ERJ Express. Published on August 6, 2008 as doi: 10.1183/09031936.00056008

Abstract Word Count: 199
Text Word Count: 3181

The computed tomography assessment of lung volume changes after bronchial valve treatment.

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Short Title: Lung volume after bronchial valve treatment.

Support: This study was funded by Spiration Inc. The funding source had no role in the quantitative CT study conception or design. All CT data analyses were conducted independently of the funding source at the Department of Radiology (Vancouver General Hospital, Vancouver, BC.). The primary data are held at the James Hogg iCAPTURE Center. HOC is a British Columbia Lung Association/Canadian Institutes of Health Research New Investigator Award. DHD, CLF and SCS are employees of Spiration Inc.

Disclosures: Dr. Coxson has received honoraria, consultant fees and contract service agreements from GlaxoSmithKline for research studies involving quantitative computed tomography and COPD. A percentage of his salary between 2003 and 2006 derived from contract funds provided to a colleague (Peter D. Paré) by GSK for the development of validated methods to measure emphysema and airway disease using computed tomography. Drs. Nasute Fauerbach, Müller, and Ms Storness-Bliss and Mr Cogswell do not have a conflict of interest in the subject matter of this manuscript. Messers Dillard and Finger and Dr Springmeyer are employees of Spiration Inc.

This study uses data obtained from a Pilot Study which has been registered at clinicaltrials.gov

(NCT00145548)

Presented in part at 2007 ATS (Nasute Fauerbach)

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ABSTRACT:

Purpose: To correlate clinical outcome measures following treatment with bronchial valves with regional lung volume.

Methods: Computed Tomography (CT) scan data from 57 subjects with severe emphysema were obtained from 9 North American clinical trial sites. IBV® Valves were placed to occlude segmental and subsegmental bronchi in right and left upper lobes using a flexible bronchoscope. Subjects underwent St. George's Respiratory Questionnaire (SGRQ), pulmonary function (PFT), and exercise capacity. CT scans were analyzed at baseline and 1, 3 or 6 months after treatment to measure total and lobar lung density, volume and mass.

Results: Total lung volumes measured using CT were strongly correlated with PFT ($R^2 = 0.79$) and did not change with treatment. However, the treated upper lobes decreased in volume in 88% of the observations, mean 335 mL ± 444 ($p<0.001$), or -10.2% in the 6 month data. The untreated lobes had an 11.6% increase in volume. Changes in regional lung volume were associated with clinically meaningful improvements in SGRQ (-8.95 ± 16.22) ($p<0.01$) but not clinically meaningful PFT changes.

Conclusions: The significant health status improvements reported by subjects following bilateral bronchial valve treatment are associated with regional lung volume changes and inter-lobar shift measured using CT.

Keywords:

Computed tomography

Emphysema

Lung Volume Reduction Surgery

Intra-Bronchial Valve;

INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) is the most common form of primary pulmonary disability [1, 2] and an important cause of mortality when severe. As COPD becomes an end- stage disease, palliative surgical procedures such as bullectomy for giant bullae, lung volume reduction surgery (LVRS) and lung transplantation are the only potential treatments remaining.

The National Emphysema Treatment Trial (NETT) and some other smaller studies have shown that in a selected population of patients with heterogeneous distribution of emphysema and upper-lobe-predominance, LVRS can improve patient's quality of life, as well as their respiratory function, exercise capacity, and survival [3-8]. However, surgery in these already high-risk patients has a significant morbidity (20-30%) and a considerable operative mortality (7.9%) within 90 days of the procedure [9].

Therefore, minimally invasive techniques have been proposed as a method to reduce lung volume in these patients without undergoing open thoracotomy [10-15]. One of these new treatments is a one-way valve which is placed in the segmental bronchi of the most diseased lobes, generally the upper lobes, to prevent air from entering these portions of the lung during normal inspiration while still allowing air to exit. The original hypothesis for this procedure was that the delivery of gas to the treated lobes would be lower than the absorption of gas in these regions resulting in lobar atelectasis, and a reduction of total volume in the diseased lung [11, 12, 15]. This overall reduction in lung volume would result in functional and clinical improvements,

similar to those seen with LVRS, but without the invasive surgical procedure. However, several studies have found that the majority of subjects with clinical improvement did not have atelectasis and total lung volume reduction, so other mechanisms of action have been considered and investigated [15, 16].

The purpose of this study was to correlate clinical outcome measures with objective and subjective quantification of lobar lung volumes in patients with severe upper-lobe predominant emphysema treated with one-way bronchial valves. Our hypothesis was that as bronchial valves block distal airflow, the treated lobes would have a decrease in volume that could not be measured using physiologic lung pulmonary function methods.

MATERIALS AND METHODS:

CT scan data from 57 subjects with severe emphysema were obtained from nine North American clinical trial sites. All studies were approved by the appropriate Institutional Review Board or Ethics Committee and all subjects gave informed consent to receive treatment with the IBV® Valve System (Spiration, Inc., Redmond, WA) and have their clinical information collected.

These 57 subjects are the subset of 98 subjects from North American pilot studies (clinicaltrials.gov identifier NCT00145548) in which CT scan data could be obtained. All 98 subjects received an initial CT scan to determine whether they met the selection criteria for severe, upper-lobe predominant emphysema. The first 34 subjects enrolled in the trial received a second CT scan after 1 month to plan for a second bronchoscopic procedure to produce 34 paired baseline and one month scans for analysis. When the quantitative CT study was initiated, subjects that had not yet reached their 6 month follow-up received another CT scan to provide 16 paired scans for baseline and 6 month analyses. Finally, subjects enrolled after the initiation of the quantitative CT scan also received a CT scan at 3 months post-valve placement to provide a total of 34 paired baseline and 3 month scans. Some subjects received CT scans at more than one time point, and accordingly, the number of paired data sets exceeds the number of patients.

The inclusion/exclusion criteria of subjects have been previously reported [15]. Briefly, subjects were included if they had severe airflow limitation ($FEV_1 \leq 45\%$ predicted), hyperinflation (TLC $\geq 100\%$ predicted and RV $\geq 150\%$ predicted), a six minute walk distance of over 140 meters and severe emphysema that was determined to be upper-lobe predominant using the radiologic

comparison method that gave predictive results in the NETT [17]. Subjects were excluded if they had the high-risk criteria defined by NETT, signs of active infection or bronchospasm, were deemed to have lower-lobe predominant, diffuse, or superior segment of the lower lobe predominant using the radiologic comparison method, or were listed for LVRS or lung transplantation.

Bronchial Valve Placement

The bronchoscopic procedure and valve placement has been described [15]. Briefly, after anesthesia and endotracheal intubation, the sizes of the target airways were determined using a calibrated balloon catheter. Valves of the appropriate size were placed in both upper lobes using previously described techniques [15].

Clinical Data:

All subjects received pulmonary function testing including spirometry (FEV_1, FVC), plethysmography for static lung volumes (TLC, RV and FRC) as well as the DLCO using the single-breath carbon monoxide method. These measures were made at baseline (N=57), 1 month (N=52), 3 months (N=53) and 6 months (N=45) after treatment with bronchial valves. Disease specific health related quality of life (HRQL) was measured using the St. George's Respiratory Questionnaire (SGRQ) at the described time points. The SGRQ was completed during clinical stability with a 4-point or greater change indicating a clinically meaningful improvement and defined as a responder.

Radiologic Imaging:

CT scans were obtained using a high resolution computed tomography (HRCT) protocol (1 or 1.25 mm slice thickness, 10 mm gap, N=4), a multi-slice CT protocol (1mm slice thickness, contiguous images, N=13) or thick slice protocol (5mm slice thickness, contiguous images N=40) and archived using the DICOM 3.0 protocol.

Data Analysis:

All CT scans were analyzed at the University of British Columbia using both a qualitative and a quantitative procedure. For the qualitative analysis, two independent readers (PVNF, NLM) reviewed the CT scans. For the baseline CT scans the following parameters were considered: distribution of emphysema (Upper-lobe predominant [UL] or Non-upper lobe predominant [NUL], predominant type of emphysema (Centrilobular, Panacinar, or Paraseptal) and the extent of emphysema (Marked: 50-75%= grade 3, and Severe: >75%= grade 4). This allowed comparison to the local site assessments for the inclusion criteria of severe, UL predominant emphysema. In the follow-up CT scans the following was reported: presence of volume loss distal to the endobronchial valve and its grade if present (No volume loss, Linear atelectasis, Mild atelectasis: volume loss equivalent to less than one segment, Moderate atelectasis: volume loss was equivalent to one or more segments or Complete atelectasis: when the whole lobe was affected).

The quantitative analysis was performed by two different readers (CSB, SC) using custom software (EmphylxJ) as previously reported [18, 19]. Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with a prior position-knowledge algorithm. Total lung volume was calculated by summing the segmented pixel area in each slice and multiplying by the slice thickness. Lobar volume was calculated by manually tracing the fissures and summing the pixels as above. Three cases were analyzed by both observers to check for inter-observer variation in the fissure tracing technique. The mean CT attenuation measured in Hounsfield Units (HU) of the lobe and total lung were calculated and converted to a measure of density in g/ml by adding 1000 to the HU number and divided by 1000 [20, 21]. The mean density of the lung was then multiplied by the lung volume to estimate lung mass.

Statistical Analysis:

The difference between contiguous variables was tested using a t-test. Correlation estimates were calculated using Spearman's method unless otherwise specified. A CT responder was defined as any subject that had a decrease in the volume of the upper lobe and an increase in the non-upper lobe volume of greater than 10%. A change in SGRQ of minus four or more points was considered a clinical responder. The association of responders with lobar volume changes and quality of life was tested using a Chi-Square test. A p value of less than 0.05 was considered significant.

RESULTS:

The clinical outcome (without CT analysis) of the initial 30 subjects in these studies has been previously reported [15]. This group of 57 subjects with paired CT scans is an extension of the same protocols and is the first time that this data has been reported. Briefly, 346 implanted valves, a mean of 6.06 ± 1.96 per subject, were placed at the initial procedure. Most valves, 84%, were placed by the catheter technique and 99.7% of the targeted upper lobe airways were successfully treated. Nearly all subjects (54/57 or 95%) had bilateral upper lobes treated; 3 subjects received unilateral treatment because of preexisting disease in one upper lobe such as volume loss from a prior pneumonia. Most of the valves (76%) were placed in segmental bronchi and the remainder in subsegmental bronchi.

There were no deaths in this group of 57 subjects within 90 days of the procedure. The most frequent adverse events occurring within a day of the procedure were pneumothorax in 4 and bronchospasm in 2 subjects. One pneumothorax resolved without tube thoracostomy and the bronchospasm episodes were transient. In a 30 day period there were 10 subjects with a COPD exacerbation with an additional 10 in a 90 day period. There were 6 subjects with episodes of bronchitis within 30 days and 2 more within 90 days. Other than episodes of dyspnea, 3 within 30 days and 2 within 90 days, no respiratory complications occurred in more than 2 subjects in the designated time periods.

Pulmonary function, exercise, and HRQL outcomes before and after treatment are shown in Table 1 and are similar to those previously reported [15]. There was no significant improvement in FEV_1, FVC or DLCO, no significant decrease in TLC or RV, and a trend for improvement in

the 6MWT distance (12 m (3.6%), p>0.10). The significant and clinically meaningful changes were improvement in HRQL as measured by SGRQ following the procedure (p< 0.0001 for mean and mean change at 6 months).

The qualitative CT data showed high agreement regarding selection for severe UL predominant emphysema between the central reviewers and the clinical sites. There was clinical site and reviewer agreement regarding UL predominance in 54 of 57 (93%) of studies while the remaining 3 disagreements were between UL predominance and diffuse disease. In 2 of those 3 cases the clinical site and one of the 2 reviewers were in agreement. All studies were grade 3 or 4 severity (except 2 were grade 2) and all but two studies were centrilobular emphysema; with one each being panacinar and paraseptal.

On follow-up, moderate or complete lobar atelectasis was observed in 12 of 57 subjects (21%) at some point in the 6 months following valve implantation (Table 2). There was no atelectasis observed at any time point in 24 subjects (42%) and a linear or mild degree of atelectasis was present in 21 subjects (37%). In addition, serial data showed that in 5 subjects with 3 scans, the degree of atelectasis decreased over time in 1, increased in 2 and was stable in the other 3 subjects (Table 2).

The quantitative CT measurements show that there was no change in the total lung volume, total lung mass or total lung density at 1, 3, or 6 months (Table 3). However, there was significant decreases at all time points in the treated upper lobe volume and mass and significant increases in the untreated non-upper lobes volumes. The average change in lobar volumes was

approximately 300 ml or 10%. The inter-observer variation in lobar volume was 2 ± 2 % (range 0 to 5%) or 35 ± 31 ml (range 4 to 80 ml).

There was a strong correlation between the functional measurement of TLC by plethysmography and the CT measurement of total lung volume. There were 56 paired samples from baseline studies obtained ($r^2 = 0.77$) and 138 total samples ($r^2 = 0.79$).

Correlations between 6MWT and PFT changes, HRQL changes, and changes in UL and NUL volumes are shown in Table 4. These indicate the correlation with improved SGRQ was a NUL volume increase. The PFT and 6MWT changes did not correlate with improved HRQL. There are correlations between some 6MWT and PFT measures and improvement in FEV_1 is correlated with greater UL volume decrease, but not with HRQL. Figure 1 shows the UL and NUL changes which indicate a 10% or greater increase in NUL volume could define a threshold for a CT response. We therefore defined a 10% increase in NUL volume and any decrease of UL volume as a CT responder. Using results from all 40 subjects with 6 month or 3 month data (using 3 month if there was no 6 month data), these CT responders were compared to subjects with a greater than 4 point change in SGRQ (Table 5). There was a highly significant correlation between subjects that had an inter-lobar volume shift and HRQL ($p< 0.01$).

DISCUSSION:

This study shows that the minimally-invasive procedure of IBV Valve placement in the upper lobe bronchial segments decreases the end-inspiratory volume of the (more diseased) upper lobes and increases the volume of the untreated (less diseased) lobes, without producing overall lung volume reduction. Furthermore, these lobar volume changes are significantly associated with clinically meaningful improvement in health-related quality of life (HRQL) in subjects with severe UL predominant emphysema.

Until recently, lung volume reduction surgery (LVRS) or lung-transplantation have been the only options for palliative treatment of end-stage emphysema. The National Emphysema Treatment Trial (NETT) demonstrated LVRS improves survival, HRQL, and exercise capacity out as far as 6 years [3]. However, due to the significant morbidity and mortality associated with LVRS many people began looking for a procedure to reduce lung volume without subjecting the patients to major surgery. Therefore, minimally invasive procedures that allow the treatment of severely diseased patients is a very active area of research [15, 22-24].

Most minimally invasive procedures started with the hypothesis that lung volume reduction via atelectasis would be the major mechanism for improvement. This study shows that, according to CT assessment, atelectasis is infrequent, can be delayed in onset, and is often transient. This finding has also been reported in studies using other bronchial valves [25], raising question about the original hypothesis that bronchial valves result in reduction of total lung volume [15, 23] .

In the present study we used quantitative CT to measure the changes in lobar lung volumes due to bronchial valve placement. These data show that while total lung volume measured by CT and many other parameters such as TLC and FEV_1 do not change, there is a significant decrease in the volume of the upper lobes. Since there is a compensatory change in the volume of the non-upper lobes, this change cannot be assessed using global measures and this likely explains why changes in pulmonary function cannot be assessed. An example of this change in lobar volume is illustrated in Figure 2 where the major fissure in the right lung is clearly shifted anteriorly following valve placement corresponding to a 1555 ml decrease in upper lobe volume and a 1200 increase in non-upper lobe volume. This change in the treated lobe lung volume is similar to that reported in a small group of subjects at seven and 30 days [26]. We document a significant volume change six months following valve implantation along with a decrease in UL mass suggesting less ventilation and perfusion to the treated lobes. Furthermore, we report an inter-lobar volume shift to the non-treated lobes that is associated with an improvement in the quality of life in the valve recipients. This improved HRQL is greatest on the impact component of the SGRQ which measures factors such as being able to do household chores, talking without dyspnea, and feeling in control of their respiratory disease. The exact physiologic mechanisms for improved HRQL is not apparent from these data, but the shift of volume and mass away from the treated lobes suggests the mechanism is related to more ventilation and perfusion to the untreated and less-diseased non-upper lobes.

We think that a possible explanation for there not being a decrease in the upper lobe volume of all subjects could be due to a higher degree of collateral ventilation. Collateral ventilation has

been shown to be an important method of gas movement in many subjects [27]. Collateral ventilation is slower than bronchial ventilation so a modest degree of collateral ventilation may prevent complete atelectasis of the treated lobe but not prevent breath-by-breath changes in the ventilation of lobes as this QCT data indicates.

Our study has some limitations. The CT technique was not initially standardized between institutions which resulted in different scanning techniques being used in this study. However, this was a lung volume study, which is different from the lung densitometry studies that are commonly reported in the emphysema literature and are very reliant on CT protocol [19, 28]. In the current study the inter-lobar fissure was identifiable in all of the CT scans so we are confident that we were able to overcome this limitation and quantify the changes in lobar volume. A second limitation of the CT protocol was that there was no standardization of inspiration during the CT scan. However, all of these subjects have very severe emphysema and since they are breathing at or near TLC continuously and there was no change in the physiologic TLC or CT measured total lung volume we think that size of breath the subjects took during the CT scans were comparable and therefore the changes in lobar volume measured are reliable. Thirdly not all of the CT scans used contiguous acquisition and therefore contained gaps between the sections. However, it is well established from pathologic studies that this type of volume sampling provides a reliable and unbiased estimate of volume so we feel confident that our measurements reflect the volume of the total lung and individual lobes [29, 30]. Another limitation of our study is that the fissures were manually traced by an observer. Furthermore, some of the CT scans were obtained using thick slices and some of the fissures were likely incomplete (data not available) all of which will produce some variation in the measurement of

lobar volume. However, we measured the inter-observer variation due to manual tracing to be 5% (80 ml) or less which is well within the standard deviation of the measured lobar volume and therefore not likely to affect the results significantly. Finally, this study has a relatively short-term follow-up with CT compared to the 6 year follow-up now reported in studies for LVRS. The IBV Valve has been shown to have durable HRQL effects for 12 months [31]. And, these studies do show that, similar to LVRS in the early stages, there is a change in some measure of lung volume and an improvement in quality of life suggesting that this technique may provide long term benefits.

In conclusion, this study shows that the implantation of bronchial valves results in changes in regional lung volumes that are associated with an improvement of patient quality of life. We propose that the most common mechanism of action of bilateral bronchial valve treatment in severe upper-lobe predominant emphysema is not total lung volume reduction but a redirection, an inter-lobar shift, of inspired air to less diseased lung tissue.

Acknowledgements:

The authors wish to acknowledge and thank the IBV® Valve Pilot Trial Research Team: Cedars-Medical Center, Los Angeles, CA Robert McKenna, MD (Principal Investigator); Zab Mohsenifar, MD (Co-Principal Investigator); Carol Geaga, RN (Principal Clinic Coordinator); Cleveland Clinic Foundation (CCF), Cleveland, OH

Atul Mehta, MD (Principal Investigator); Thomas Gildea, MD (Co-Principal Investigator); Yvonne Meli, RN (Principal Clinic Coordinator); Michael Machuzak, MD; and Sudish Murthy, MD; Columbia University Medical Center New York, NY

Roger Maxfield, MD (Principal Investigator); Mark Ginsburg, MD (Co-Principal Investigator); Fran Brogan (Principal Clinic Coordinator); Angela Di Mango, MD; Bryon Thomahow, MD; Chun Yip, MD; Joshua Sonett, MD; and Patricia Jellen, RN; Duke University Medical Center, Durham, NC Momen Wahidi, MD (Principal Investigator); Thomas D'Amico, MD (Co-Principal Investigator); Linda S. Brown (Principal Clinic Coordinator); and John Davies, MA, RRT; Indiana University Hospital, Indianapolis, IN Praveen Mathur, MD (Principal Investigator); Francis Sheski, MD (Co-Principal Investigator); Kathleen Keller, RN (Principal Clinic Coordinator); and Annette Hempfling, RN; North Shore – Long Island Jewish Health System, Manhasset, NY David Ost, MD (Principal Investigator); Talwar Arunabh, MD (Co-Principal Investigator); Romona Ramdeo, RN (Principal Clinic Coordinator); and Shirley Lilavois, RN; Ohio State University, Columbus, OH

Philip Diaz, MD (Principal Investigator); Patrick Ross, MD (Co-Principal Investigator); Mahasti Rittinger, RCP, RRT (Principal Clinic Coordinator)

Abbas El-Sayed Abbas, MD; Bonnie Massey; Janice Drake, CRTT, CCRP; Maria Lucarelli, MD; Nitin Bhatt, MD; Rachael Compton; and Shaheen Islam, MD; University of Alabama at

Birmingham, Birmingham, AL Robert Cerfolio, MD, (Principal Investigator); Sara Pereira, MD, (Co-Principal Investigator); Jeana Alexander, RN, BSN, (Principal Clinic Coordinator); Ayesha Bryant; Chad Miller, MD; Keith Willie, MD; and Sandra Calloway; University of Pennsylvania Medical Center, Philadelphia, PA Daniel Sterman, MD (Principal Investigator); Ali Musani, MD (Co-Principal Investigator); Barbara Finkel, MSN, RN, CCRC (Principal Clinic Coordinator); Andrew Haas, MD; Colin Gillespie, MD; David Lipson, MD Michael Machuzak, MD; Michael Sims, MD; and Steven Leh, MD; University of Virginia Health System, Charlottesville, VA Jonathon Truwit, MD (Principal Investigator); Yun Michael Shim, MD (Co-Principal Investigator); Peggie Donowitz, RN (Principal Clinic Coordinator); Ajeet Vinayak, MD; Halim Hanna, MD; Monojkumar Patel, MBBS; and Renee Campbell, RN; University of Washington Medical Center, Seattle, WA Douglas Wood, MD (Principal Investigator); Michael Mulligan, MD (Co-Principal Investigator); Jo Ann Broeckel Elrod Ph.D (Principal Clinic Coordinator); and Linda Harrison, CCRC.

The authors also wish to acknowledge Anh-Toan Tran (Department of Radiology, VGH) for the development and support of the CT analysis software and database and Andrew Mugglin, PhD (University of Minnesota) for statistical analysis and advice.

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Table 1: Clinical Outcome Measures over Time: Mean ± SD and (n) for each value before and after treatment and the difference between baseline and time after treatment.

	Baseline	**1 Month**	**3 Month**	**6 Month**
FEV_1 (L) **Difference (L)** **n**	0.84 ± 0.23 57	0.82 ± 0.22 -0.03 ± 0.14 55	0.80 ± 0.22 -0.03 ± 0.17 54	0.79 ± 0.23 -0.04 ± 0.16* 45
FVC (L) **Difference (L)** **n**	2.76 ± 0.84 57	2.75 ± 0.83 -0.03 ± 0.48 55	2.61 ± 0.74 -0.12 ± 0.46 54	2.59 ± 0.73 -0.11 ± 0.60* 45
TLC (L) **Difference (L)** **n**	7.78 ± 1.40 56	7.65 ± 1.41 -0.11 ± 0.68 55	7.74 ± 1.49 -0.03 ± 0.73 54	7.64 ± 1.51 -0.12 ± 0.63 45
RV (L) **Difference (L)** **n**	4.90 ± 1.04 56	4.90 ± 1.05 0.03 ± 0.87 55	5.10 ± 1.15 0.19 ± 0.93 54	4.98 ± 1.26 0.02 ± 0.94 45
DLCO (ml/min) **Difference (ml/min)** **n**	9.50 ± 3.13 56	9.67 ± 3.26 0.09 ± 2.11 54	8.97 ± 3.06 -0.49 ± 2.17 54	9.10 ± 2.76 -0.29 ± 1.99 45
6MWT (m) **Difference (m)** **n**	336 ± 85 57	345 ± 90 4 ± 56 54	349 ± 85 9 ± 57 54	348 ± 97 12 ± 65 45
SGRQ **Difference** **n**	58.2 ± 12.6 56	52.7 ± 13.6 -5.49 ± 13.60** 55	54.5 ± 18.0 -4.28 ± 15.81* 54	50.0 ± 19.1 -8.95 ± 16.22*** 45

*p<0.05, **p<0.01, ***p<0.0001

Table 2: Subjects with moderate or complete lobar atelectasis observed by CT scan over time

Case number	Baseline	1 month	3 month	6 month
1	0	L-3	nd	nd
2	0	R-3	nd	nd
3	0	R-4	nd	nd
4	0	L-2	nd	L-3
5	0	R-3	R-3, L-3	nd
6	R-2	R-2, L-3	nd	nd
7	0	R-2, L-3	R-2, L-3	nd
8	0	nd	R-3, L-2	nd
9	0	R-4	nd	R-4
10	0	nd	R-4	nd
11	0	R-3	R-2	nd
12	0	R-2, L-3	nd	R-2, L-3

Left (L) or Right (R) side, and 0-4 categories- 0= none, 1= linear, 2= mild, 3= moderate, 4= complete lobe nd = scan not done

Table 3: Quantitative CT measurements at baseline and after treatment:

		Baseline N = 57	**1 Month N = 34**	**3 Months N = 34**	**6 Months N = 16**
Total Lung	**Volume (ml)** **Difference (ml)** **% Change**	6840 ± 1375	6737 ± 1383 -54 ± 495 -0.6 ± 7.8	6852 ± 1456 -45 ± 347 -0.9 ± 5.4	6429 ± 1605 39 ± 305 0.6 ± 5.3
Upper Lobe	**Volume (ml)** **Difference (ml)** **% Change**	3419 ± 872	3058 ± 845**** -328 ± 511**** -9.3 ± 14.1	3165 ± 976**** -319 ± 427**** -9.5 ± 12.2	3025 ± 1212*** -335 ± 444*** -10.2 ± 12.7
Non-Upper Lobe	**Volume (ml)** **Difference (ml)** **% Change**	3421± 867	3679 ± 869**** 274 ± 419 **** 9.2 ± 13.9	3687 ± 982**** 274 ± 334**** 8.4 ± 10.2	3404 ± 1025**** 374 ± 387**** 11.6 ± 11.6
Total Lung	**Mass (g)** **Difference (g)** **% Change**	728 ± 183	714 ± 165 2 ± 126 1.2 ± 15.3	715 ± 181 -15 ± 139 -0.6 ± 16.6	680 ± 195 -62 ± 108 -7.3 ± 13.0
Upper Lobe	**Mass (g)** **Difference (g)** **% Change**	301 ± 90	259 ± 75** -36 ± 67** -10.5 ± 19.3	266 ± 111*** -37 ± 72*** -12.3 ± 19.5	238 ± 99*** -71 ±63*** -22.6 ± 15.9
Non-Upper Lobe	**Mass (g)** **Difference (g)** **% Change**	427 ± 111	455 ± 105 37 ± 75* 10.2 ± 16.8	449 ± 86 22 ± 96 8.0 ± 17.5	442 ± 113 9 ± 71 3.0 ± 15.0
Total Lung	**Density (g/ml)** **Difference (g/ml)** **% Change**	0.108 ± 0.026	0.107 ± 0.020 0.000 ± 0.026 2.8 ± 19.2	0.105 ± 0.019 -0.001 ± 0.020 0.5 ± 17.2	0.107 ± 0.021 -0.012 ± 0.025 -7.2 ± 16.0
Upper Lobe	**Density (g/ml)** **Difference (g/ml)** **% Change**	0.090 ± 0.024	0.087 ± 0.020 -0.003 ± 0.028 1.2 ± 27.3	0.084 ± 0.022 -0.003 ± 0.019 -1.9 ± 22.5	0.080 ± 0.022 -0.016 ± 0.028 * -12.1 ± 22.4
Non-Upper Lobe	**Density (g/ml)** **Difference (g/ml)** **% Change**	0.129 ± 0.037	0.126 ± 0.023 -0.002 ± 0.027 1.8 ± 16.1	0.128 ± 0.035 -0.002 ± 0.028 0.0 ± 16.2	0.136 ± 0.040 -0.013 ± 0.024 -7.3 ± 12.8

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Table 4 Correlations between changes Delta or D. HRQL, QCT, PFT, and 6MWT results. Percentage changes were used for the QCT measures, and absolute change for the other measures in these analyses.

Quantity 1	Quantity 2	Spearman's Correlation	P-value
D.SGRQ	D.6MWT	-0.2436	0.1298
D.SGRQ	D.FVC	-0.2417	0.1329
D.SGRQ	D.UL	0.1659	0.305
D.SGRQ	D.NUL	-0.3809	0.0159
D.SGRQ	$D.FEV_1$	-0.2245	0.1637
D.6MWT	D.FVC	0.4783	0.0018
D.6MWT	D.UL	-0.3316	0.0366
D.6MWT	D.NUL	0.2991	0.0608
D.6MWT	$D.FEV_1$	0.2734	0.0878
D.FVC	D.UL	-0.3105	0.0512
D.FVC	D.NUL	0.3049	0.0557
D.UL	D.NUL	-0.473	0.0023
D.UL	$D.FEV_1$	-0.449	0.0037
D.NUL	$D.FEV_1$	0.3709	0.0185

Table 5: SGRQ and CT Volume comparisons using all 40 subjects with 3 or 6 month paired CT data. Correlation is significant at $p < 0.01$ using chi-squared testing with continuity correction

	CT Responder	**CT Non-Responder**
SGRQ Responder	14 (35%)	7 (18%)
SGRQ Non-Responder	4 (11%)	15 (40%)

Figure Legends:

Figure 1: Scatter plot of percentage change in Upper Lobe (UL) volume change compared to Non-Upper Lobe (NUL) volume change. Solid points are SGRQ responders and open points are SGRQ non-responders with a responder defined as a 4 point or greater change. The dotted vertical line indicates the threshold for a NUL response at 10%.

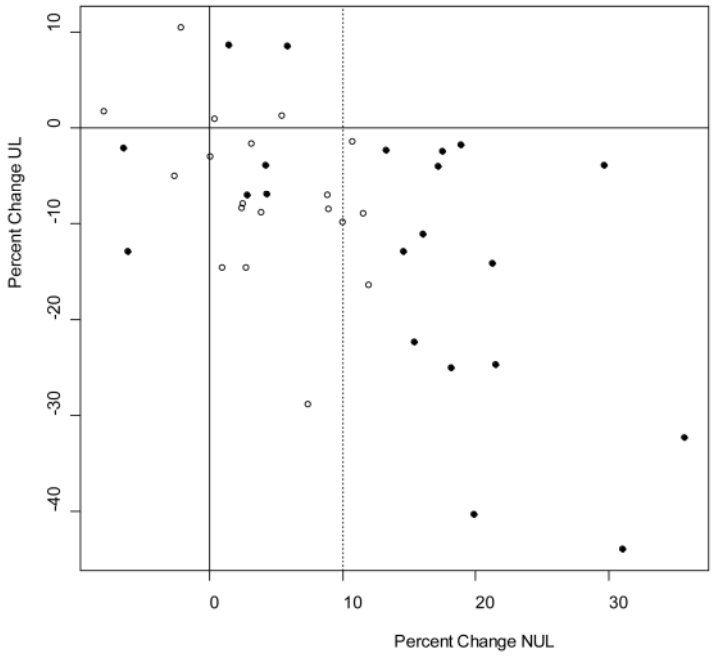

Figure 2: This figure shows a CT scan taken at baseline before the IBV® Valve treatment (A) and a matched CT scan acquired six months following treatment (B). Notice the shift in the major fissure (arrow) in the right lung which was associated with a 1555 ml decrease in upper lobe volume and a 1200 ml increase in non-upper lobe volume.