Validation and pilot clinical study of a new bronchoscopic method to measure collateral ventilation before endobronchial lung volume reduction

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Submitted 10 August 2008; accepted in final form 21 November 2008

Aljuri N, Freitag L. Validation and pilot clinical study of a new bronchoscopic method to measure collateral ventilation before endobronchial lung volume reduction. J Appl Physiol 106: 774–783, 2009. First published November 26, 2008; doi:10.1152/japplphysiol.91075.2008.—Endobronchial lung volume reduction (ELVR) may be helpful in a selected group of patients with advanced stages of emphysema. However, collateral ventilation (CV) from adjacent lobes through collateral channels often prevents target lobe atelectasis, which presumably mediates clinical responses after ELVR. With the goal of identifying patients who are more or less likely to benefit, we propose endobronchial CV assessment (ECVA), a novel catheter-based endobronchial approach, to quantitatively determine the resistance of collateral channels (Rcoll). ECVA relies on measurement of the spontaneous airflow from the sealed and isolated target compartment during spontaneous respiration in an awake subject, thereby providing a direct, simple, and minimally invasive method of assessing Rcoll in lungs. In this study, we validated ECVA in a controlled laboratory setup and tested ECVA’s clinical feasibility in 11 emphysematous human subjects undergoing ELVR treatment. To evaluate ECVA in a controlled laboratory setup with known CV levels, we built a benchtop model mimicking a simple one-compartment model of the lungs during temporary compartmental occlusion and spontaneous respiration, which could be adapted to hold restrictors of different sizes representing collateral airways, and applied ECVA to estimate the resistance of various benchtop model restrictors. We then rated ECVA’s performance by direct comparison between estimated and actual restrictor resistance and found a correlation coefficient near one. To test ECVA’s clinical performance, post-ELVR radiological assessments were made to determine the occurrence of atelectasis in the treated lobe, and interlobar Rcoll was estimated in the target lobe via ECVA pre-ELVR. ECVA could be completed in all patients with no adverse events, and a high Rcoll by ECVA predicted absorption atelectasis following ELVR (P = 0.005). We believe that ECVA may be helpful to distinguish those patients with and without interlobar CV by identifying the critical value of Rcoll above which atelectasis is likely to occur.

collateral resistance; minimally invasive; emphysema; absorption atelectasis; patient selection

RECENT ADVANCES IN THE TREATMENT of chronic obstructive pulmonary disease (COPD) have led to a heightened interest in collateral ventilation (CV). Open, surgical resection of the most emphysematous lung regions has been shown to improve lung function, exercise tolerance, and quality of life symptoms in carefully selected, hyperinflated emphysema patients (3). However, because of the morbidity of this major surgical procedure, various bronchoscopic COPD treatments are in development to facilitate the removal of trapped air and reduce hyperinflation. The concept guiding these approaches is that absorption atelectasis of emphysematous lung regions can reduce lung volume without the need to remove tissue. One such type of COPD treatment is endobronchial lung volume reduction (ELVR), which uses a catheter-based system to endobronchially reduce lung volume. With the aid of fiberoptic visualization and specialty catheters, a physician can selectively collapse a segment or segments of the diseased lung. An occlusive implant is then positioned within the lung segment to prevent the segment from reinflating. The greatest improvement in lung function has been measured in patients who develop radiologically visible atelectasis after ELVR (8). Unfortunately, only a minority of patients undergoing ELVR develop atelectasis. As a result, overall treatment responses to ELVR have been modest at best (24, 25). CV across lung lobes is the postulated explanation for the failure of previous endobronchial techniques to induce absorption atelectasis of the target area (2, 21). In the presence of CV, air can enter the target lobe through collateral channels, preventing atelectasis. Collateral channels that cross lobar fissure have been described in normal and emphysematous lungs, occurring in up to two-thirds of patients with emphysema (5, 7). Preprocedural measurement of the collateral resistance (Rcoll) of potential target lobes may allow selection of the best lobes or patients most likely to benefit from ELVR. In this study, we propose endobronchial CV assessment (ECVA), a novel catheter-based endobronchial approach, to quantitatively determine the resistance of the collateral channels (Rcoll) in human lungs. ECVA relies on measurement of the spontaneous flow of air from the sealed and isolated target compartment during normal, spontaneous respiration in an awake subject, thereby providing a direct, simple, and minimally invasive method of assessing Rcoll in lungs.

The aims of this study are as follows: 1) present ECVA and its mathematical analysis; 2) validate ECVA’s ability to discriminate between different known degrees of CV; 3) test ECVA’s clinical feasibility; and 4) evaluate ECVA’s performance in a clinical setting. To validate ECVA in a controlled laboratory setup with known degrees of CV, we first built a benchtop model mimicking a simple, one-compartment model of the lungs during temporary compartmental occlusion and simulated spontaneous respiration, which could be adapted to hold restrictors of different sizes representing the collateral airways. We subsequently correlated Rcoll values as measured by ECVA and independent means. To test the clinical feasibility of ECVA, we attempted ECVA in 11 emphysematous human subjects undergoing ELVR treatment of a target lobe before device implantation. Finally, to evaluate ECVA’s per-
formance in a clinical setting, we made post-ELVR radiological assessments to determine the occurrence of absorption atelectasis in the treated lobe and correlated this outcome with the degree of interlobar CV present in the target lobe estimated via ECVA before ELVR treatment.

**ECVA**

Our method requires temporary obstruction of a bronchus with a balloon catheter introduced through the working channel of the bronchoscope to isolate a target compartment from the rest of the lung and use of a one-way valve at the proximal end of the catheter system, while airflow through the catheter system (Q\text{cath}) and pressure (P\text{cath}) are continuously monitored at the distal end of the one-way valve. ECVA can best be described via the simple one-compartment model illustrated in Fig. 1, where a one-way valve prohibits passage of air during inspiration (Fig. 1A) and permits airflow during expiration (Fig. 1B). A balloon composed of a rigid neck and an elastic bag representing the target lung compartment C is securely positioned inside a chamber, which can be pressurized to varying subatmospheric pressures to represent the pleural pressure (P\text{pl}). A balloon catheter seals the area between the catheter shaft and the balloon neck, such that only the lumen inside the catheter, which extends the length of the catheter and represents airway resistance (R\text{aw}), allows for direct communication between the sealed compartment and atmosphere. On the opposite end of the catheter, a flow-measuring device and a pressure sensor are placed in series to detect air pressure and flow in the catheter’s inside lumen. A one-way valve positioned next to the pressure sensor allows for the passage of air.

**Fig. 1.** One-compartment model of the lungs during temporary compartmental occlusion demonstrating inspiratory and expiratory phases of the respiratory cycle after running the model for enough cycles to reach a steady state in the system. A: one-compartment pneumatic model during the inspiratory phase. B: one-compartment pneumatic model during the expiratory phase. C: model’s collateral flow (Q\text{coll}). D: model’s airflow through the catheter system (Q\text{cath}). E: model’s compartmental pressure (P\text{c}) and catheter pressure (P\text{cath}). R\text{coll}, resistance of collateral channels; P\text{pl}, pleural pressure; R\text{aw}, airway resistance; C, capacitance element. Refer to main text for details and definition of other acronyms.
in only one direction, namely from the elastic compartment to atmosphere during expiration. The elastic compartment, however, continuously communicates with the atmospheric environment through $R_{coll}$.

Figure 1C shows flow through the collateral pathway ($Q_{coll}$), and Fig. 1D depicts $Q_{cath}$. During inspiration (valve is closed) and in the presence of collateral channels, atmospheric air moves into the sealed compartment solely through collateral channels from surrounding lung as a result of the pressure gradient created by inspiration against a closed one-way valve. During expiration, the valve opens, and compartmental air is exhaled through both collateral channels and the catheter system, depending on these two components’ relative resistances. As a result, the only flow into the sealed compartment is through the collateral channels. Visual inspection of the pressure signals depicted in Fig. 1E shows that, during the inspiratory phase, $P_{cath}$ equals compartmental pressure ($P_c$), since no air can enter or leave the isolated compartment via the catheter’s inside lumen. During expiration, however, $P_{cath}$ equals 0, since it is measured at the valve opening where pressure is atmospheric, while $P_c$ must still overcome the resistive pressure losses produced by the passage of flows through the catheter’s inside lumen and collateral channels, as graphically illustrated by the yellow-colored area in Fig. 1E. At steady state, air through the collateral channels continues to flow out of the catheter system, and the outflow through the one-way valve must equal the inflow. Therefore, mean $P_{cath}$, $P_{cath}$ divided by mean $Q_{cath}$, $Q_{cath}$, provides an estimate for the resistance through the serial airway circuit composed of $R_{aw}$ and $R_{coll}$. Please refer to the APPENDIX for a mathematical analysis of the model.

MATERIALS AND METHODS

Benchtop Validation

Experimental procedures. Five tubes of varied length and diameter designed to produce resistances varying from $\sim 1$ to 100 cmH$_2$O·m$^{-1}$·s$^{-1}$ were used. Pressure-flow relations were plotted using controlled flows from 0–10 ml/s and fitted to Rohrer’s equation $P = aQ + bQ^2$, where $P$ is pressure, $Q$ is flow, and $a$ and $b$ are constants related to tube geometry, gas viscosity, and gas density (18). Measured pressures closely matched the line fit by Rohrer’s equation ($r^2 > 0.9996$), as graphically illustrated in Fig. 2A. The resistances measured at the mean flows shown in Fig. 2B ranged from 0.8 to 96.5 cmH$_2$O·m$^{-1}$·s$^{-1}$.

A benchtop model, as illustrated in Fig. 1, was built to test the proposed method to measure CV. A plastic tube representing the target airway was securely connected to a Plexiglas chamber simulating the pleural cavity, and an elastic balloon (Qosina-liter breathing bag) was attached to the lower portion of the plastic tube to simulate the target lung compartment. To recreate flow and pressure fluctuations consistent with spontaneous respiration, a vacuum generator (Cole Parmer 78165-20) and a respirator pump (Harvard Apparatus 55-0715) connected to the pleural chamber were configured to inflate and deflate the balloon, with negative pressures oscillating at a frequency of 20 breaths/min. A balloon catheter (TACTX Medical, inner diameter = 1.88 mm, length = 115 cm) was inserted into the plastic tube and inflated to seal the target airway. To monitor flow and pressure in the catheter’s inside lumen, $Q_{cath}$ and $P_{cath}$, the proximal end of the catheter was connected in series with a flow meter (Honeywell International Awm3303V), together with a pressure sensor (Honeywell International 143PC01D) and a one-way valve (Parker Hanninfin 990-001439-001), which could be electronically triggered to shut during expiration once $Q_{cath}$ became slightly negative, and to open during expiration once $P_{cath}$ slightly exceeded zero. A connector pipe adapted to hold different restrictors representing the collateral airways was securely attached to the distal portion of the target airway in between the target airway seal and the elastic balloon to provide for an alternative passage of air from atmosphere to the target compartment. Restrictor resistance was separately measured by applying the proposed method to quantitatively determine CV during a 3-min assessment period. To measure the catheter resistance ($R_0$), no restrictor was connected to the connector pipe. To reproduce the case with no CV, namely $R_{coll} = \infty$, the connector pipe was closed to prohibit passage of air from and to atmosphere.

Data analysis. $Q_{cath}$ and $P_{cath}$ were continuously recorded digitally in a personal computer, and data analysis was completed using Matlab (Matlab version 7, MathWorks). The recorded signals were sampled at 100 Hz and passed through a digital low-pass filter to remove the high-frequency respiratory variations. Restrictor resistance was estimated by ECVA for each restrictor as $P_{cath}$ divided by $Q_{cath}$, where $P_{cath}$ and $Q_{cath}$ represent the filtered $P_{cath}$ and $Q_{cath}$ signals, respectively, averaged over the last 30 s of the assessment period.

Clinical Feasibility

ECVA was attempted in 11 emphysematous human subjects (36% men, age 59 ± 5 yr) undergoing ELVR treatment of a target lobe before device implantation at the Lungenklinik Hemer (Germany),...
and post-ELVR radiological assessments were made by the hospital radiologist by visual inspection of computed tomography images (Fig. 3) taken 14 days after complete lobar occlusion to determine the occurrence of absorption atelectasis in the treated lobe. Ethics committee approval was obtained before subject enrollment, and informed consent was obtained from all participants. All subjects underwent ECVA of the target lobe during a routine bronchoscopy procedure while breathing spontaneously. The radiologist judging the presence of atelectasis in the treated lobe. Ethics committee approval was obtained before subject enrollment, and informed consent was obtained from all participants. All subjects underwent ECVA of the target lobe during a routine bronchoscopy procedure while breathing spontaneously. The radiologist judging the presence of atelectasis in the treated lobe. 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All subjects had severe pulmonary dysfunction (vital capacity: 2.6 ± 0.9 liters, 78 ± 20%; forced expiratory volume in 1 s: 0.9 ± 0.3 liter, 35 ± 8%; total lung capacity: 7.3 ± 1.3 liter, 132 ± 21%; residual volume: 4.7 ± 0.6 liters, 230 ± 29%; and carbon monoxide diffusion capacity: 2.6 ± 0.8 mmol·min⁻¹·kPa⁻¹, 31 ± 8%), depressed exercise capacity [6-min walking distance (6MWD): 278 ± 112 m, bicycle load: 37 ± 11 W], and impaired quality of life (St. George Respiratory Questionnaire: 55 ± 14). Patients were included if they were potential candidates for lung volume reduction surgery by virtue of meeting the following criteria: forced expiratory volume in 1 s < 45% predicted, total lung capacity > 100% predicted, residual volume > 145% predicted, carbon monoxide diffusion capacity 20–80% predicted, recently completed a 6-wk course of pulmonary rehabilitation and radiological evidence of bilateral emphysema (by computed tomography scan). Subjects were excluded if they were current smokers or had smoked within the last 6 mo, had homogeneous emphysema, bullae > 30% of the lung, α1 antitrypsin deficiency, previous lung volume reduction surgery, pleural or interstitial lung disease, clinically significant bronchiectasis, malignancy, non-upper lobe emphysema with high baseline exercise capacity, cardiovascular disease, or other comorbidities.

RESULTS

Benchtop Validation

We found that ECVA was able to effectively discriminate among the different resistance levels tested, as graphically illustrated in Fig. 4. Figure 4A displays resistance estimated from the filtered Q_cath and P_cath signals using ECVA for the catheter (R0 = 0.8 cmH2O·ml⁻¹·s⁻¹) and all restrictors. Figure 4B exhibits a graphical comparison between the actual and estimated resistance values, demonstrating a correlation coefficient near one.

Clinical Feasibility

ECVA could be completed in all 11 subjects in whom it was attempted. No subject had an adverse event as a result of ECVA. A total of four subjects (36%) developed target lobe atelectasis after ELVR treatment. We found that a high resistance measured by ECVA predicted atelectasis following the ELVR procedure. An unpaired Student’s t-test on the resistances in the groups who did and did not develop atelectasis yielded a statistical significant difference (P = 0.005) between the groups. Figure 5 demonstrates that the four subjects who developed atelectasis had relatively large mean resistances (161 ± 43.8 cmH2O·ml⁻¹·s⁻¹), whereas all seven subjects who did not develop atelectasis yielded substantially different mean resistances two orders of magnitude smaller (1.2 ± 0.98 cmH2O·ml⁻¹·s⁻¹). Figure 6 displays a representative ECVA example of one subject who did not develop atelectasis after ELVR treatment of the right upper lobe. In contrast, Fig. 7 shows a representative ECVA example of one subject who developed atelectasis after ELVR treatment of the right upper lobe. Specifically, Fig. 6 demonstrates that, in the presence of significant CV, airflow out of the catheter is incessant and resistance is finite, whereas with minimal (or in the absence of) CV as indicated in Fig. 7, airflow drops to nearly zero and resistance rapidly rises. Table 1 shows mean baseline values with standard deviations in subject resistance, pulmonary function tests, exercise capacity, and quality of life parameters by atelectasis status.

Fig. 3. X-ray and computed tomography images before and after endobronchial lung volume reduction (ELVR) treatment of right upper lobe (RUL). The posttreatment computed tomography scan shows two implants in the RUL bronchi, as well as prominent absorption atelectasis (high lightened region with gray border). With RUL atelectasis, the right middle (RML) and right lower lobe (RLL) have expanded. The chest X-ray shows right hemidiaphragm elevations as well. LUL, left upper lobe.
CV can be assessed in vivo by several methods. One such method uses an inert-gas technique, whereby air is sampled from a sealed target lobe while the patient is inhaling heliox (15, 16). Detecting helium with a mass-spectrometer in the sampled air proves the presence of significant collateral flow. This technique requires a mass spectrometer and is not quantitative. Specifically, if gas entered a small segment compared with a large one, the same volume of collaterally transferred gas would lead to a greater percent rise in helium concentration, incorrectly indicating a difference in $R_{coll}$. A variety of other catheter-based methods to detect CV have been used in the past, but the simplest and most versatile way to assess CV was first described by Hilpert in 1970 (6). Hilpert’s method involves forcing a constant airflow into the lungs after sealing the spontaneous flow of air from the sealed and isolated target compartment during normal, spontaneous respiration in an awake subject, thereby providing a direct, simple, and minimally invasive method of quantitatively assessing $R_{coll}$ in lungs. The one-way valve present in the system transiently mimics the same physiological conditions to which a target lobe would be subjected after ELVR, thereby testing the potential for target lobe absorption atelectasis to develop if treated.

Low $Q_{cath}$ does not automatically mean low CV, as it may be possible to measure low $Q_{cath}$ during different situations having completely opposite meanings. For instance, net $Q_{cath}$ may be low because $Q_{coll}$ is low due to a high $R_{coll}$. However, net $Q_{cath}$ may also be low because net $Q_{coll}$ is low due to a low $R_{coll}$. Namely, with a low $R_{coll}$, the amplitude of $Q_{coll}$ traveling back and forth via collateral channels is high, but the net pressure differential across the collateral channels is low, and net $Q_{coll}$ (hence net $Q_{cath}$) traveling back to atmosphere through the catheter is low. Accordingly, a prediction just based on low $Q_{cath}$ would result in the prediction of both a high and a low CV. Measurement of pressure is, therefore, needed to avoid this ambiguity and to provide a measurement that uniquely separates high from low CV. This measurement is $R_{coll}$.

During ECVA, airflow has two phases: 1) an emptying phase, during which excess native air empties from the isolated lung compartment; and 2) a steady-state phase, in which air is drawn into the isolated lung compartment through collaterals.
(if they exist) during inspiration and exits the catheter during expiration. Figure 6 illustrates, with measured human data, how with substantial interlobar CV present, the emptying phase is of short duration and steady-state flow through existing collateral channels is reached quite rapidly. As a result, target lobe emptying is minimal. In contrast, Fig. 7 indicates that, with considerably less interlobar CV, while target lobe emptying may be significant, the interpretation of the emptying mechanism appears to be more complex and grants at least two plausible explanations. 1) Measured flows and pressures fluctuate between emptying and steady-state phases, consistent with asynchronous emptying of separate air pockets within the

Fig. 6. ECVA example of physiological measures (pre-ELVR) in a human subject who did not develop target lobe atelectasis after ELVR treatment of the RUL, showing considerable collateral ventilation (CV). Dashed lines denote measured catheter flow and pressure signals passed through a digital low-pass filter to remove the high-frequency respiratory variations.

Fig. 7. ECVA example of physiological measures (pre-ELVR) in a human subject who developed target lobe atelectasis after ELVR treatment of the RUL, showing negligible CV. Dashed lines denote measured catheter flow and pressure signals passed through a digital low-pass filter to remove the high-frequency respiratory variations.
Target lobe. Emptying of hyperinflated segments may allow previously partially compressed and/or fully isolated neighboring segments to expand. Such expansion may "tent open" segmental airways, resulting in decreased expiratory obstruction and subsequent emptying of the previously isolated segments. 2) Partially empty parts of the isolated lobe may refill as the patient takes more vigorous breaths. As regions empty completely, airways and/or collateral channels close and more vigorous efforts no longer refill these regions, since inspiratory efforts may no longer be sufficient to exceed their critical opening pressure. The two explanations above are not mutually exclusive, and both mechanisms may operate.

The two clinical examples in Figs. 6 and 7 not only indicate that the target lobe experiences some degree of volume reduction during the emptying phase of the assessment period, but also that lobar emptying is determined by the degree of interlobar CV, as expected. Moreover, the observed volume reduction occurs quite rapidly and independently from absorption atelectasis, since it is not the relatively slow gas absorption that causes air emptying during the assessment period from the isolated lung compartment: it is simply native lobar air escaping through the assessment catheter. For illustration purposes only, Fig. 8A graphically demonstrates the transition between the emptying and steady-state phases in $Q_{\text{cat}}$ by means of a computer-generated $Q_{\text{cat}}$ signal obtained from running the model in Fig. 1 and subsequently low-pass filtering $Q_{\text{cat}}$ to remove the high-frequency respiratory variations. The shaded area near the start of the assessment period denotes compartmental volume reduction occurring during the emptying phase, given a moderate degree of CV. Toward the end of the assessment period, once $Q_{\text{cat}}$ has reached a steady state, $Q_{\text{cat}}$ equals collateral flow. Compartmental volume reduction dependency on CV during the assessment period can be illustrated, for example as in Fig. 8B, by means of successively running the model in Fig. 1 with varying degrees of CV and plotting the resulting compartmental volume reduction as a function of $R_{\text{coll}}$.

Despite the fact that ECVA predicted atelectasis, interestingly, our results imply that complete absence of collateral

Fig. 8. Graphical representation of volume reduction dependency on CV during the assessment period. A: transition between the emptying and steady-state phases in $Q_{\text{cat}}$ by means of a computer-generated $Q_{\text{cat}}$ signal obtained from running the model in Fig. 1 and subsequently low-pass filtering $Q_{\text{cat}}$ to remove the high-frequency respiratory variations. The shaded area near the start of the assessment period denotes compartmental volume reduction occurring during the emptying phase, given a moderate degree of CV. Toward the end of the assessment period, once $Q_{\text{cat}}$ has reached a steady state, $Q_{\text{cat}}$ equals collateral flow. B: compartmental volume reduction dependency on CV during the assessment period by means of successively running the model in Fig. 1 with varying degrees of CV and plotting the resulting compartmental volume reduction as a function of $R_{\text{coll}}$.

Table 1. Subject parameters

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<th>Subject parameter</th>
<th>ATL+</th>
<th>ATL−</th>
<th>P Value</th>
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<tr>
<td>Age, yr</td>
<td>62±7.5</td>
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<td>VC, liters</td>
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<td>VC, %predicted</td>
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<td>RV, liters</td>
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<td>RV, %predicted</td>
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<tr>
<td>RV/TLC</td>
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<tr>
<td>DLco, %predicted</td>
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<td>SGRQ</td>
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</tr>
<tr>
<td>Bicycle load, W</td>
<td>41±10.3</td>
<td>34±11.3</td>
<td>0.334</td>
</tr>
</tbody>
</table>

Values are means ± SD in resistance by endobronchial collateral ventilation assessment (ECVA), age, body mass index, pulmonary function tests, quality of life, and exercise tolerance by atelectasis status at baseline; n, no. of subjects. ATL+, atelectasis, ATL−, no atelectasis; R, resistance by ECVA averaged over the 3-min assessment period; BMI, body mass index; VC, vital capacity; FEV1, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; DLCO, diffusion capacity for carbon monoxide; SGRQ, St. George Respiratory Questionnaire; 6MWD, 6-min walking distance. P values compare mean changes in ATL+ vs. ATL− groups.
channels may not be a prerequisite for absorption atelectasis of a treated lung compartment to take place. Volume reduction via absorption atelectasis occurs because the net rate of gas transfer from the sealed lung compartment into the blood perfusing this lung compartment exceeds the collateral airflow into the target compartment. Accordingly, a critical $R_{\text{coll}}$ ($R_{\text{crit}}$) must exist below which collateral airflow into the sealed compartment exceeds its absorptive capacity and atelectasis does not occur. The results presented in Fig. 5, although preliminary, support this hypothesis. All four subjects who developed target lobe atelectasis post-ELVR treatment had finite resistances significantly different from the seven subjects who did not: $161 \pm 43.8$ vs. $1.2 \pm 0.98 \text{ cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$. We cannot rule out, however, that, with longer assessment periods, $R_{\text{coll}}$ in the four subjects who developed atelectasis would have become infinite.

An apparent limitation of ECVA is that it cannot distinguish between an elevated $R_{\text{coll}}$ and an elevated $R_{\text{aw}}$; however, the values of $R_{\text{aw}}$ reported in the literature are too small ($0.0001$–$0.3 \text{ cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$) to merit the need for this distinction. For instance, Hogg et al. (7) measured $R_{\text{aw}}$ and $R_{\text{coll}}$ in incomplete interlobar fissures of normal and emphysematous excised human lungs and found lobar $R_{\text{aw}}$ ranging between $0.01$ and $0.3 \text{ cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$ in the emphysematous lungs and lobar airway resistance smaller than $0.001 \text{ cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$ in the normal lungs. Other investigators (9, 19, 20) believe that, although $R_{\text{aw}}$ could exceed $R_{\text{coll}}$ in emphysematous subjects, causing air to flow preferentially through collateral pathways, this was only the case for very low $R_{\text{coll}}$, namely $R_{\text{coll}} < 0.01$. These reported values for $R_{\text{aw}}$ are considerably lower than the resistance of the bronchoscopic catheter, making the need to effectively and accurately discriminate between an elevated $R_{\text{coll}}$ and an elevated $R_{\text{aw}}$ in this context practically unnecessary. Since the bronchoscopic $R_0$ is already known, even a greatly increased $R_{\text{aw}}$ would not significantly contribute to ECVA’s estimate for the resistance through the airway circuit composed of collateral channels, airways, and the bronchoscopic catheter, and virtually all measurable fluctuations in ECVA’s resistance would have to be due to changes in $R_{\text{coll}}$. In this study, the clinical data suggest that ECVA’s resistances around $3 \text{ cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$ and below can be considered low, and therefore subjects with these resistances are not likely to develop atelectasis, whereas resistances around $100 \text{ cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$ and above can be considered high (perhaps indicating lack of interlobar collateral channels), and subjects with these resistances are prone to develop atelectasis. Given this range and order of magnitude, the only way ECVA’s resistance can be measurably elevated is if it is due to an increase in $R_{\text{coll}}$, since any reasonable increase in $R_{\text{aw}}$ would be negligible and considered to be within the margin of measurement error. As a result, it is not surprising that the elevated resistances measured by ECVA in emphysema patients seem to reliably predict the occurrence of atelectasis, albeit in a small group of patients.

The gray area in Fig. 5 depicts a rather wide transition zone, where $R_{\text{crit}}$ may reside and very well vary from patient to patient, since it should depend on each target lobe’s absorptive capacity. As the goal of ECVA would be to identify patients who are more or less likely to benefit, we recognize that, although ECVA was clinically feasible and yielded encouraging results, larger clinical studies are necessary to support this extreme separation illustrated in Fig. 5 or, alternatively, narrow this transition zone. Either way, the result would be a robust $R_{\text{crit}}$ zone common to COPD patients undergoing ELVR treatment above which atelectasis must occur and below which no atelectasis can take place if treated. Ultimately, ECVA could prove very useful in identifying those patients on whom ELVR treatment would be successful; ELVR would only be attempted in patients with interlobar $R_{\text{coll}}$ greater than $R_{\text{crit}}$. Even though patients who do not develop complete lobar atelectasis may still benefit from ELVR if their functional residual capacity and dynamic hyperinflation with exercise are reduced, target lobe atelectasis seems to be the major mediator of response to ELVR treatment. As a result, lack of interlobar collateral channels (or substantially reduced interlobar CV) provides a treatment advantage.

Even though the subject numbers are small, it is noteworthy that the group of patients with atelectasis seems to be less severely impaired at baseline (Table 1). Not only did this group yield greater $R_{\text{coll}}$ values during ECVA, but also baseline 6MWD values were significantly different from those of the group without atelectasis ($P = 0.018$). Although not significant, all baseline pulmonary function tests, exercise tolerance, and quality of life values for the group with atelectasis consistently indicate that patients who developed atelectasis after ELVR were in a less advanced disease stage. This is consistent with the notion that, as emphysema becomes more severe, more collateral channels may appear. Except for a small difference in 6MWD, no baseline measurement except ECVA was able to distinguish patients who would or would not develop atelectasis. Furthermore, the trend toward worse lung function in patients who had low resistance and failed to develop atelectasis suggests that there may be a window of impairment within which ELVR is useful. Once emphysema is too severe and $R_{\text{coll}}$ too low, this procedure may no longer be effective.

**Summary and Conclusions**

This study provides a theoretical framework and validation of a new bronchoscopic method to quantitatively determine the collateral channel resistance in lungs of spontaneously breathing subjects. ELVR remains a promising treatment for patients with emphysema, and the present study is the first to use any method to predict the outcome from ELVR treatment. Target lobe atelectasis appears to predict the clinical response to ELVR treatment, and interlobar CV is probably the major cause of failure to obtain target lobe atelectasis after ELVR. As such and in view of the results presented in this study, we believe that ECVA may be helpful to distinguish those patients with and without interlobar CV by identifying, before ELVR treatment, the critical value of interlobar $R_{\text{coll}}$, $R_{\text{crit}}$, above which target lobe atelectasis can occur. However, more clinical studies are necessary to further evaluate ECVA with a larger number of patients in its ability to successfully and consistently provide a predictable outcome that can be used to guide ELVR treatment and patient selection.

**APPENDIX**

**Mathematical Analysis**

Referring to Fig. 1, conservation of mass states that, once steady state has been reached, the total volume of air entering the target compartment during inspiration must equal the total volume of air...
leaving the same target compartment during expiration. During inspiration, air flows through the collateral pathway only; no air flows through the flow-measuring device, since the one-way valve prevents such flow. The total volume of air $V_0$ entering and inflating the target compartment via collateral channels during inspiration can be represented by the colored area enclosed by the negative $Q_{\text{coll}}$ curve in Fig. 1C, where $V_0$ may be denoted as

$$V_0 = V_1 + V_2$$  \hspace{1cm} \text{(A1)}

where $V_1$ may be defined as the fraction of $V_0$ entering the target compartment via the collateral channels and returning to atmosphere through the same pathway during expiration (indicated in Fig. 1D by the gray-shaded area under the positive $Q_{\text{coll}}$ curve labeled $V_3$), so that $V_2$ must equal the volume of air expelled via the catheter’s inside lumen during expiration (indicated by the yellow-colored area under the positive $Q_{\text{cath}}$ curve of Fig. 1D labeled $V_4$). Accordingly,

$$V_3 = -V_1$$  \hspace{1cm} \text{(A2)}

and

$$V_4 = -V_2$$  \hspace{1cm} \text{(A3)}

As a result, during a complete respiratory cycle, $T$, the net flow rate of air entering the target compartment via the collateral channels and returning to atmosphere through the catheter can be represented as

$$Q_{\text{cath}} = \frac{V_4}{T}$$  \hspace{1cm} \text{(A4)}

whereas the net collateral flow rate can be represent as

$$Q_{\text{coll}} = \frac{V_2}{T}$$  \hspace{1cm} \text{(A5)}

Hence substitution of $V_4$ from Eq. A3 into Eq. A4 yields

$$Q_{\text{coll}} = -Q_{\text{cath}}$$  \hspace{1cm} \text{(A6)}

demonstrating that the net flow of air captured by the flow measurement device is identical in magnitude to the net flow of air through the collateral channels.

ECVA can also be described by the simple lumped parameter electrical model analog illustrated in Fig. 9, where an on and off switch, which is closed during expiration and opens during inspiration, characterizes the one-way valve. The air storage capacity of the alveoli confined to the isolated compartment is designated as a capacitance element $C$. The viscous pressure loss from the alveoli to atmosphere ($P_{\text{aw}}$) caused by the passage of airflow through the small bronchial airways and catheter system is represented by resistor $R_{\text{aw}}$, while the pressure gradient from the alveoli to atmosphere ($P_c$) generated by the resistance to collateral flow through the collateral pathway is represented by resistor $R_{\text{coll}}$. A variable pressure source responsible for the $P_{\text{pl}}$ fluctuations exerted during spontaneous respiration drives the system.

In the steady state, the model in Fig. 9 effectively behaves like a simple serial flow circuit, where the same exact volume of air entering the target compartment from atmosphere during inspiration via collateral channels travels back to atmosphere during expiration through the catheter’s inside lumen. Accordingly, $P_c$ represents the mean inflation pressure in the target compartment, and $P_{\text{cath}}$ denotes the mean pressure necessary to overcome the viscous pressure losses produced by the movement of this air volume through the serial circuit composed of $R_{\text{coll}}$ and $R_{\text{aw}}$. Therefore

$$P_{\text{cath}} = \frac{Q_{\text{coll}} \cdot R_{\text{coll}} - Q_{\text{cath}} \cdot R_{\text{aw}}}{P_c}$$  \hspace{1cm} \text{(A7)}

where substitution of $Q_{\text{coll}}$ from Eq. A6 into Eq. A7 and subsequently solving for resistance finally results in

$$R_{\text{aw}} + R_{\text{coll}} = -\frac{P_{\text{cath}}}{Q_{\text{cath}}}$$  \hspace{1cm} \text{(A8)}

DISCLOSURES

N. Aljuri is a consultant to Pulmonx and reports stock ownership in the company. L. Freitag received a research and educational grant from Pulmonx to support his laboratory and reports stock ownership in the company.

REFERENCES


