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Bronchoscopic Measurement of Collateral Ventilation in a Sheep Model of Emphysema

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For editorial comment see p. 493

Key Words
Bronchoscopy · Collateral ventilation · Emphysema · Lung volume reduction · Papain · Sheep

Abstract
Background: The development of bronchoscopic therapies for emphysema has renewed interest in collateral ventilation. The success or failure of bronchoscopically placed valves or biologic glues may be determined by collateral ventilation, which is exaggerated in emphysema. Furthermore, the validity of various animal models of emphysema for testing such techniques must be understood in the context of their species-specific collateral ventilation. ***Objectives:*** To quantify collateral ventilation in a sheep model of emphysema using a simple in vivo bronchoscopic method. ***Methods:*** Collateral ventilation was measured in 8 anesthetized sheep using a simple method which measured pressure and flow through the working channel of a bronchoscope wedged in a segmental lung orifice. Animals then underwent nebulized papain treatments to generate emphysema, followed by repeat bronchoscopic measurements. ***Results:*** There was a 33% decrease in resistance to collateral ventilation following papain treatment. Changes in collateral resistance were closely correlated with disease severity as measured by changes in segmental compliance, which increased 267%. ***Conclusions:*** Collateral ventilation is significantly increased in sheep following nebulized papain. Bronchoscopic measurement of collateral ventilation may be useful for evaluating other animal models of emphysema and for predicting the response to bronchoscopic therapies in human emphysema patients.

Introduction

Collateral ventilation refers to the ventilation of gas-exchanging airspaces via pathways other than the regular branching airways. Although the pores of Kohn were first described in the 19th century, the existence of collateral ventilation was not described until 1930, when Van Allen noted that segmental obstruction did not always result in atelectasis [1]. Subsequently, interbronchiolar and bronchiole-alveolar collateral channels were described in addition to the interalveolar pores of Kohn. The resistance of these pathways has been measured via a number of techniques across species including sheep, dog, pig, horse, and humans (see table 1). In humans, the resistance of the collateral channels was found to be 714–3,060 cm H_2O/

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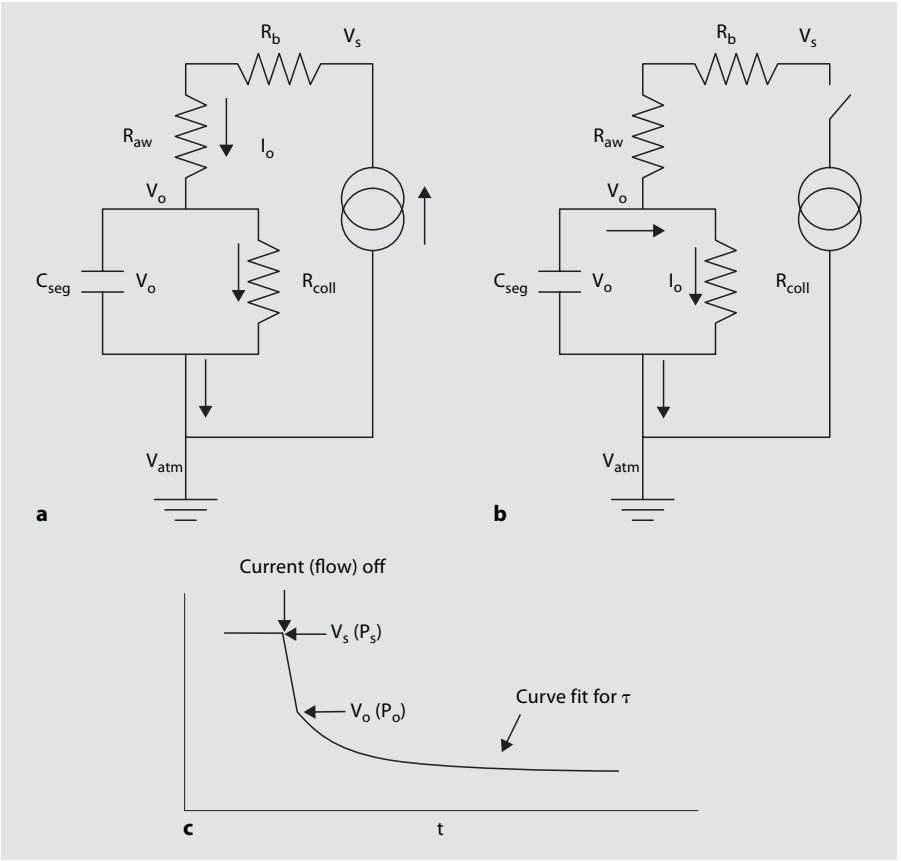

Fig. 1. Electrical circuit model of the bronchoscopic method for measuring collateral resistance. The gas source is depicted as a current source, the bronchoscope, airways, and collateral pathways as separate resistors (R_b, R_{aw}, and R_{coll}), and the elastic lung tissue as a capacitor. **a** With flow on, V_s is the voltage proximal to the bronchoscope at steady state (equivalent to P_s). V_o is the voltage across the capacitor at steady state, which must also equal the voltage across R_{coll}. **b** Immediately after interruption of flow, V_o is unchanged, therefore I_o is unchanged. Because there is no current across R_{aw} or R_b, V_s equals V_o (equivalent to P_o). **c** An idealized pressure time-time tracing showing P_s, P_o, and the segment used to calculate τ.

l/s [2–4], or approximately 100–500 times the resistance of the regular branching airways. However, in emphysema, while airway resistance is typically increased, collateral resistance may be as low as 5–16 cm H_2O/l/s [3–5], less than the resistance of the regular branching airways. Hence, in emphysema airflow to some regions may occur preferentially via collateral channels rather than through the narrowed airways. Furthermore, in emphysema, collateral flow can even occur between adjacent lobes [3, 6]. It is believed that these findings explain the failure of bronchoscopically placed airway valves to produce significant segmental or lobar atelectasis in most patients [7].

Because of the physiologic and therapeutic implications of collateral ventilation, a simple in vivo technique to measure it would be useful. Several techniques for quantifying collateral ventilation have been described, mostly in ex vivo lung preparations [2, 3, 8–10]. Two bronchoscopic techniques have been described for measuring collateral ventilation in the intact lung. The first technique involves placing the bronchoscope in wedge position and ventilating the remaining lung with a tracer gas while measuring the rate of increase in concentration of the tracer gas in the segment occluded by the bronchoscope [5]. The second technique involves placing the bronchoscope in wedge position and introducing a constant flow of gas through the working channel until a steady-state pressure is reached. When the flow of gas is interrupted, the drop in pressure can be used to directly calculate the resistance to collateral flow. Furthermore, the subsequent exponential decline in pressure can be used to calculate the time constant for collateral ventila-

Table 1. Collateral resistance and time constant in animals and man

Species	R_{col} cm H_2O/l/s	τ s
Human, normal [3, 4]	714–3,060	5.7
Human, emphysema [3]	5–16	–
Sheep [7]	–	0.36–1.34
Dog [7, 9]	0.13–1.75	0.13–0.40
Pig [7]	–	92–234

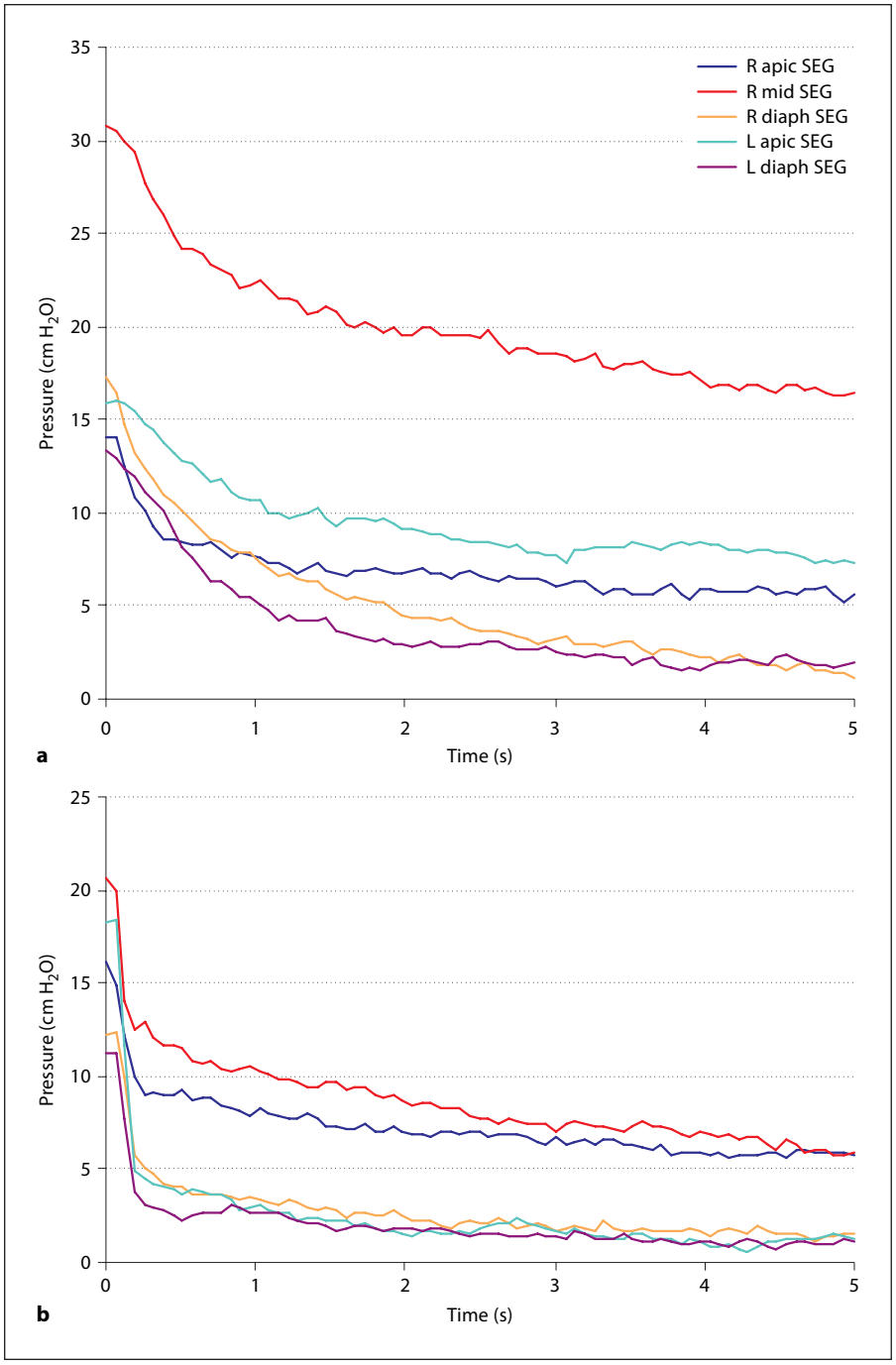

Fig. 2. Sample raw data (sheep 618) showing pressure-time tracings pre- (**a**) and postpapain (**b**) exposure. Note the larger initial drop in pressure and slower subsequent decay following papain exposure, consistent with increased airway resistance and time constant. apic = Apical (cranial); mid = middle; diaph = diaphragmatic (caudal); SEG = segment.

tion and the compliance of the occluded segment [4]. This technique can be modeled using a simple electrical circuit as shown in figure 1.

In this study, we used the latter bronchoscopic technique to measure collateral ventilation in a sheep model of emphysema previously shown to exhibit physiologic changes consistent with mild-to-moderate emphysema including a 60–86% increase in RV, 35–36% decrease in DLco, and a 32% increase in chord compliance [11, 12]. We hypothesized that emphysema would be associated with decreased collateral resistance, and that the degree of change would correlate with the regional severity of alveolar destruction.

Materials and Methods

Study Design

Eight healthy adult female sheep underwent bronchoscopic measurement of collateral ventilation at baseline and following the generation of emphysema.

Methods

All measurements and treatments were performed under light anesthesia with intravenous propofol (0.2–0.4 mg/kg/min) while animals were mechanically ventilated via an endotracheal tube (tidal volume 10 ml/kg, frequency 12 breaths/min, peak inspiratory flow rate 30 liters/min, fraction of inspired oxygen 0.6, positive end-expiratory pressure 0).

Bronchoscopic measurements were made as follows: an endoscope (GIF type 30, Olympus, Japan) with a small piece of tubing around its tip such that the outside diameter was 8 mm was introduced through the endotracheal tube and wedged into the orifice of a segmental airway. Wedge position was verified by feel and by observing airway collapse and very large negative pressure fluctuations during suctioning, measured at the proximal end of the working channel of the bronchoscope. One hundred percent oxygen from a wall source was connected to the proximal end of the working channel of the endoscope via a three-way stopcock. Pressure was measured via a transducer (Validyne, Northridge, Calif., USA) connected to the sideport of the stopcock. Flow was measured via an inline pneumotach (Fleisch No. 0, Hugo Sachs, Germany) and adjusted to 8.3 ml/s (0.5 liter/min). Pressure and flow were recorded continuously (Biosystem XA V2.7.4, Buxco Electronics, Wilmington, N.C., USA). Once pressure reached a steady state value, flow was interrupted by turning the stopcock. The process was repeated at 3–5 sites per animal in defined locations that sampled dorsal and ventral segments of the cranial, middle, and caudal lobes. Measurements at each site required less than 1 min to complete.

Following baseline measurements, animals underwent four once-weekly treatments with nebulized papain 75 IU/kg (Sigma). One month after the final papain treatment, collateral ventilation measurements were repeated in the same locations in each animal. Sample raw pressure-time tracings are shown in figure 2.

Analysis

Pressure-time tracings were fit to the equation:

$$P(t) = P_o e^{-t/\tau}$$

where P is pressure, P_o is the pressure immediately after interruption of flow, τ is the time constant for collateral ventilation, and t is time. Airway resistance, R_{aw}, was calculated by subtracting P_o from the steady state pressure immediately prior to interrupting flow (P_s) and dividing by flow, then subtracting the resistance of the working channel of the bronchoscope. P_o was divided by the flow to derive collateral resistance, R_{col}. τ was then divided by R_{col} to derive the segmental compliance, C_{seg}.

R_{aw}, R_{col}, τ, and C_{seg} pre- and postpapain were compared by the two-sided paired t test. Correlation between R_{col} and C_{seg} was analyzed by Pearson's coefficient. All results are presented as mean ± SE.

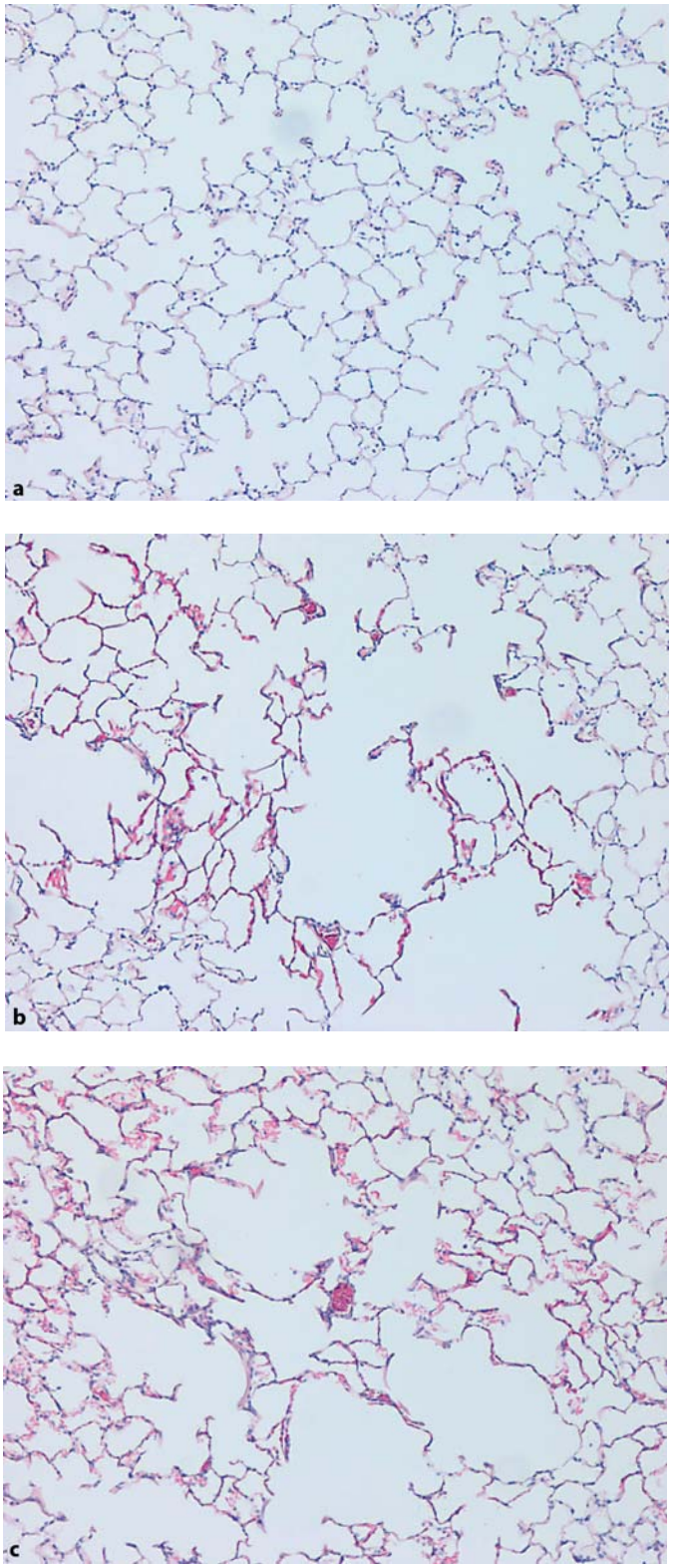

Fig. 3. Histopathology. **a** Untreated. **b**, **c** Postpapain lung. ×100.

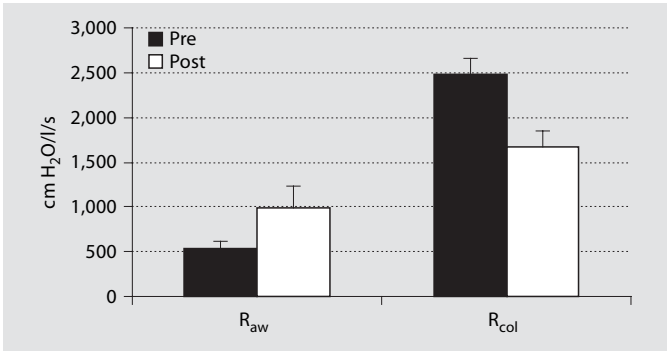

Fig. 4. Airway and collateral resistance pre- and postpapain.

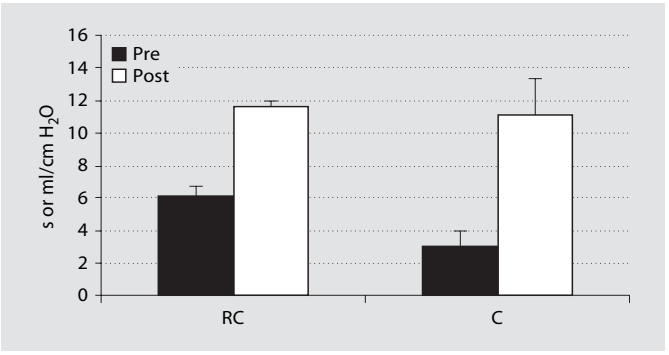

Fig. 5. τ (= RC) and compliance (C) pre- and postpapain.

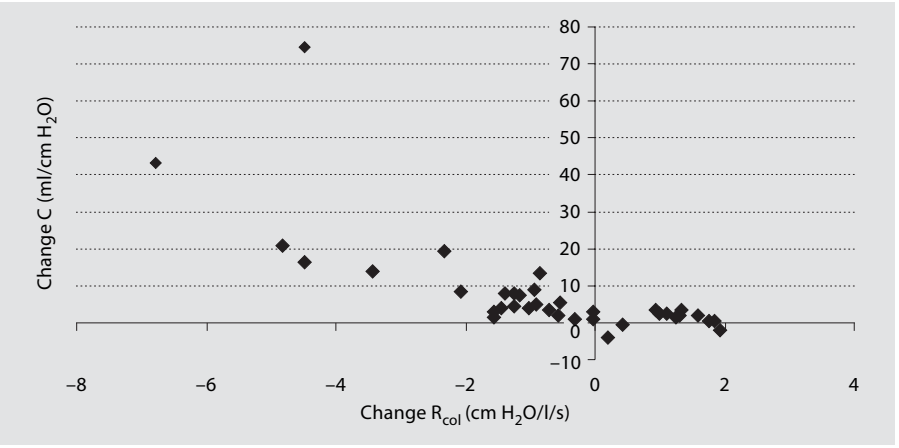

Fig. 6. Correlation of collateral ventilation with local disease severity.

Results

After papain treatment, animals showed no evidence of respiratory difficulty or decreased exercise tolerance.

Histopathology revealed disruption of alveolar walls and airspace enlargement consistent with emphysema primarily around the alveolar ducts. Representative photomicrographs are shown in figure 3.

Collateral ventilation measurements were collected and analyzed from 36 sites in the 8 animals. At baseline, R_{aw} averaged 538 ± 78 cm H_2O/l/s. R_{col} averaged 2,479 ± 240 cm H_2O/l/s. The mean time constant for collateral ventilation was 6.1 ± 0.63 s. The mean C_{seg} was 3.0 ± 0.36 ml/cm H_2O.

Following papain exposures, there was a statistically significant increase in R_{aw} of 455 ± 20 cm H_2O/l/s ($p = 0.033$), resulting in a postpapain mean of 993 ± 175 cm H_2O/l/s. There was a statistically significant decrease in R_{col} of 812 ± 341 cm H_2O/l/s ($p = 0.023$) (fig. 4). The postpapain mean R_{col} was 1,667 ± 176 cm H_2O/l/s. Time constant increased by 5.5 ± 1.0 s ($p < 0.001$) to a postpapain mean of 11.6 ± 0.93 s. C_{seg} increased by 8.1 ± 2.4 ml/cm H_2O ($p = 0.002$) (fig. 5) to a postpapain mean of 11.1 ± 2.24 ml/cm H_2O. Individual changes in R_{col} were fairly strongly correlated with changes in C_{seg} with Pearson's coefficient –0.73 (fig. 6).

Discussion

In this study, we used a previously described bronchoscopic technique to quantify collateral ventilation in vivo in a sheep model of emphysema [8]. The technique proved to be simple and safe, and we were able to detect a mean 33% drop in segmental collateral resistance following papain exposure that correlated with disease severity as measured by the change in segmental compliance. Despite the significant drop, the collateral resistance re-

mained relatively high (70% higher than airway resistance) compared with values in human emphysema patients. This may have been because the severity of emphysema in the model was only mild-to-moderate, lacking the large cysts and bullae that characterize advanced emphysema in humans. We also measured the time constant for collateral ventilation, which increased 90% following papain exposure due to a 267% increase in segmental compliance. This finding of an increased time constant despite decreased collateral resistance has been described in human emphysema [4].

Compared with the single report in the literature on the time constant for collateral ventilation in sheep, the baseline time constant we measured was somewhat longer [8]. This may be attributable to differences in the measurement techniques used and the locations in which the measurements were made. In our study, the outside diameter of the bronchoscope tip was 8 mm, causing it to wedge in a segmental airway. In the study by Kuriyama and Wagner [8], a 14-french (4.7 mm) catheter was used, which likely wedged in a more distal airway. Furthermore, Kuriyama and Wagner performed their measurements in isolated lungs over a range of inflation pressures. Our measurements were performed at FRC in intact, live animals.

The finding that the drop in collateral resistance correlated with disease severity may offer some insight into the mechanism by which collateral resistance decreases in emphysema and may also have important implications for bronchoscopic therapies for emphysema. The collateral ventilation pathways could be very simply modeled as a chain of resistors connected in series. Destruction of alveolar units, as occurs in emphysema, can be simulated by removing some of the resistors from the chain. Since the resistors are connected in series, this should result in a proportional decrease in the total resistance to collateral flow, even if the resistance of the remaining resistors is unchanged. This mechanism assumes that the airways, which act as resistors in parallel to the collateral pathways, are relatively unaffected by the destruction of the alveolar units. Regardless of the mechanism, if a similar correlation between collateral resistance and local compliance is present in human emphysema, this implies that the most diseased lung regions, and thus the most desirable targets for volume reduction, are the least likely to become atelectatic. Any bronchoscopic therapy that targets such regions without favorably modifying the collateral resistance may be doomed to failure.

Various animal species including sheep, pigs, and dogs, with or without experimental emphysema, have been used to test bronchoscopic therapies for emphysema [13]. Of note, one-way endobronchial valves have been tested primarily in normal pigs and sheep, both of which have high resistance to collateral ventilation. Segmental and lobar collapse has been observed consistently in these animal models. However, such collapse has not been observed in most humans with emphysema after bronchoscopic valve placement [7]. This finding can be explained by the large differences in collateral resistance between the normal animals used in testing and human emphysema patients. Biologic glues have been tested in sheep with emphysema induced by the nebulized papain method used in the current study [14, 15]. Theoretically, the glue method is less influenced by collateral ventilation, since the glue itself may block collateral channels. However, as the results of the current study confirm, the sheep model used to test this technique also does not display increased collateral ventilation to the extent seen in human emphysema and the effect of the glue method on collateral resistance has never been directly quantified. Other experimental procedures for emphysema treatment, such as the 'airway bypass procedure', may also depend heavily upon collateral ventilation; in this case, collateral ventilation may actually assist the emptying of trapped gas via the bypass tracts [16, 17] and the technique should be less effective in patients with very little collateral ventilation. Thus, quantification of collateral ventilation in any animal model used to develop bronchoscopic therapies for emphysema may be critical to predicting the success of the technique in humans with emphysema.

Despite its limitations, the animal model used in this study did exhibit significant decreases in collateral resistance, which allowed validation of the measurement technique. The technique used to measure collateral resistance in this study has previously been used in a limited number of normal humans and humans with emphysema [4]. The technique appeared to be safe and was able to detect the expected changes in the emphysema patients. Given the simplicity of the technique, we feel that it may become a useful diagnostic study for measuring local collateral ventilation and disease severity when evaluating patients for bronchoscopic therapies for emphysema. Quantification of collateral ventilation could provide prognostic information about the likelihood of response to treatment and could aid in the selection of appropriate target treatment sites.

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