Predicting Atelectasis by Assessment of Collateral Ventilation prior to Endobronchial Lung Volume Reduction: A Feasibility Study

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Key Words

Emphysema · Bronchoscopy · Endobronchial lung volume reduction · Collateral ventilation

Abstract

Background: The advent of endoscopic lung volume reduction (ELVR), especially relying on valve technology to achieve atelectasis, has aroused new interest in the assessment of collateral ventilation, which has been implicated in ELVR failures. We are reporting on the use of a catheter-based device that measures airway pressures and flows, and calculates airway resistance in vivo. **Objectives:** To assess the safety of this catheter-based system and the feasibility of obtaining measurements predictive of atelectasis after ELVR. **Methods:** Patients undergoing ELVR were prospectively included in this double-blind cohort study. Each lobe targeted for ELVR was blocked with a catheter system (Chartis[®] System; Pulmonx, Inc., Redwood, Calif., USA); pressures and flows were assessed continuously. The primary endpoints were to evaluate the safety and feasibility; the secondary endpoint was to assess whether there was a relationship between the measurements and the incidence of atelectasis following ELVR. **Results:** From June 2008 to November 2008, 25 patients were included in the study. All procedures could be performed without any complications. Due to pneumothorax in 1 case and inability to assess the catheter-based measure-

ments in 4 cases, the final analysis included 20 patients. Atelectasis occurred in 8 out of 20 cases following implantation. In 18 patients (90%), the resistance measurements correlated with the postimplantation atelectasis visualized on a chest X-ray; in 2 patients (10%), a mismatch was detected. **Conclusions:** Resistance measurements were safely and successfully achieved. In 90% of the analyzable cases, the resistance measurements correlated with the occurrence of atelectasis after ELVR. The clinical impact of these findings will need to be evaluated in subsequent trials.

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Introduction

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide that is characterized by progressive and not fully reversible airflow limitation. The goal of treatment is to slow down progression by the avoidance of causative agents, especially smoking, reducing the breathlessness by administration of bronchodilators and preventing acute exacerbations [1]. However, pulmonary emphysema is not responsive to medical management.

The National Emphysema Treatment Trial performed a multicenter randomized trial and concluded that lung volume reduction surgery could be a palliative treatment

for severe emphysema. However, limited patient eligibility and published operative mortality rates varying from 0 to 19% [2–5] with high postoperative morbidity have led to poor acceptance by patients and physicians.

In 2003, Toma et al. [6] showed that lung volume reduction can be achieved with unilateral bronchoscopically placed valve implants with acceptable short-term safety and meaningful functional benefits in patients with severe emphysema. The concept guiding this approach is that absorption atelectasis of emphysematous lung regions achieved by the implanted valves can reduce lung volume without the need to remove tissue surgically.

The greatest improvement in lung function after endoscopic lung volume reduction (ELVR) has been measured in patients who develop radiologically visible atelectasis after ELVR [7]. Since only a minority of patients undergoing ELVR develops atelectasis, the treatment outcome averaged across all patients has been modest [8, 9]. It has been postulated that collateral ventilation from adjacent lobes through collateral channels could prevent target lobe atelectasis, which potentially limits clinical responses after ELVR [10, 11].

The goals of this study were to test the clinical feasibility and safety of measuring collateral ventilation with an endobronchial catheter system and to quantify collateral ventilation in terms of collateral resistance in order to predict the occurrence of atelectasis after placing endobronchial valves.

Material and Methods

Patient Selection Criteria

This clinical trial was a double-blind cohort study. The study was approved by the local ethics committee and all patients signed the consent forms. Bronchoscopy was performed by two teams: team A performed a diagnostic assessment on the target lobe for ELVR and team B performed the ELVR without knowledge of the measurements obtained by team A. All procedures were performed at Thoraxklinik, Heidelberg, Germany, by R.E., A.E. and F.H. The inclusion criteria were: symptomatic chronic obstructive pulmonary disease stages III and IV based on the Global Initiative on Chronic Obstructive Pulmonary Disease classification, persistent moderate to severe dyspnea, evidence of a highly heterogeneous emphysema by high-resolution computed tomography (CT) scans, age >18 years and the following results on pulmonary function tests: forced expiratory volume in 1 s (FEV₁) 20–45% of predicted, transfer factor of the lungs for carbon monoxide (TLCO) 20–40% of predicted, total lung capacity (TLC) >100% of predicted; residual volume (RV) >200% of predicted.

CT Imaging and ELVR Targeting

The distribution and severity of emphysema were determined from high-resolution CT scans of the chest. All images were ac-

quired on multidetector scanner platforms. Two sequences were acquired supine at suspended TLC and at RV, each in a single breath holding. They were reconstructed in both thick (5 or 10 mm) and thin (1.25–3 mm) series. The CT data were analyzed using in-house software (YACTA) which differentially highlights the lung regions based on the severity of emphysema [12] and the most hyperinflated lobe was selected as target lobe for valve placement.

Procedure

The bronchoscopists were divided into two groups: one group performing the catheter-based measurements prior to ELVR and the other group performing the ELVR. The operator performing ELVR was unaware of the diagnostic measurements. All investigations were performed under local anesthesia plus moderate sedation allowing for spontaneous breathing. The catheter-based system consists of a single-patient use catheter and a reusable console. The catheter is inserted into the working channel of a bronchoscope and is connected to the console. Each lobe targeted for ELVR was blocked via the catheter system by inflating a balloon at the tip of the catheter, as previously described [13]. The air of the isolated targeted lobe was directed to the console through the catheter, enabling continuous assessment of the pressures and flows. Based on these measurements, the resistance of the collateral channels was calculated as averaged pressure divided by averaged flow.

When the air flow from the target lobe being assessed decreases over time and tends towards zero, indicating that there is limited cross-communication between the lobes, the collateral resistance is high. However, if the air flow from the target lobe is persistent and positive, without a decreasing trend towards zero, indicating that there likely is cross-communication between the lobes, the collateral resistance is low [13]. Generally, a cumulative resistance >10 cm H₂O × ml/s was considered as a high resistance, whereas a cumulative resistance <10 cm H₂O × ml/s was considered as a low resistance. But the decision for high or low resistance also depended on the combined flow and pressure trends. The results for such typical subjects are presented in figures 1 and 2, respectively.

After the measurements, ELVR with complete occlusion of the targeted lobe was performed by placing the endobronchial valves (Zephyr endobronchial valve; Pulmonx, Inc., Redwood City, Calif., USA) as previously described [14–16]. The occurrence of atelectasis was examined by a chest X-ray 24 h after the procedure and high-resolution CT.

Outcome Measures

The primary efficacy endpoint was the feasibility of using the catheter-based system, measured by successful placement and deployment of the catheter and the ability of the console to display measurements of pressure, volume and collateral resistance at the lobar level. The secondary technical endpoint was to assess the correlation between lobar-level collateral resistance measurements and the post-ELVR radiological assessment for pulmonary atelectasis. Due to the limited sample size, Fisher's exact test was used to determine whether there is a statistically significant correlation between resistance and atelectasis. Atelectasis and resistance were used as categorical variables, i.e. presence or absence of atelectasis and high or low resistance, respectively. A p value <0.05 was considered statistically significant. Statistical analysis was performed using STATA 11.0 (College Station, Texas, Tex., USA).

Fig. 1. Results of a patient with high collateral resistance.

Fig. 2. Results of a patient with low collateral resistance.

Table 1. Patient demographic and physiological data (25 patients)

Age	64.6 ± 8.8
Male/female	17/08
FEV ₁ , l	0.96 ± 0.24
FEV ₁ , % predicted	34.27 ± 8.69
FVC, l	2.74 ± 0.68
FVC, % predicted	75.06 ± 14.87
FEV ₁ /FVC	0.36 ± 0.07
RV, l	5.56 ± 1.59
RV, % predicted	235.88 ± 53.11
TLC, l	8.30 ± 1.79
TLC, % predicted	131.46 ± 14.78
TLCO, mmol/min/kPa	2.34 ± 0.98
TLCO, % predicted	27.3 ± 9.78
6-min walk, m	315 (100–565)

Data are presented as mean ± SD or median and range (in parentheses).

Table 2. Factors affecting CV measurement

Patient	Findings
3	Multiple plugs, patient coughing, cannot maintain seal
10	No waveform patterns detected, possibly due to user error, stopcock usage or incorrect positioning of the catheter
11	No waveform patterns detected, possibly due to incorrect catheter positioning or mucus plugs, or obstruction by airway wall
13	No waveform patterns detected, possibly due to incorrect catheter positioning or mucus plugs, or obstruction by airway wall

Results

Baseline Demographics

From June to November 2008, 25 patients with an indication for ELVR were consecutively enrolled.

Preoperative demographics and physiological data are shown in table 1.

Safety Results

All patients were followed up 30 days for adverse events. Six adverse events related to ELVR were reported. These events include pneumothorax (2 cases), pneumonia (1 case), valve migration (1 case), increased dyspnea (1 case), and mild hemoptysis (1 case). All adverse events occurred

during the hospital stay after the procedure. Only 1 of the pneumothorax cases and the patient with pneumonia required prolonged hospitalization for treatment. These adverse events were expected following ELVR.

Efficacy Results

The console was able to measure, calculate and display lobar flow, pressures and collateral resistance in 84% (21/25) of the study subjects. There were 4 subjects for whom the measurements could not be displayed or no conclusions could be drawn due to various factors as described in table 2.

The secondary endpoint was to evaluate the correlation between the predictions derived from the catheter-based measurements and the post-ELVR radiological assessment for pulmonary atelectasis via a chest X-ray recorded 24 h after ELVR. Due to missing data in each category, i.e. presence of atelectasis (patient 23's radiograph could not be assessed for atelectasis because of a pneumothorax) and resistance (4 patients), the final analysis was run on 20 patients, 12 without and 8 with atelectasis. A statistically significant correlation between resistance and presence/absence of atelectasis was found with a p value of 0.02 using a 2-tailed Fisher's exact test.

Table 3 summarizes the measurements. Figure 3 shows an example of high-resolution CT and X-ray images for a patient who developed atelectasis after ELVR.

Discussion

Mendelssohn performed experiments on atelectasis by introducing gum into an animal's bronchi already in 1845. Almost a century later, Van Allen et al. [17] recognized that obstructive pulmonary atelectasis did not occur in every case and hypothesized the existence of collateral ventilation. Collateral ventilation is present in the normal lung, but its importance in the distribution of ventilation is negligible because the resistance to airflow is higher in the collateral channels than in the airway [18], but its importance increases in case of emphysema [19]. The absence of atelectasis following ELVR is due to this phenomenon of collateral ventilation. Therefore, the interest in measuring collateral ventilation increased with the advent of ELVR. To accurately quantify collateral ventilation, the measurement of pressure and flow is needed [20–25]. Based on this theory, a catheter-based endobronchial approach to quantitatively determine the resistance of collateral channels has been proposed [25]. Unlike previous methods which involved pressurizing

Fig. 3. a Chest X-ray (a, b) and corresponding high-resolution CT (c, d) of a 55-year-old patient (patient 12) before (a, c) and after (b, d) ELVR with atelectasis of the right upper lobe.

lung compartments [21], which could be detrimental in patients with hyperinflated emphysema, or using trace gases with a mass spectrometer [26, 27], this technique measures pressures and flows during respiration and calculates the resistance of the collateral channels [13]. Our study is the first clinical trial of these catheter-based measurements of collateral ventilation prior to ELVR. The measurements in the various lobes were safely and successfully achieved in 84% of patients. In 90%, the

measurements directly correlate with the atelectasis visualized on the chest X-ray made after placement of the endobronchial valves. These results show that the catheter-based system for measuring collateral ventilation can be used to effectively preselect patients who will achieve atelectasis and thus benefit from ELVR. Nevertheless, there are some limitations that have to be considered. Measurements in the lower lobes can lead to false results if the inflated balloon occludes the B6 segment. It is hy-

Table 3. Summary of catheter measurements and atelectasis outcomes

Pt. No.	Target lobe	Catheter measurements	Cumulative resistance cm H ₂ O/ml/s	24-hour postop. CXR	Match with catheter-based measurement (yes/no)
1	LLL	HR	>10	atelectasis	yes
2	LLL	HR	>10	atelectasis	yes
3	LLL	unable to assess	–	atelectasis	unable to correlate
4	RUL	LR	<10	no atelectasis	yes
5	RLL	LR	<10	no atelectasis	yes
6	RUL	LR	<10	no atelectasis	yes
7	RUL	LR	<10	no atelectasis	yes
8	RUL	LR	high flow ^a	no atelectasis	yes
9	RML	LR	<10	no atelectasis	yes
10	LLL	unable to assess	–	no atelectasis	unable to correlate
11	LUL	unable to assess	–	no atelectasis	unable to correlate
12	RUL	HR	>10	atelectasis	yes
13	LUL	unable to assess	–	no atelectasis	unable to correlate
14	RLL	HR	>10	atelectasis	yes
15	LLL	HR	>10	atelectasis	yes
16	LLL	HR	>10	atelectasis	yes
17	RML	LR	<10 ^b	atelectasis	yes
18	LLL	HR	low flow ^a	atelectasis	yes
19	LLL	HR	>10	no atelectasis	no
20	RLL	HR	>10	no atelectasis	no
21	RUL	LR	<10	no atelectasis	yes
22	RML	LR	<10	no atelectasis	yes
23	LLL	LR	<10	pneumothorax	unable to correlate
24	LLL	LR	<10	no atelectasis	yes
25	LLL	LR	high flow ^a	no atelectasis	yes

LLL = Left lower lobe; RUL = right upper lobe; RML = right middle lobe; LUL = left upper lobe; RML = right middle lobe; HR = high resistance; LH = low resistance.

^a Resistance calculation not usable due to clog. Decision based on flow and pressure.

^b Patient 17 has previously placed valves in the right upper lobe without achieving atelectasis. Assessment of the right mid-

dle lobe indicated low resistance. The nontarget assessment of the right lower lobe indicated high resistance, confirming that the right upper lobe and the right middle lobe were communicating. Following placement of valves into the right middle lobe, the ‘right upper lobe + right middle lobe unit’ should now achieve atelectasis.

Fig. 4. Inaccurate assessment due to B6 exclusion.

pothesized that if the isolation balloon of the catheter inadvertently occludes the B6 segment while assessing the collateral flow from the lower lobes, the result could be misleading since the contribution of flow from the B6 segment is not taken into account. Figure 4 describes the potential issues while assessing the lower lobes related to balloon positioning.

Furthermore, multiple mucus plugs can complicate the correct placement of the catheter, making the measurements impossible. Another issue is the increase in the collateral ventilation by opening the collateral channels following the occlusion of the targeted lobe by ELVR. Currently, it is not possible to measure the collateral ventilation after placement of the valves.

In conclusion, the catheter-based system enables quantification of collateral ventilation and was predictive of whether ELVR would be successful. For evaluation of physiological and functional improvements, larger randomized controlled trials are warranted.

Conflict of Interest

This study was supported by Pulmonx, Inc., Redwood City, Calif., USA, with equipment and devices. A.E. received travel support to participate in the study. No author has any ownership interest in the company and had full access to the data. The company had no editorial influence on the manuscript and only reviewed the draft for potential release of proprietary information.

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