

Transpleural ventilation of explanted human lungs

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ABSTRACT

We tested the hypothesis that ventilation of emphysema lungs would be enhanced by communications with the parenchyma through holes in the pleural surface. Fresh human lungs were obtained from patients with emphysema undergoing lung transplantation. Control human lungs were obtained from organ donors whose lungs, for technical reasons, were not considered suitable for implantation. Lungs were ventilated through the bronchial tree, or transpleurally via a small hole communicating with the underlying parenchyma over which a flanged silicone tube had been cemented to the surface of the lung (spiracle). Measurements included: 1) flow-volume-time curves during passive deflation via each pathway; 2) volume of trapped gas recovered from lungs via spiracles when no additional gas was obtainable passively from the airways; and 3) magnetic resonance imaging assessment of spatial distribution of hyperpolarized helium (^3He) administered through either the airways or spiracles. In emphysema lungs, 1) passively expelled volumes at 20 seconds were 94% greater through spiracles than via airways; 2) following passive deflation from the airways, an average of 1.07 L of trapped gas volume was recoverable via spiracles; and 3) regions were ventilated by spiracles that were less well ventilated via bronchi. Because of the extensive collateral ventilation present in the emphysematous lungs, direct communication with lung parenchyma through nonanatomic pathways has potential to improve the mechanics of breathing, and hence ventilation.

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INTRODUCTION

Hyperinflation and gas trapping are devastating consequences of severe emphysema. The increase in total lung capacity (TLC) compromises chest wall mechanics as the thorax approaches the limit of expansion. Gas trapping increases the residual volume (RV) to TLC ratio and reduces both the slow and forced vital capacity (VC and FVC, respectively). This in turn is a major cause of reduction in forced expiratory volume in one second (FEV_{1.0}). The progressively narrowing gap between RV and TLC increases the work of breathing and continues to decrease ventilatory capacity until the patient becomes flow-limited even while breathing at rest. Thus, a major objective of treatment must be to decrease the amount of trapped gas.

Collateral ventilation in emphysema greatly exceeds that in normal lungs as demonstrated in lungs removed at autopsy by Hogg and associates in 1969 [1] and confirmed using a different technique in patients by Terry and associates in 1978 [2] and reconfirmed more recently by Morrell and associates.[3] Macklem in an editorial comment stated, "...if collateral flow resistance is less than airway resistance... ventilation... through openings directly through the chest wall into the parenchyma should bypass the obstruction, decrease work of breathing, increase alveolar ventilation and improve dyspnea. Insects breathe through openings on their body surface...called spiracles".[4]

Lausberg and associates recently reported that the creation of fistulas between segmental bronchi and adjacent lung parenchyma increased FEV₁ and FVC in explanted emphysema human lungs.[5] The present study was designed to test the hypothesis that ventilation of low resistance collateral pathways in emphysema via spiracles through the pleura will allow trapped gas to escape and increase passive flow and volume on deflation. We made openings directly into the parenchyma through tubes glued to the pleural surface (spiracles) in order to measure flow and volume that traversed the spiracles. We studied emphysema lungs explanted from lung transplant recipients and compared them to nearly normal lungs obtained from donors but rejected for transplantation because of minor abnormalities.

METHODS

Preliminary studies on four emphysema lungs demonstrated the feasibility of studying ventilation through transpleural communications. This allowed us to develop a protocol by which we measured: 1) volume-flow-time relationships during passive deflation through either the bronchial tree or the spiracles from full inflation; 2) the amount of trapped gas that could be removed via the spiracles after the lung was completely deflated passively through the airways; 3) the distribution of ventilation as assessed by MRI imaging of hyperpolarized ^3He . The complete protocol was successfully carried out in two control lungs (#1 and 2) from one donor whose lungs for technical reasons were rejected for implantation and from a consecutive series of five left lungs (#3-7) explanted from five patients (3 female, 2 male) with end-stage emphysema undergoing double lung transplant surgery. In the preliminary studies we did not complete all three parts of the protocol in any of the four lungs. We report the complete data from lungs 1-7 and, where appropriate, limited measurements on the lungs from the preliminary studies.

The mean values of preoperative pulmonary function studies are presented in Table 1. The Institutional Review Board for human studies approved the protocol and informed written consent was obtained from each subject. The spiracle (Hood Laboratories, Pembroke, MA) made of medical grade silicone (1.7 mm thick) was a quasi-elliptical tube (9 x 18 mm externally) with a flange (33 x 21 mm) that was glued with tissue cement to the lung as shown in Figure 1. The pleura was incised through the lumen of the tube and a 3x10 mm area of pleura was removed. The lung parenchyma was thus accessed directly through the lumen of the spiracle. Spiracles were attached to both upper and lower lobes in each emphysema lung while the control lungs each had only one spiracle.

TABLE 1. MEAN PREOPERATIVE PULMONARY FUNCTION STUDIES

	FVC	FEV ₁	RV	TLC	Raw cm/L/s
L/%	1.64/46	0.42/15	6.4/314	8.3/147	4.92/273
SD L/%	0.70/13	0.17/6	1.9/77	2.7/33	2.2/111

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; RV, residual volume; TLC, total lung capacity; Raw, airway resistance; cm/L/s, centimeters H₂O/liter/second; L, liters; %, percent of predicted normal; SD, standard deviation.

Each main stem bronchus was securely fitted with a cannula. The lung was inflated to total lung capacity as judged by visual inspection with a series of small volume bursts of pressure delivered manually from a compressible respirator bag. Aside from this, we employed only gentle massage and repeated filling-emptying cycles with airway pressure limited to 20 cm H₂O to achieve full inflation. A major difficulty studying the mechanical properties of emphysematous lungs *ex vivo*, is air leakage. To circumvent this problem, major vessels were ligated to avoid leakage from the vascular and perivascular spaces. Small tears or cuts on the surface were identified by immersion in isotonic saline solution and repaired by focal ligation or tissue cement. When the lung was considered fully inflated, the bronchial cannula was opened and the lung was allowed to deflate passively through the airways.

With the spiracles closed, the lung was re-inflated via the bronchus to transpulmonary pressures that varied from 8.1 to 15.1 cm H₂O in the emphysema lungs (14.0 to 20.6 in control lungs) and allowed to deflate passively via the airway [6] through a pneumotachometer (RSS100-HR, sensor model: 3700 flow range: 0 to 160 L/min that includes airway and auxiliary pressure transducers; Hans-Rudolph, Kansas City, MO) with commercial software (RSS100-HR Research Pneumotach System version 3.0.7b; KORR Medical Technologies, Salt Lake City, UT). The lung was again re-inflated to a roughly similar pressure (± 1 cm H₂O) through the bronchus. The bronchial cannula was then closed and flow and volume were measured during passive deflation through the spiracle(s). At least three passive flow-volume curves were obtained through each pathway; the results were averaged. We also measured the volumes expelled passively at 1, 5, 10, 15, and 20 seconds and beyond, to or near, completion through each pathway.

The lung was then fully re-inflated through the bronchus (to pressure between 10 and 15 cm H₂O), the bronchus was opened and the lung allowed to expel as much air as possible by passive deflation through the airways. The time was not recorded but commonly exceeded one minute and uniformly exceeded 30 sec. The bronchial cannula was then clamped and the spiracle(s) were opened, allowing gas trapped behind closed airways to exit passively through the spiracles into a Mylar bag. A Y connector was used to collect gas from both lobes simultaneously in the emphysema lungs. The volume of trapped gas expelled was measured from the bag into a calibrated syringe.

Magnetic resonance imaging (MRI) [7][8] was used to compare the breath by breath distribution of ventilation of hyperpolarized helium (³He) (n=2 control, 5 emphysema lungs).

Hyperpolarized ^3He of nominal polarization 40% was prepared with two locally constructed and one commercial polarizer (Amersham Health). To prevent ^3He depolarization by contact with O_2 , we first ventilated the lung with 100% nitrogen (N_2) for 20 minutes using an open circuit technique and stored the lung in an air tight plastic bag containing 100% N_2 . With intrabronchial pressure set at 2-3 cm H_2O , a tidal volume of approximately 300 mL of hyperpolarized ^3He ($P \geq 40\%$) was instilled via gas syringe to either the bronchus or spiracle. The lung was tidally ventilated by closed circuit rebreathing with the same volume for up to 10 breaths. Images were obtained at the end of each inflation cycle on a Siemens Magnetom Vision whole-body scanner at 48.47 MHz (the ^3He frequency at a nominally 1.5-T field). A homebuilt four-turn, in-parallel, solenoid-like coil with high-Q took advantage of the lack of saline and low rf loss.

Following the last ^3He deflation-inflation cycle, 300 mL of lung gas were removed, replaced with 300 mL room air from the syringe, and open circuit washout of ^3He imaging was performed for up to 6 cycles. ^3He imaging was repeated at the end of each inflation. Regions of interest (ROI) were chosen in each lobe near where the spiracles were located, to represent a macroscopic gas-exchange volume that was significantly more efficient when delivered via spiracles than via the bronchus. These ROI were hand drawn to encompass a region approximately 0.5 L in volume in each lobe and generally encompassed three image slices. The total ROI signal (equivalent to the total magnetic moment in the region, and thus the total volume of ^3He , absent the minimal effects of T_1 here) was integrated and fit to a linear function. Then, after the first extraction of 300 mL gas and subsequent insertion of 300 mL of room air, the ROI signal was again integrated.

Mean values are presented with standard deviation [SD]. We analyzed differences of mean values with Student's t-test.[9] Time constants (Tau) were calculated for the mean volume-time curves of each lung with the equation:

$$V_{\text{exp,aw}}(t) = V_{\text{exp,aw}} [1 - \exp(-t/T_{\text{aw}})]$$

or

$$V_{\text{exp,sp}}(t) = V_{\text{exp,sp}} [1 - \exp(-t/T_{\text{sp}})]$$

using the software Systat® version 11 (Systat Software, Inc., Richmond, CA, USA) where: $V_{\text{exp,aw}}(t)$ and $V_{\text{exp,sp}}(t)$ is the volume expelled via each route at each time point (t); $V_{\text{exp,aw}}$ and $V_{\text{exp,sp}}$ is the total volume expelled by each route; exp is e, the base of the natural system of logarithm; -t is the time in seconds to total volume; and Tau is the time constant. The values for R^2 were all 0.97 or greater.

RESULTS

A critical determinant of lung inflation is mean airway pressure. For this series of measurements in the emphysema lungs, mean initial pressure was 10.7 [2.6] cm H₂O (n = 30). For the bronchial curves, it was 10.2 [2.3] cm H₂O (n = 15), and for the spiracle curves 11.3 [2.9] cm H₂O (n = 15). While this is perhaps more variation than ideal, it is evenly distributed between two groups of observations and unlikely to have distorted the results. Inflation pressures for the control lungs averaged 18.8 cm H₂O (n = 12). Curves for the bronchial route averaged 20.5 [2.8] cm H₂O (n = 6) and for the spiracle pathway 17.1 [3.9] cm H₂O (n = 6). Nonlinear regression was performed according to the equation described in the Methods section in order to obtain time constants (Tau) for the mean volume-time curves of each lung.

Figure 2 compares volumes passively expelled from bronchus and spiracles of lungs inflated as described above. In Figure 2A, the volumes are given as absolute values. In the control lungs (#1 and 2), the rates and volumes expelled via the bronchus greatly exceeded results via spiracles and the time constants were much shorter. In the emphysema lungs (#3-7), absolute volume of gas expelled from the spiracles usually exceeded the rate and volume observed via the bronchus as shown in Table 2. The table also includes mean initial airway pressure for the three curves studied and duration to the time considered complete to total volume. These results varied from 26 to 47 seconds in the lungs with emphysema. Even so, explanted emphysema lung airways continue to expel air (although slowly) even beyond these periods. The mean duration to total volume of the emphysema lungs was 36 seconds via the bronchial route and 34 seconds via spiracle. The mean total gas volumes expelled from the emphysema lungs at 20 seconds via spiracle(s) was $194 \pm 61\%$ of that via the bronchus ($p = 0.01$, $n = 5$). During preliminary studies, we encountered three lungs in which bronchial flow and volume exceeded spiracle values. In those lungs, bronchial and spiracle results were nearly identical in two, while the bronchial rate and volume considerably exceeded the spiracle results in the other.

TABLE 2. PASSIVELY EXPELLED VOLUMES IN ML

Passive Volume-Time Curves								
Lung #	Mean initial airway pressure*	1 sec	5 sec	10 sec	15 sec	20 sec	Final total volume	Time (sec) to total volume
Bronchial pathway								
1	20.3	110 2	185 3	1941	1974		1974	15
2	20.6	700	148 8	1588	1631	1681	1681	20
3	12.2	390	826	1080	1235	1460	1528	42
4	9.6	260	696	1035	1267	1444	1669	28
5	9.8	400	750	822	853	870	926	26
6	8.1	153	400	582	704	800	953	37
7	10.8	131	390	503	544	596	632	47
Spiracle pathway								
1	14.0	128	446	793	1070	1258	1476	30
2	20.2	150	574	960	1163	1295	1327	30
3	15.1	410	962	1507	1895	2074	2384	38
4	8.1	280	119 0	1603	2044	2361	3205	44
5	10.1	340	944	1308	1509	1636	1662	32
6	9.4	300	128 3	1950	2444	2783	3049	25
7	13.7	253	743	1012	1105	1152	1197	30
All airways								
7	14.4	469	978	1125	1175	1197	1200	25

*cm H₂O, of 3 curves

Figure 2B shows the volumes normalized as a percentage of the total volume expelled. The data points are on (#6, 7), or close to (#3, 4) the line of identity for all emphysema lungs except #5. Thus in lungs #4, 6, and 7, the time constants for emptying were roughly similar for both pathways, while in lung #5, which emptied faster through the bronchial tree than it did through the spiracles, the time constant for the bronchial pathway was much smaller than that for the spiracles. This was confirmed by the values of Tau shown in Table 3. In the control lungs, the Taus were 9.3 and 3.9 times longer for emptying through the spiracles than through the airways. Lung #5 had the shortest Tau for emptying via the airways and the largest percent difference between airway and spiracle Taus of the emphysema lungs. In Figure 2B, this lung showed an airway emptying pattern close to normal. In the emphysema lungs the difference between the two Tau values varied from 10 to 60% of the larger value.

Figure 3 presents additional examples of flow-volume and volume-time curves passively expelled.

TABLE 3. TIME CONSTANTS (TAU)

Lung #	Bronchial Route (seconds)	Spiracle Route (seconds)	All Airways (seconds)
1	1.3	12.1	
2	2.0	7.8	
3	7.2	9.6	
4	9.9	14.0	
5	2.4	6.0	
6	10.3	9.3	
7	5.8	5.2	2.5
Mean	7.1	9.3	
SD	3.3	3.5	

Table 4 presents the volume of gas recovered from upper and lower lobe spiracles simultaneously after full inflation and complete passive airway deflation of the emphysema lungs. The average volume was 1.07 L with a range from 0.21 to 1.57 L. The fact that the trapped gas in emphysema lungs was expelled passively through the spiracles indicates it was under positive pressure, i.e. small airways close and trap gas prematurely when alveolar pressure is still positive. This gas did not communicate with the bronchial cannula when the lung was fully deflated. Table 4 also presents the recovery of trapped gas RV from 5 upper and 5 lower individual lobe spiracles. These data (n=10) averaged 0.69 L and varied from 0.18 to 1.41 L. During the preliminary studies in one explanted emphysema lung, we recovered 1.49 L of trapped gas from one spiracle. A preliminary report was published as an abstract.[10]

TABLE 4. TRAPPED GAS VOLUME RECOVERED FROM EMPHYSEMA LUNGS

Lung #	A. Volume recovered simultaneously from two spiracles (L)	B. Volume recovered from single upper lobe spiracle (L)	C. Volume recovered from single lower lobe spiracle (L)
3	1.14	1.31	0.89
4	1.57	0.60	0.51
5	1.04	0.54	0.69
6	1.41	0.56	1.41
7	0.21	0.25	0.18
MEAN	1.07*	0.65*	0.74*
SD	0.53	0.39	0.46

*not significantly different statistically

Column A is the gas recovered via two spiracles simultaneously after full lung inflation and complete passive deflation via the bronchus.

Columns B and C are the trapped gas (L) volumes recovered from single upper and lower lobe spiracles, respectively after full lung inflation and complete passive deflation via the bronchus.

Figure 4 shows the breath by breath distribution of ^3He in a slice of a control left lung (#1) (left panel) and a slice of an emphysema left lung (#6) (right panel). In each panel the left hand column shows the ^3He distribution for breaths 1, 3, and 5 via the bronchial tree whereas the right panels illustrate the distribution for the same breath numbers via the spiracles. In the control lungs, the distribution of ^3He gas was similar by both routes.

This contrasts with the distribution of ^3He in the explanted emphysema lung. When ventilation occurred via the airways, most of the ^3He entered the left lower lobe. The sharp line of demarcation extending toward the left and slightly downward is caused by the major fissure. Immediately above the fissure, the upper lobe remained essentially unventilated. The apex of the upper lobe received a small amount of ^3He , but after five breaths the entire upper lobe remained very poorly ventilated compared to the lower lobe. In contrast, when ventilation took place simultaneously via spiracles in both lobes, the distribution of ^3He was more even. After five breaths, only regions bordering the fissure remained poorly ventilated, and even there, more ^3He entered through the spiracles than through the bronchial tree. Figure 4 illustrates that: 1) trapped gas regions accessed by spiracles tended to be large (the size of segments and even lobes); 2) within them ventilation distribution was reasonably uniform; 3) gas was distributed via spiracles to regions that were not as well ventilated by the bronchus. Although each emphysema lung differed from the others in terms of regional heterogeneity, all lungs demonstrated these three features illustrated in Figure 4. This indicates that spiracles can provide low resistance pathways for ventilatory flow to much of the emphysema lung.

Similarly, tidal ventilation with room air on an open circuit technique via spiracles produced large areas of gas depletion that corresponded to the bright regions seen earlier on the

initial ^3He inflation. Regions of interest (ROI) were selected near sites of spiracle placement to quantify gas depletion of specific volume. The mean ROI volume of 467 mL was depleted on the average of 55% of ^3He on the first cycle. In contrast, only 9% of ^3He was depleted in the ROI after a single cycle via the bronchus tree. Detailed results are presented in Table 5 and Figure 5.

TABLE 5. FIRST BREATH SIGNAL REDUCTION OF HYPERPOLARIZED ^3He

Lung #	Lobe	ROI volume (mL)	Bronchus %	Spiracle %
3	U	522	9.8	18
	L	430	0.2	28
4	U	629	0	52
	L	476	0	69
5	U	450	0	55
	L	329	20	59
6	U	373	24	44
	L	560	0	73
7	U	520	33	78
	L	385	8	74
Mean		467	9.5*	55*
SD			12	20

*paired t-test, $p = 0.001$

Abbreviations: U, upper; L, lower; ROI, region of interest; %, percent signal reduction; SD, standard deviation

DISCUSSION

Laennec described the handling of an emphysematous lung as that perceived when handling a pillow of down. Hogg and associates [1] suggested this sensation due to the ease with which air can be pushed from one area of an emphysema lung to another. Thoracic surgeons are familiar with the fact that emphysema lungs remain inflated after excision except when the presence of a small puncture or tear in the pleura results in complete collapse. This feature can be attributed to the extensive collateral ventilation in emphysema. Can one imagine any way to destroy the delicate parenchyma of the lung without causing an increase in collateral ventilation?

Previous measurements of collateral ventilation in excised emphysema lungs have shown that the resistance to collateral flow across an incomplete major fissure was less than the resistance to flow through the airways; whereas in normal lungs the result was opposite.[1, 11] The first measurements in living patients with emphysema performed by Terry and associates [2] confirmed low resistance of collateral ventilatory pathways. Morrell and associates [3] devised an ingenious bronchoscopic method to demonstrate a functionally important correlation between increased collateral ventilation and increased oxygen tension in the peripheral lung parenchyma. When the patient (or subject) inspired heliox (79% helium, 21% oxygen), the concentration of helium distal to a blocked peripheral bronchus rose ten fold faster in patients with moderately severe emphysema than in those with healthy lungs. Compared to healthy lungs, emphysema lungs regularly exhibit increased collateral ventilation.

Higuchi and associates [12] recently documented interlobar collateral ventilation in 15 of 23 explanted emphysema lungs. The authors cannulated and ventilated the bronchus to one lobe, and witnessed active ventilation of a companion lobe that was not cannulated. They analyzed preoperative results of CT scans and V/Q scintigraphs in a carefully blinded manner in order to classify the emphysema of each lung as homogeneous or heterogeneous. Interlobar collateral ventilation was almost uniformly present in the lungs of those patients with homogeneous emphysema while only 40% of patients classified with heterogeneous emphysema exhibited significant interlobar collateral ventilation. An accompanying editorial by Cetti, Moore, and Geddes [13] suggested the range of anatomic changes in emphysema must be more complicated than two categories would allow. The authors also pointed out interlobar ventilation must be an advanced stage of collateral ventilation that almost surely is a continuous variable in the spectrum of emphysema. Our group correlated the long range diffusion of hyperpolarized ^3He to morphometric measurements of lung surface area/volume ratios in normal and emphysema lungs by measuring the decay of spatially modulated longitudinal ^3He magnetization.[14] The technique will assess collateral ventilation with sensitivity greater than that of interlobar ventilation. We agree with Cetti and associates [13] that understanding collateral ventilation is important for planning bronchoscopic methods of treatment for patients with advanced emphysema.

Lungs in the present study were typical for patients undergoing transplantation for emphysema at our center as shown in Table 1. Mean values of FEV_1 of 15% and RV of 314% of predicted normal clearly demonstrate severe expiratory flow limitation with marked hyperinflation characteristic of advanced emphysema. Subjects in the present study had more severely impaired preoperative pulmonary function results than those in the group studied by Morrell.[3] Dramatically increased collateral ventilation can be safely predicted in the lungs of the present study, but it remains to be demonstrated whether the functional benefits observed would also be found in lungs with less severe functional abnormalities or in living patients.

Main Finding

The main finding of this study is that transpleural ventilation via spiracles communicates with areas of the parenchyma that do not communicate with the trachea at RV. As a result, our hypothesis that the introduction of spiracles would decrease trapped gas, increase VC and expiratory flows proved to be correct. Measured preoperatively, the mean RV in this series of patients with emphysema was 6.40 L. We recovered 17% of this amount (1.07 L) via transpleural spiracles after the completion of passive bronchial deflation from one lung. While the amount might seem small it approaches one-third of RV for both lungs and would be highly significant for a patient with COPD.

Pathophysiology of Emphysema

We believe that our results shed interesting new information about functional abnormalities in emphysema that warrants a detailed consideration of the pathophysiology.

Lung mechanics have been modeled for several decades using electrical analogs. In these models, capacitors represent the elastic properties of the lung and its compliance (C_L), whereas resistors are analogous to the flow resistance of airways. Expressed as conductances the airway conductance (G_{aw}) and the spiracle conductance (G_{sp}) sum ($G_{aw} + G_{sp}$) to express the total conductance when breathing takes place through both pathways simultaneously. The time constant for emptying of the lung through the tracheobronchial tree is then given by C_L/G_{aw} , while that for emptying through the spiracle is C_L/G_{sp} . If emptying occurs through both pathways the time constant is given by $C_L/(G_{aw} + G_{sp})$. Alveolar pressure (P_A) is the pressure producing flow (P_{fr}) and is analogous to the voltage across the resistors. P_A relative to pleural pressure (P_{pl}) or lung elastic recoil pressure ($P_A - P_{pl} = P_{el}$) is analogous to the voltage across the capacitors. When P_{pl} is atmospheric as in our experiments, P_{fr} and P_{el} are identical. Furthermore, P_{fr} is common to both airways and spiracles and the resulting flow is the product of $P_{fr} = P_A = P_{el}$ and the appropriate conductance. If one assumes that a patient with severe emphysema has a G_{aw} of 0.1 L/s/cm H₂O, a G_{sp} of 0.3 L/s/cm H₂O, then flow rates would be threefold faster through the spiracle than the airways and fourfold faster through both pathways than through the airways alone.

In one emphysema lung (#7) we measured flow-volume (Fig. 6A) and volume-time (Fig. 6B) relationships during passive deflation 1) through the airways, 2) through both spiracles simultaneously, and 3) via both spiracles and the airway simultaneously. Flows and volumes were greater through both spiracles and airways together than with either pathway alone. This simulates the case of a living patient breathing through both spiracles and the tracheobronchial tree. The time constants via the bronchus and the spiracles were similar at 5.8 and 5.2 seconds respectively, while the time constant emptying through all airways was 2.5 seconds. The result might suggest conductance through each pathway (bronchial and spiracle) is equal. This corroborates the graphic presentation in Figure 6 and fits the electrical analogy as a capacitor discharging through two resistors in parallel.

It is reasonable to assume that during passive deflation, both the bronchial tree and the spiracles share the same lung compliance, the capacitance of the model. If so, the driving pressure for flow through both pathways is the lung's recoil pressure; any difference in flow between the two routes must be due to differences between G_{aw} and G_{sp} . Since the time constants in most of the emphysema lungs were closely similar by both routes, lung compliance C_L might have been greater when emptying through the spiracle than through the bronchial tree. This could be explained if the spiracles communicate with a greater volume of the lung parenchyma than the tracheobronchial tree.

This means that there were regions of trapped gas within the lung that communicate rapidly with the spiracles but do not communicate with open airways (or do so very slowly). As compliance is proportional to the total volume of communicating parenchyma, the lower resistance of the spiracle pathway would be counterbalanced by the higher compliance of the communicating parenchyma, so that the time constant of emptying via the spiracles could be similar to that via the airway. This would explain why more gas emptied via the spiracles than via the bronchial tree while the time course for emptying was almost identical for both pathways. The implication of this explanation is that gas trapping is not simply a phenomenon

of small airways closing as RV is approached, but that the gas remains effectively trapped at nearly all lung volumes.

If these ideas are correct, the bronchial tree in emphysema does not communicate directly with all of the parenchyma except perhaps at volumes near TLC. The noncommunicating parts presumably receive most of their gas from collateral channels. These channels however must either be: 1) sufficiently slow so that emptying through them into the bronchial tree takes a longer time than is available during an expiration, or 2) closed at the lung volumes over which the expiration takes place. As a result, gas is effectively trapped with serious adverse effects on lung function. The amount of trapped gas that can escape from these regions via artificial airways through the pleural or bronchial wall [5] is substantial and might lead to clinical benefit.

Therapeutic Implications

Ventilation Distribution: The initial ^3He distribution in the control lungs was focal and irregular but generally similar via both the bronchial and spiracle routes. This probably relates to the fact that the tidal volume of 300 mL was imposed on the lung through the spiracle. Being normal, the lung elastic properties were uniform. Thus, the ^3He would not remain localized to a region of parenchyma close to the spiracle, but would be forced through high resistance pathways to more central airways and then back down to the parenchyma subtended by these central airways. In emphysema, on the other hand the ^3He was probably distributed by low resistance collateral channels, so there was no necessity for the gas to travel to central airways and then back down to the parenchyma. In any event, after a few breaths the ^3He distribution via airways and via spiracles was not strikingly different between the control and the emphysema lungs. Abnormalities in the distribution of ventilation in emphysema occurred over large macro regions on the scale of segments or even lobes. Within these regions the distribution was relatively homogeneous. ^3He distribution via spiracles tended to fill regions which were poorly ventilated by the bronchial tree even after several breaths. This further supports the evidence that the bronchial tree communicates poorly with large volumes of parenchyma that are accessed by spiracles. If breathing had taken place through both airways and spiracles simultaneously, the distribution would be similar to a superimposition of the left and right panels of Figure 4. In all instances this would have provided a more even distribution of ^3He in emphysema.

The present data are in agreement with the results of Lausberg and associates [5] which were obtained by stent-supported fenestration through airway walls directly into lung parenchyma. Those authors studied control and 12 explanted emphysema lungs inflated with 10 cm H₂O negative pressure in a chamber. Chamber pressure was rapidly converted to 20 cm H₂O positive pressure for measurement of the forced expiratory flow-volume curve. Forced expiratory curves in a control lung were not changed by placement of transbronchial stents. In the emphysema lungs mean FEV₁ was 245 ± 107 mL before placement of transbronchial stents (3 mm diameter) and 447 ± 199 mL after 3 stents (n=12) and 666 ± 284 mL after 5 stents (n=6). Similarly striking increases occurred also in total FVC in emphysema lungs. Careful analysis of forced and passive expiration from full lung inflation in healthy subjects demonstrated no difference in the rate of flow over the vast majority of vital capacity.[6] The forced curves

differed only by an earlier onset by about 0.2 seconds. It may seem counterintuitive that the trapped gas residual volume of an emphysema lung would be reduced equally well by small openings in either the bronchi or the pleura, but the data strongly support this. If the same trapped gas can be accessed both through the pleural surface and an airway, nonanatomic collateral channels must connect distant regions of trapped gas. It seems feasible to take advantage of this pathophysiology to develop effective treatment.

We conclude that supplementing the bronchial tree with additional parallel pathways to lung parenchyma deserves further evaluation as a therapy for severe emphysema. Access to collateral ventilatory channels has the ability to diminish RV/TLC, increase expiratory flow rates and VC, and improve distribution of ventilation. This technique may have therapeutic potential as a modality for relief of symptoms and improvement of lung function in patients with severe COPD (Gold stage 4).

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Ethics

The approval number from our Institutional Review Board is 90-0510.

References

- 1 Hogg JC, Macklem PT, Thurlbeck WM. The resistance of collateral channels in excised human lungs. *J Clin Invest* 1969;**48**:421-431.
- 2 Terry PB, Traystman RJ, Newball HH, *et al.* Collateral ventilation in man. *N Engl J Med* 1978;**298**:10-15.
- 3 Morrell NW, Wignall BK, Biggs T, Seed WA. Collateral ventilation and gas exchange in emphysema. *Am J Resp Crit Care Med* 1994;**150**:635-641.
- 4 Macklem PT. Collateral ventilation. *N Engl J Med* 1978;**298**:49-50.
- 5 Lausberg HF, Chino K, Patterson GA, *et al.* Bronchial fenestration improves expiratory flow in emphysematous human lungs. *Ann Thorac Surg* 2003;**75**:393-398.
- 6 Pierce JA. Studies of free collapse in the intact human lung. *J Lab Clin Med* 1959;**54**:96-106.
- 7 Saam BT, Yablonskiy DA, Kodibagkar VD, *et al.* MR imaging of diffusion of ³He gas in healthy and diseased lungs. *Magn Reson Med* 2000;**44**:174-179.
- 8 Yablonskiy DA, Sukstanskii AL, LeaWoods JC, *et al.* Quantitative in vivo assessment of lung microstructure at the alveolar level with hyperpolarized ³He diffusion MRI. *Proc Natl Acad Sci* 2002;**99**:3111-3116.
- 9 Dowdy S, Wearden S. *Statistics for research*. New York, John Wiley & Sons 1983;173-200.
- 10 Chino K, Pierce J, Cooper J, *et al.* Ventilation of excised human lungs via spiracles through the pleura. *Am J Respir Crit Care Med* [abstract] 2003;**167** (suppl):A546.
- 11 Woolcock AJ, Macklem PT. Mechanical factors influencing collateral ventilation in human, dog, and pig lungs. *J Appl Physiol* 1971;**30**:99-115.
- 12 Higuchi T, Reed A, Oto T, *et al.* Relation of interlobar collaterals to radiologic heterogeneity in severe emphysema. *Thorax* 2006;**61**:409-413.
- 13 Cetti EJ, Moore AJ, Geddes DM. Collateral ventilation. *Thorax* 2006;**61**:371-373.
- 14 Woods JC, Yablonskiy DA, Choong Ck, *et al.* Long-range diffusion of hyperpolarized ³He in explanted normal and emphysematous human lungs via magnetization tagging. *J Appl Physiol* 2005;**99**:1992-1997.

Figure legends

Figure 1: Transpleural spiracle: Panel A is a photograph of the quasi-elliptical silicone tube with a 33 x 21 mm flange. Panel B illustrates the device secured to the pleura with tissue cement. A segment of pleura was excised through the lumen of the tube to permit communication with lung parenchyma. Panel C shows the site of the transpleural communication following removal of the silicone spiracle tube.

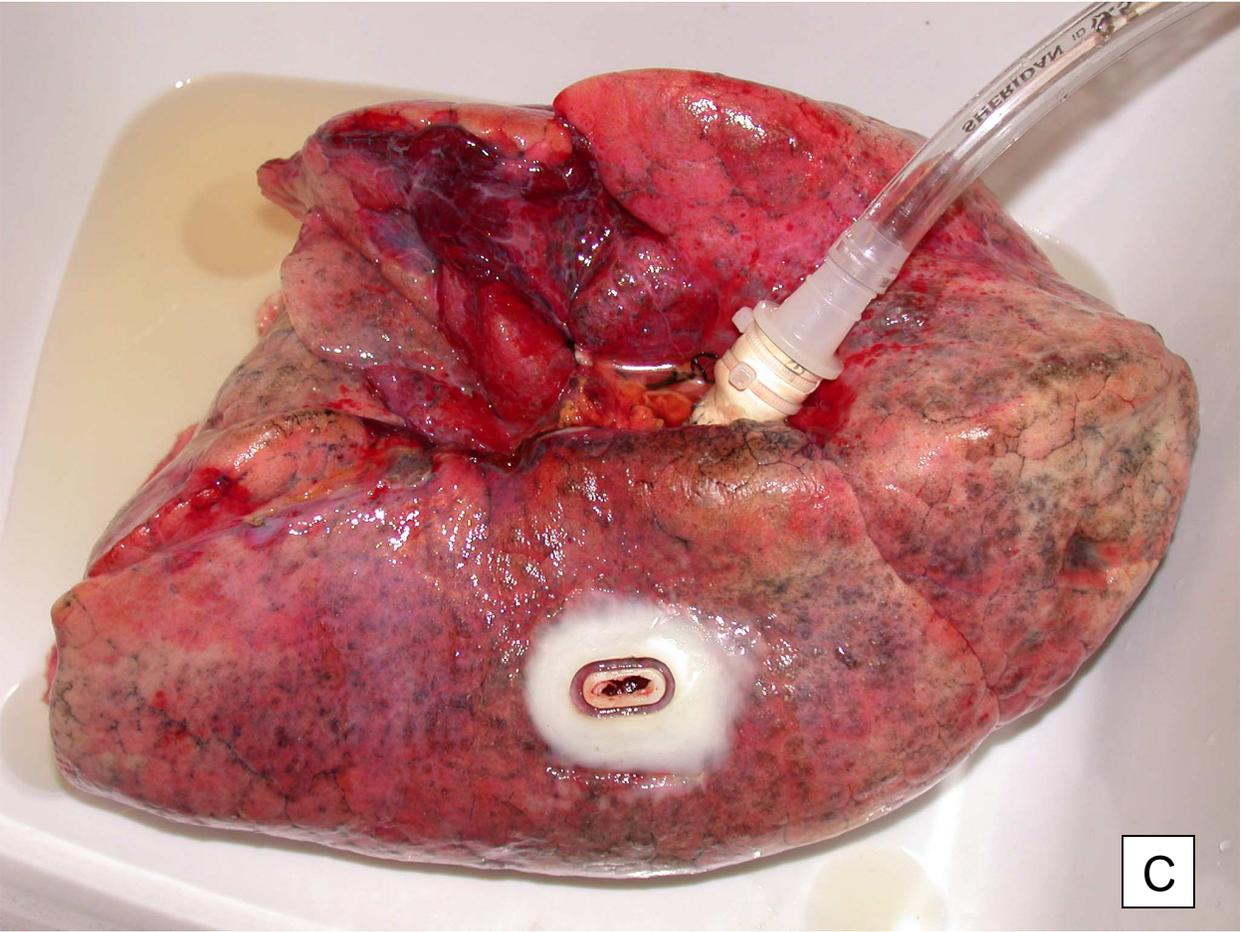
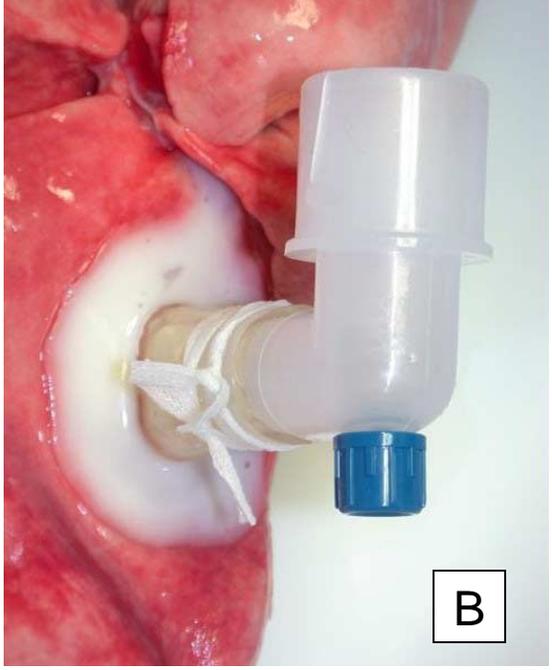
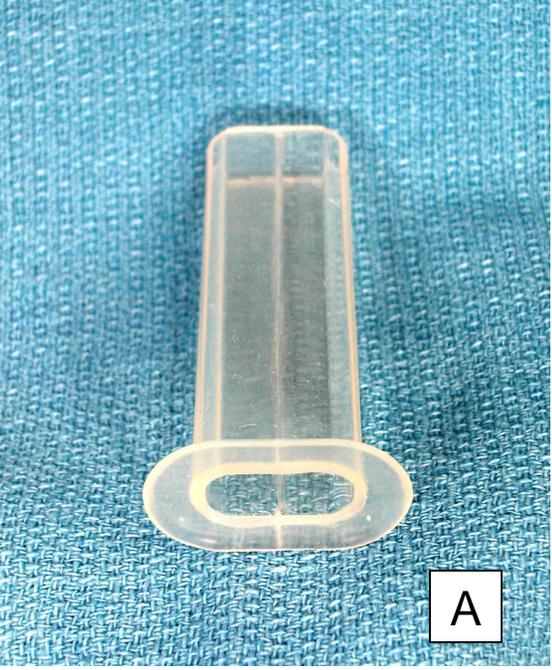
Figure 2: Panel A is an isotime identity plot of passive deflation from full lung inflation (control pressure ~20 cm H₂O, emphysema pressure ~10 cm H₂O). The absolute volume expelled from the bronchial tree is plotted on the ordinate against the absolute volume expelled from the spiracle on the abscissa at 1, 5, 10, 15, and 20 seconds after onset of passive deflation. Numbers near the final data points identify each lung. Panel B presents the same data plotted on similar coordinates as percent of total volume expelled.

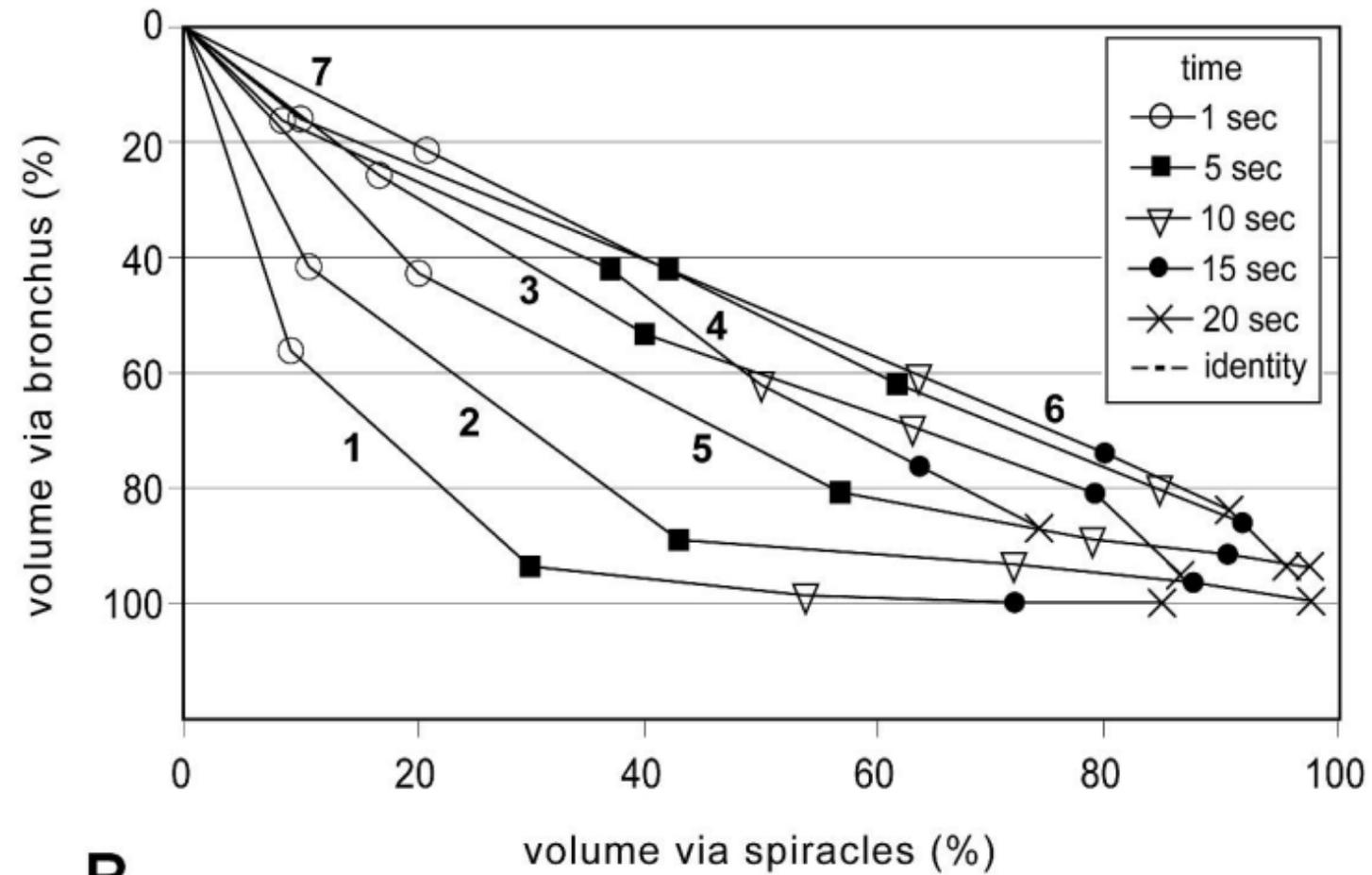
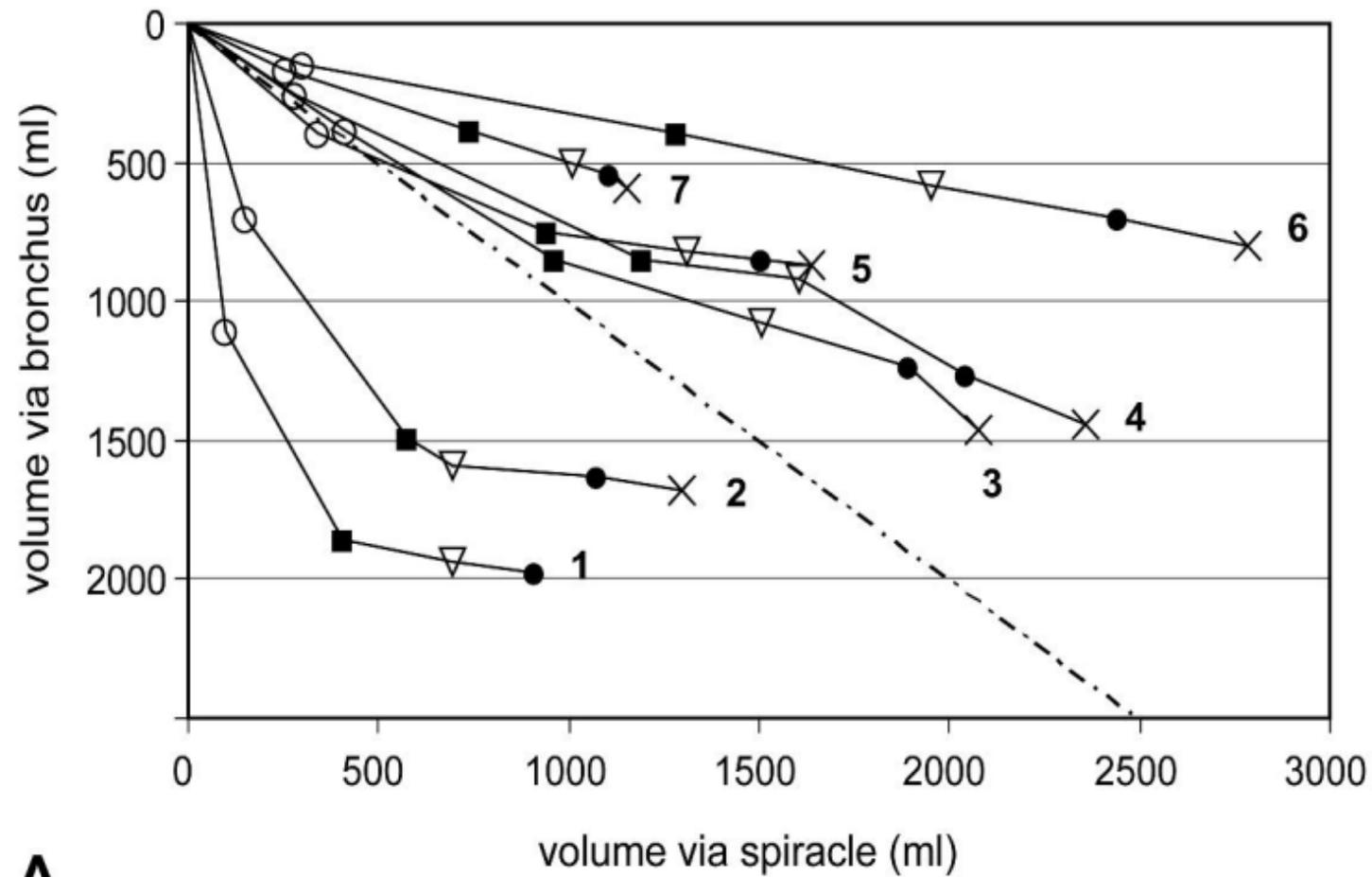
Figure 3: Flow-volume (A and B) and % volume-time curves (C and D) during passive emptying (free collapse). Transbronchial flow is illustrated by closed squares and spiracle flow by open circles. Data points appear every 0.2 seconds for the first second and each second thereafter to 15 seconds. Panel A recorded from a near normal lung (#1) shows bronchial flow greatly exceeds spiracle flow. Panel B is a representative tracing from the lung of a patient with severe pulmonary emphysema (#6) and shows that passively expelled flow and volume via spiracle exceeds that via the bronchial tree. Panels C and D provide a different perspective of the same data in which volume on the ordinate is expressed as % of the total volume expelled passively vs. time. Panel D shows that when volume is expressed this way, the pattern of emptying from the emphysema lung via the airways and spiracles was nearly identical. This indicates that the time constant for emptying in this example was similar for both routes.

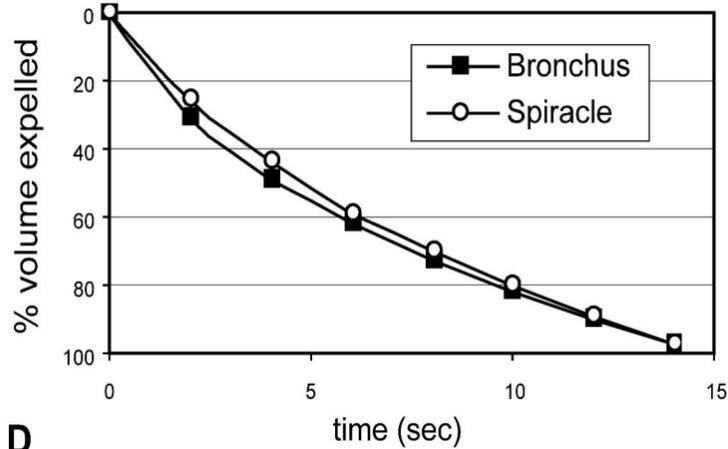
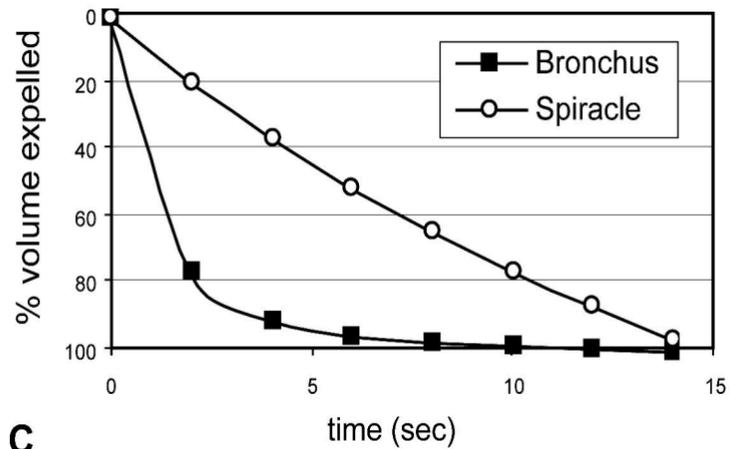
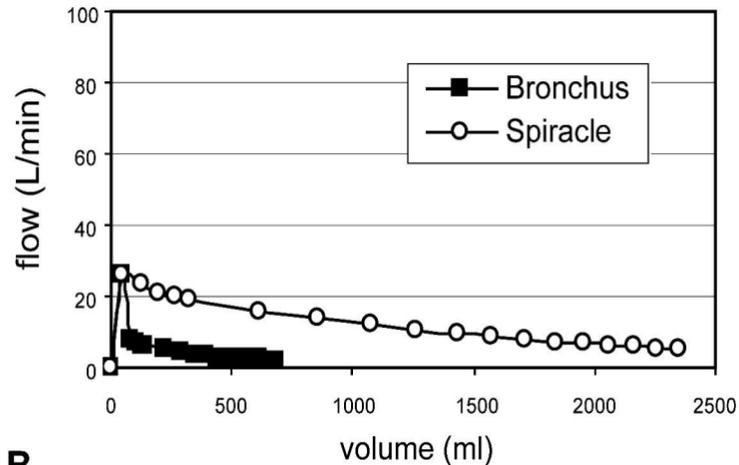
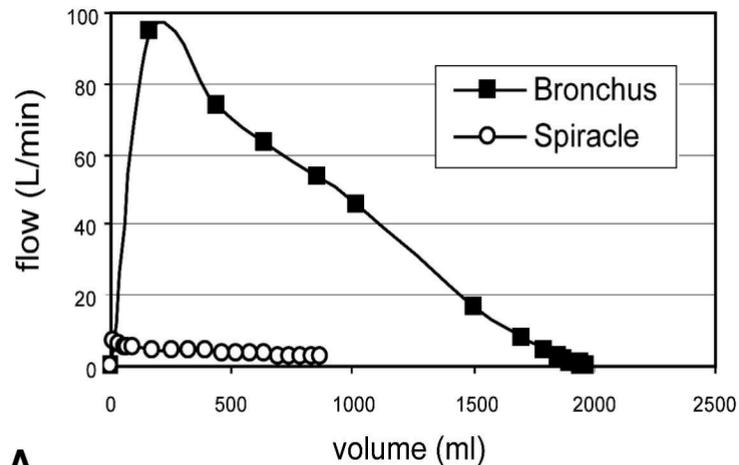
Figure 4: MR images of the distribution of hyperpolarized ³He ventilation via bronchus and spiracles in a healthy left lung (#1) with one spiracle (left panels) and an emphysema left lung (#6) with spiracles in both upper and lower lobes (right panels). The light areas depict the location of the hyperpolarized ³He. Images made following the initial inflation presented at the top are followed by images after the 3rd and 5th breaths respectively in the center and lower panels. The distribution of ventilation was similar via bronchus and via one spiracle in the healthy lung. The emphysema lung, however, showed preferential ventilation of the lower lobe via the bronchus, and large dense areas of rather uniform ventilation around the area of the spiracles during sequential breaths.

Figure 5: Wash-out ³He images of lung #5 comparing bronchial (B) to spiracle (S) pathways. The left panels show distribution of the gas following the final closed circuit ³He deflation-inflation (300 mL) cycle with the selected regions of interest (ROI) outlined in white. Center panel illustrates the result following one open circuit deflation-inflation (300 mL) cycle with room air. The right panel shows the result following a second room air deflation-inflation wash-out cycle. The striking reduction in intensity during the first cycle is represented as % of total signal depletion in ROI for lung #5 in this figure. Data for all the emphysema lungs are in Table 4.

Figure 6: Flow-volume (A) and % volume-time (B) curves of passive collapse obtained from the lung of a patient (#7) with severe emphysema. Flow through the bronchus is illustrated by closed squares and the open circles show flow simultaneously from both upper and lower lobe spiracles. In addition, a curve plotting flow simultaneously from all three routes is marked with closed triangles. The % volume-time relations were similar for passive emptying through the bronchus and via the spiracles, indicating similarity in emptying times via both routes. However, when emptying occurred through both the airways and spiracles simultaneously the emptying time was shortened. Thus there was a reduction in the time constant for passive emptying when this occurred through spiracles and airways simultaneously (see text).







bronchus

spiracle



breath #1



breath #3



breath #5

bronchus

spiracle



breath #1



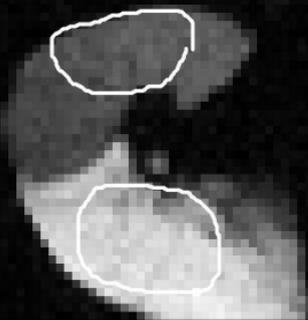
breath #3



breath #5

before washout

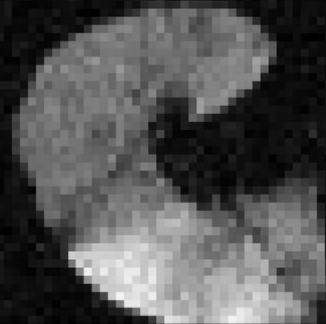
B



after 1 cycle



after 2 cycles



S

