reduce the pleural CO_2 levels.

RESULTS: Poisson analyses revealed that every 1% increase in CO_2 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 CO_2 increased the odds of PAL by 10-fold (95% CI, 2.2 to 47.8; $P = .003$). In patients with pleural CO_2 ≥ 6%, a reduction in CO_2 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. CHEST 2016; 149(1):220-227

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 FEV_1, 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 CO_2 and oxygen were recorded after sampling for 1 minute.

Intervention to Reduce Pleural CO_2

Under conditions of normal ventilation, the alveolar P_{CO_2} is between 35 and 45 mm Hg (4.9%-6.3% in patients at sea level), which is similar to the mixed venous P_{CO_2}. This defines the predicted "normal" range of P_{CO_2} in the presence of a bronchopleural fistula between 0.04% (atmospheric) and 6.3% (alveolar). Patients with intrapleural CO_2 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 CO_2 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 CO_2 levels) are summarized by using means $\pm$ 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 CO_2 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 CO_2 levels.