AIRWAY BYPASS IMPROVES THE MECHANICAL PROPERTIES OF EXPLANTED EMPHYSEMATOUS LUNGS

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ONLINE DATA SUPPLEMENT

Our laboratory demonstrated that lungs with severe emphysema empty more rapidly following inflation and by a greater volume after airway bypass (stent-supported transbronchial fenestrations) [E1]. The marked increase of collateral ventilation documented in emphysematous lungs by others [E2-E6] was confirmed by imaging hyperpolarized helium with transpleural ventilation [E7]. We designed a protocol to elucidate additional alterations in the pathophysiology of emphysema induced by transbronchial stents (airway bypass).

METHODS AND RESULTS

This report describes results from 10 of 21 lungs designated for study. Four lungs were not suitable most often because of an inadequate bronchial stump. Seven lungs were not studied successfully because we were not able to place the transbronchial stents. The 10 lungs studied derive from 8 patients whose mean preoperative pulmonary function results are shown in Table E1. Presented for comparison with other series, these results are typical of patients who receive lung transplants at this center. Radiographic examinations included routine PA and lateral chest radiographs, computed tomography of the chest often with contrast, and ventilation perfusion scans. All subjects were reported to have bilateral hyperinflation of the lungs with severe or advanced panacinar or centrilobular emphysema. The disease predominantly involved the upper lobes in 6 of the 8 patients. Ventilation and perfusion scans were usually patchy and irregular on both wash-in and wash-out phases. Bullous disease was reported in 4 patients and asymmetrical disease defined as unilateral imbalance of at least 2/3 ventilation and perfusion occurred in 3. Anatomic pathology confirmed the presence of advanced or severe emphysema in every instance.

TABLE E1. MEAN PREOPERATIVE PULMONARY FUNCTION STUDIES (N=8)

	FVC	FEV1	RV	TLC	Raw cm/L/s
L/%	1.64/45	0.47/16	6.98/337	8.62/144	6.46/417
SD L/%	0.65/15	0.13/4	0.99/50	1.14/12	4.87/327

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 water/liter/second; L, liters; %, percent of predicted normal; SD, standard deviation

The lungs were stored in a plastic bag on ice for transport from the operating room. The bronchus was cleared of mucus by suctioning with a few ml of isotonic sodium chloride solution. Each lung was weighed and served as its own control. The main bronchus was anastomosed with continuous suture to an appropriately sized polytetrafluoroethylene vascular prosthesis as described in previous publications (E1, E7). Additionally, we everted a small (2 mm) prosthesis cuff in order to suture through the cuff and the bronchus and avoid leaving puncture sites on the exposed surface of the prosthesis. Finally, we covered the porous prosthesis and the anastomotic site with a finger segment cut from a rubber glove and placed a tiny drop of tissue cement between the glove segment and the prosthesis to obtain an airtight conduit.

The study of severely emphysematous lungs *ex vivo* is impaired by air leaks. These were detected by inflating the completely immersed lung in sodium chloride solution. Leaks appeared most often in the perihilar region and were repaired by focal ligation or application of a small latex (glove) patch coated lightly with tissue cement. During the experiment it was often difficult to detect the appearance of a new leak that needed repair. Furthermore, in sharp contrast, to healthy lungs, the airways in severe emphysema do not close at any specifically predictable time on deflation. Zero flow is problematic since such lungs may continue to deflate slowly, often for well over a minute. This leads to a haunting and persistent uncertainty about the precise level of inflation of explanted emphysematous lungs.

Full inflation of the lung to ETLC was achieved principally with short bursts of pressure delivered manually from a collapsible respirator bag. We employed additionally, only gentle massage and repeated filing-emptying cycles. Following full inflation, the bronchus was open to the room for 5 minutes before minimal volume (ERV) was measured in a vertically walled 6.2 L plastic box (11.8 x 18.5 x 29 cm) that contained 2 L of isotonic sodium chloride solution. The deflated lung was floated on the saline. A rigid top with a round central opening to accommodate the bronchus was placed on top of the lung. The top fit snugly inside the walls of the box. The lung was completely immersed by pressing down and carefully leveling the top. This allowed placement of a mark on the side of the box. From this mark we were able to measure the displaced liquid volume. The weight of the lung in grams was subtracted from the displaced volume of liquid in milliliters to estimate the volume of trapped gas in milliliters. Replicate measurements on the same lung were reproducible. But the numerical values reported for ERV could be erroneously low because the bronchial connector was not occluded prior to complete immersion of the lung. Thus, the lung was subjected to the positive pressure of immersion (2-3 cm water) that would have forced air out of the lung if any lung parenchyma communicated with the airway opening at theoretical zero transpulmonary pressure. This possibility would be greater following than prior to airway bypass. The immersion, however, was brief (less than one minute in most instances) and a large error seems quite unlikely. The gross appearance of the lungs following airway bypass is illustrated in Figure 1.

Table E2 presents the data on lung weights and compartmental volumes.

TABLE E2. LUNG WEIGHT AND COMPARTMENTS VOLUME

Lung #		Weight (g)	ERV (L)	EVC
1	PRE	300	2.35	1.49
	POST		0.9	2.49
2	PRE	350	2.95	0.73
	POST		1.49	1.96
3	PRE	370	2.30	0.99
	POST		1.60	2.05
4	PRE	518	2.34	1.46
	POST		1.04	2.60
5	PRE	320	3.25	1.30
	POST		0.75	2.95
6	PRE	462	2.84	0.87
	POST		0.94	2.10
7	PRE	373	2.48	0.75
	POST		0.93	1.96
8	PRE	324	1.63	0.71
	POST		0.23	2.26
9	PRE	468	2.85	0.67
	POST		0.91	2.80
10	PRE	240	2.01	0.87
	POST		0.84	1.62
Mean	PRE	373	2.50*	0.98**
	POST		0.96*	2.28**
SD	PRE	86	0.48	0.32
	POST		0.38	0.42

*p<0.001

**p<0.001

Maximal expiratory flow-volume (EMEFV) curves were measured by inflating the lung to roughly +10 cm water transpulmonary pressure with a syringe, pausing a few seconds, and opening the bronchus with a solenoid valve to a 55 gallon barrel previously adjusted to a pressure of -10 cm water. The pneumotachograph (RSS100-HR, sensor model: 3700, flow range: 0 to 160 L/min; Hans Rudolph, Kansas City, MO) together with commercial software (RSS-HR Research Pneumotach System version 3.07b; Korr Medical Technologies, Salt Lake City, UT) was placed on a port to connect the interior of the plexiglass chamber with room air.

Under these circumstances the chamber became a variable flow plethysmograph. During EMEFV curves the pneumotachograph measured forced expiratory flow, while its integral measured expired volume.

The question arose whether minus 10 cm water pressure is adequate to produce maximal rates of expiratory flow from emphysematous lungs. The fact that following peak flow at ~0.2 seconds after exposing the lung to -10 cm water, the flow abruptly decreased in spite of a constant negative pressure in the large reservoir is strong evidence that expiratory flow was limited by dynamic airway compression. The pleural pressure required to limit flow in patients with emphysema is substantially less than in normal lungs (E8, E9) and decreases systematically with lung volume. In excised lungs it is even less because there is no upper airway to maintain tracheal pressure greater than the pressure at the airway opening. Thus at the instant that the bronchus was exposed to the reservoir pressure it was dynamically compressed by 10 cm water. This is sufficient to limit expiratory flow (E10-E12) so we are confident that maximal expiratory was achieved in all lungs studied. Table E3 presents the numerical data on EMEFV curves.

TABLE E3. EXPLANTED MAXIMAL EXPIRATORY FLOW-VOLUME CURVES

* = mean value

Lung #		1 sec	5 sec	10 sec	20 sec	Total	t to end (sec)
1	*PRE	156	434	591	813	1494	72
	*POST	151	671	1122	1854	2296	49
2	*PRE	118	304	410	520	641	44
	*POST	141	361	804	1116	1638	66
3	*PRE	83	288	452	810	1125	60
	*POST	258	813	1203	1678	1678	59
4	*PRE	133	428	658	977	1898	62
	*POST	383	939	1307	1730	2689	60
5	*PRE	95	186	262	346	418	62
	*POST	295	973	1424	1945	3116	53
6	*PRE	36	128	209	320	536	60
	*POST	399	1354	1832	2232	2517	46
7	*PRE	264	581	793	1045	1043	37
	*POST	286	1069	1559	2141	2352	43
8	*PRE	139	388	532	660	710	48
	*POST	442	1139	1473	1758	2252	51
9	*PRE	35	108	188	314	635	89
	*POST	207	878	1462	2128	3008	69
10	*PRE	116	303	512	652	828	73
	*POST	194	581	844	1120	1532	62

Explanted emphysematous lungs are easily inflated to volumes greater than that of the original thorax. Accordingly, the volume of inflation employed to measure the pressure volume diagrams was monitored to avoid the risk of structural damage due to hyperinflation. This contrasts with assessment of the EMEFV curves where all lungs were inflated to a pressure of 10 cm water before measurement of the flow volume curve. Yet the mean results between the EMEFV and pressure volume measurements of EVC before bypass were closely similar (within 8%). Following bypass, mean EVC was 0.4 L (19%) greater from EMEFV curves than from pressure volume data.

The slope of the static pressure volume curve or static compliance was measured as the slope of the tangent to the curve at 40% EVC on the deflation limb of the static pressure volume curve (E13). Data are included for only 9 of the lungs since the data for lung #10 were lost. When there is progressive air trapping during lung deflation, the volume of communicating airspaces decreases progressively. This tends to decrease static compliance and linearize the deflation static pressure volume curve so the lung volume at zero transpulmonary pressure, ERV, is large. The lung volume where air trapping starts is the volume at which the slope of the post-bypass deflation pressure volume curve increases while the pre-bypass slope remains relatively low. This generally occurred at high lung volumes. Thus airway bypass revealed the true hypercompliant nature of the severely emphysematous lung parenchyma that was masked by progressive air trapping before the bypass procedure. The steep deflation slope post bypass allowed for more gas to leave the lung before zero transpulmonary pressure was reached; as a result ERV decreased. The results shown in Table E4 are variable, but the pattern shows significant increases in static compliance following airway bypass.

TABLE E4. STATIC COMPLIANCE

Lung #		
1	PRE	441
	POST	667
2	PRE	578
	POST	1515
3	PRE	562
	POST	769
4	PRE	740
	POST	869
5	PRE	
	POST	666
6	PRE	834
	POST	1176
7	PRE	500
	POST	1429
8	PRE	648
	POST	580
9	PRE	430
	POST	1650
Mean	PRE	591*
	POST	1035**
SD	PRE	143
	POST	412

*p<0.001

**p=0.008

Expiratory rates of flow for each lung were matched with static elastic recoil pressure at identical lung volumes. This was done at four different levels of inflation. The static recoil pressure was divided by maximal expiratory flow to obtain the airway resistance upstream from equal pressure points, which is the uncompressed segment of the tracheobronchial tree (E14). The mean data for each lung are presented in Table E5.

TABLE E5. EXPLANTED MAXIMAL EX FLOW STATIC RECOIL CM WATER/L/SEC

Lung #		A	B	C	D	Mean
1	Pre	24	21	30	23	24.5
	Post	17	22	19	19	19
2	Pre	46	52	40	20	39.5
	Post	33	28	20	13	23.5
3	Pre	26	32	35	208	75
	Post	9.2	7.1	5.8	23	11.3
4	Pre	39	29	32	22	30.5
	Post	9.6	12.8	13.5	4.8	10
5	Pre	58	38	32	45	43
	Post	9.4	5.0	4.3	3.6	5.6
6	Pre	86	92	92	93	91
	Post	8.1	2.1	2.3	4.3	4.2
7	Pre	11	13	14	11	12.3
	Post	5.3	3	4	5	4.3
8	Pre	54	52	73	46	56
	Post	12	8.6	1.2	0.8	5.7
9	Pre	128	132	96	46	101
	post	13	4.6	3.0	10	7.7

A-D Levels of lung inflation
Pre - control
Post – following stent placement

Overall mean
Pre 52.5
Post 10

DISCUSSION

Fletcher and Peto characterized the natural history of emphysema by a progressively accelerating decline in FEV_1 over the years (E15). Because a good part of this decline is due to a progressive reduction in VC secondary to gas trapping, an alternative view of the natural history of this disease is a progressive increase in gas trapping. The schematic in Figure E1 shows that RV increased over three fold while TLC expanded less than 50% and VC decreased slightly more than 50%. This puts the decrease in FEV_1 in the perspective of resulting from gas trapping. But the decrease in VC only mandates a fall in FEV_1 if the FEV_1/FVC does not increase (E16).

The remainder of the fall in FEV_1 is due to both the loss of lung elastic recoil a *sine qua non* of emphysema (E17) and the obstruction in small airways that characterizes chronic obstructive pulmonary disease (E18). Both of these abnormalities, in turn, are presumably the proximate cause of gas trapping. Loss of lung elastic recoil leads to loss of small airway support through radial traction at progressively higher lung volumes, while anatomical changes in the small airways render these airways more susceptible to closure.

The most important observation in the present study is the marked reduction of trapped gas residual volume effected by airway bypass. We believe bypass accounts for the increased flow and volume of emptying reported earlier by Lausberg and associates [1], and confirmed in this study.

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FIGURE LEGENDS

Figure E1. Schematic characterization of the natural history of pulmonary emphysema (E15) with progressive increase in residual volume (RV) of 5.8 L (483%) while total lung capacity (TLC) increased 2.6 L (43%). Vital capacity (VC) decreased (to 45%) while functional residual capacity (FRC) increased (100%), and forced expiratory volume in one second was reduced to 12% of normal (data not shown). The mean age of our subjects at the time of lung studies was 61 years. The left ordinate displays data for a healthy young male subject. Data for the right ordinate closely approximate the mean preoperative pulmonary function results obtained in the patients of this study.

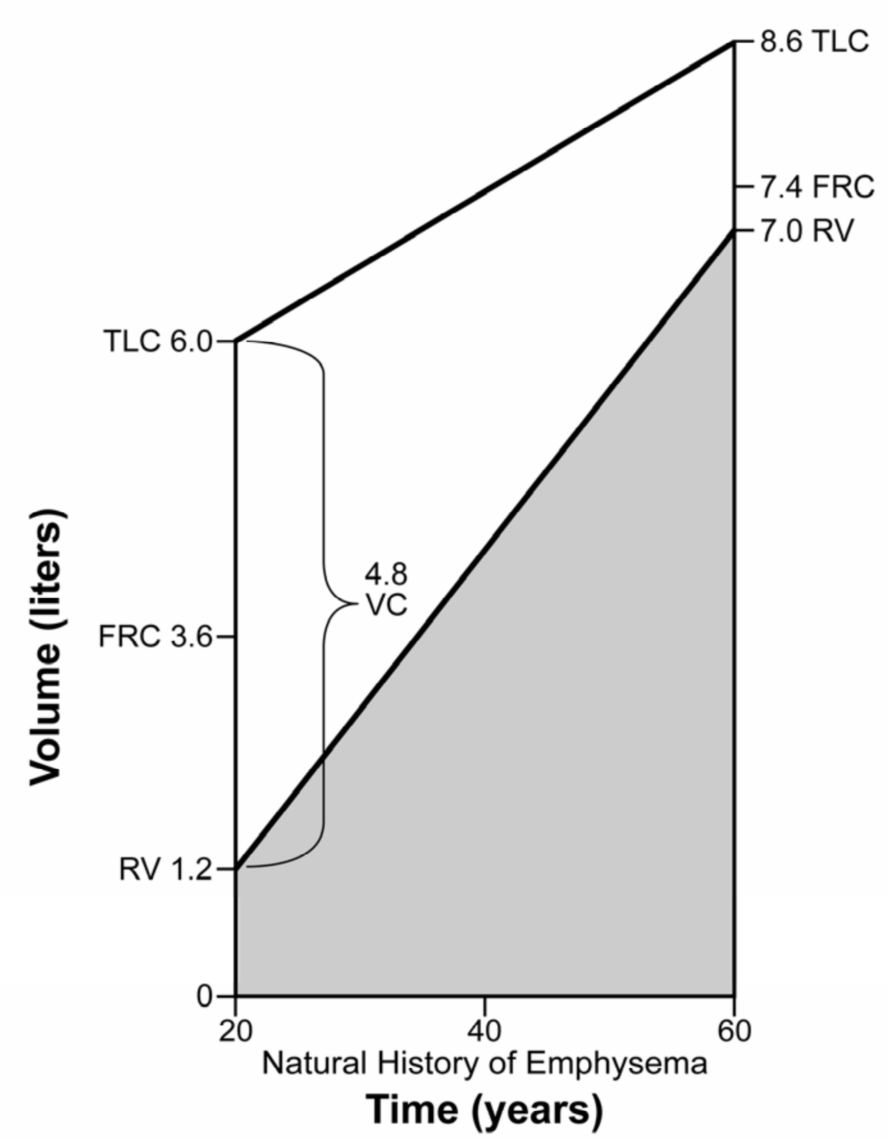
8.6 TLC
7.4 FRC
7.0 RV
TLC 6.0
4.8
VC
FRC 3.6
RV 1.2
0
20
40
60
Volume (liters)
Natural History of Emphysema
Time (years)

Figure E1