CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Altered thoracic gas compression contributes to improvement in spirometry with lung volume reduction surgery

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Background: Thoracic gas compression (TGC) exerts a negative effect on forced expiratory flow. Lung resistance, effort during a forced expiratory manoeuvre, and absolute lung volume influence TGC. Lung volume reduction surgery (LVRS) reduces lung resistance and absolute lung volume. LVRS may therefore reduce TGC, and such a reduction might explain in part the improvement in forced expiratory flow with the surgery. A study was conducted to determine the effect of LVRS on TGC and the extent to which reduced TGC contributed to an improvement in forced expiratory volume in 1 second (FEV_1) following LVRS.

Methods: The effect of LVRS on TGC was studied using prospectively collected lung mechanics data from 27 subjects with severe emphysema. Several parameters including FEV_1, expiratory and inspiratory lung resistance (Rle and Rli), and lung volumes were measured at baseline and 6 months after surgery. Effort during the forced manoeuvre was measured using transpulmonary pressure. A novel method was used to estimate FEV_1 corrected for the effect of TGC.

Results: At baseline the FEV_1 corrected for gas compression ($NFEV_1$) was significantly higher than FEV_1 ($p<0.0001$). FEV_1 increased significantly from baseline ($p<0.005$) while $NFEV_1$ did not change following surgery ($p>0.15$). TGC decreased significantly with LVRS ($p<0.05$). Rle and maximum transpulmonary pressure (TP_{peak}) during the forced manoeuvre significantly predicted the reduction in TGC following the surgery (Rle: $p<0.01$; TP_{peak}: $p<0.0001$; adjusted $R^2=0.68$). The improvement in FEV_1 was associated with the reduction in TGC after surgery ($p<0.0001$, adjusted $R^2=0.58$).

Conclusions: LVRS decreased TGC by improving expiratory flow limitation. In turn, the reduction in TGC decreased its negative effect on expiratory flow and therefore explained, in part, the improvement in FEV_1 with LVRS in this cohort.

C hronic obstructive pulmonary disease (COPD) is a progressive and debilitating disease. Expiratory flow limitation is the hallmark of COPD. Lung elastic recoil pressure, frictional pressure loss upstream of the choke point, and the relationship between cross sectional area and transmural pressure of the airways at the choke point determine the maximal expiratory flow.[1] Absolute lung volume influences the lung elastic recoil pressure.[2] Reduced lung elastic recoil pressure, increased lung resistance, and mismatch between size of the lung and the chest cavity are proposed mechanisms of airflow limitations in emphysema.[1 2]

During a forced expiratory manoeuvre, thoracic volume diminishes due to both exhaled air and compressed air. At high and mid lung volumes, as flow increases to equal that of wave speed, flow limitation will occur regardless of the driving pressure gradient.[3–5] It is at this point that thoracic gas compression (TGC) may occur even in areas of the lung with access to open airways. Furthermore, dynamic narrowing of airways during a forced manoeuvre in subjects with flow limitation may create areas of trapped gas in the lung and may result in gas compression.[5] The TGC is greatest in subjects with a large lung volume, strong expiratory muscles, and expiratory flow limitation.[6] Jaeger and Otis,[7] in a study of normal subjects, showed that TGC increased with increasing airway resistance, increasing expiratory effort, and increasing lung volume. Large lung volume and expiratory flow limitation are hallmarks of COPD. Thus, subjects with COPD can generate large TGC during forced expiratory manoeuvres. By reducing the absolute lung volume, the TGC reduces the retractive forces that keep the airways open and hence both forced expiratory flow and forced expired

volume in 1 second (FEV_1) diminish. Because of the TGC, the highest values for FEV_1 are associated with forced vital capacity (FVC) manoeuvres performed with submaximal effort.[6]

Lung volume reduction surgery (LVRS) has shown promise in improving lung function, exercise capacity, and quality of life in patients with severe emphysema. Several studies have reported significant improvements in FEV_1 with LVRS, but always with wide individual variability.[8–11] Studies of LVRS have proposed an improvement in lung elastic recoil pressure, a reduction in lung resistance, and a reduction in hyperinflation (RV/TLC) as mechanisms of expiratory flow improvement.[9 10 12] LVRS reduces lung resistance and lung volume and increases lung elastic recoil pressure;[9 12] it should therefore reduce the TGC and its negative effect on expiratory flow and FEV_1. In this study we report the effect of LVRS on TGC and explore the effect of TGC reduction on the improvement in FEV_1.

METHODS

Twenty seven subjects with severe emphysema were enrolled in a randomised controlled trial of bilateral LVRS through

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Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LVRS, lung volume reduction surgery; $NFEV_1$, FEV_1 obtained using no compression method; absolute $DFEV_1$, $NFEV_1 - FEV_1$; percentage $DFEV_1$, absolute $DFEV_1/FEV_1$; PEF, peak expiratory flow; P_{el}, elastic recoil pressure at TLC/TLC; Rle, expiratory lung resistance; Rli, inspiratory lung resistance; RV, residual volume; TGC, thoracic gas compression; TLC, total lung capacity; TP_{peak}, peak transpulmonary pressure during a forced expiratory manoeuvre

median sternotomy at the Michael E DeBakey VA Medical Center. The subjects underwent lung function measurements at baseline and at 6 months follow up. All subjects were clinically stable at the time of the study, and all had ceased smoking for at least 3 months before the beginning of the study. The study protocol was approved by the Institutional Review Board and each subject gave written consent.

Physical measurements

Standard spirometric measurements were obtained before the study. Lung mechanics were measured with the subjects seated in an air conditioned volume displacement plethysmograph. The characteristics of this type of plethysmograph are described elsewhere.[13] Flow at the mouth level was measured by a no. 3 Fleisch pneumotachograph connected to an MP 45 Validyne (Northridge, CA, USA) pressure transducer (± 2 cm H_2O). Transpulmonary pressure was measured by a 10 cm long thin latex balloon positioned in the lower third of the oesophagus (38–45 cm from the nostril) and connected to a pressure transducer (352 cm H_2O; Statham 131). The flow, transpulmonary pressure, and volume displacement transducers were connected to Validyne CD19A high gain carrier demodulator amplifiers and the signals were digitally collected with a personal computer (133 MHz Pentium Dell) using a National Instruments 12 bit data acquisition board (Lab-PC+).[14] The data collection system is described in detail elsewhere.[15] Signals were collected at a rate of 100 Hz. During each session we obtained at least three reproducible forced expiratory manoeuvres. For the forced manoeuvres, each subject was instructed to inspire to total lung capacity (TLC) then, with maximal effort, to expire to residual volume (RV). Quality control measures as outlined by the American Thoracic Society were used to select appropriate manoeuvres.[16] Each subject was instructed to expire forcefully for at least 6 seconds. In addition, expiratory and inspiratory lung resistances were measured during quiet breathing using the model reported previously.[17] This model examines the whole breath with the addition of a term (R'_E) to account for the increasing resistance during expiration in subjects with dynamic hyperinflation. The R'_E term measures an interaction between volume and resistance during expiration.[17] TLC and RV were measured in all subjects at baseline and after intervention. We used the coefficient of retraction—the ratio of static recoil pressure at TLC to absolute lung volume at TLC—as an indicator of elastic recoil.[18] Reference values for lung function parameters published by Black and Hyatt were used.[19][20] The software

was written and developed in MATLAB (Natick, MA, USA) to compute the estimated parameters for the described methods.[21]

After data collection the computational program in the MATLAB environment was used to calculate the FEV_1 corrected for the effect of TGC. The specification of the method (No Compression Method or NCM) is described elsewhere.[22] The software was developed based on the following assumptions. A plot of the expiratory flow signal versus the box volume signal in an x–y graph is generated. This plot represents the forced expiratory flow-volume loop with units of litre/second (l/s) on the y axis and litres (l) on the x axis. Subsequently, the software inverts the expiratory flow signal between TLC and RV, plots the box volume signal (l) on the x axis and the inverted expiratory flow signal (s/l) on the y axis, and generates a graph. This new graph contains a very steep negative slope at the beginning of the manoeuvre that reverses to a positive shallow slope during the effort independent portion (below 80% of TLC) of the FVC manoeuvre. Integration of the area under this curve produces a measure with a unit of seconds (computed time). The computed time (a time based on volume and flow) is the mouth transit time for increments of box volume. Likewise, mouth transit time is smaller at the start of the forced manoeuvre (at TLC) than at the end of the manoeuvre (at RV). As an individual becomes more obstructed near the end of a forced manoeuvre, the likelihood of the gas compression is higher. By summing each computed time point, the software reconstructs a time line that represents volume changes based on expiratory mouth flow and body plethysmograph volume.

After generating the computed time, the software calculates the subject's FEV_1 corrected for TGC ($NFEV_1$). The software uses the computed time and the backward extrapolation technique to determine the start time for the $NFEV_1$ calculation.[23] To estimate the magnitude of TGC, we used the equation $DFEV_1 = (NFEV_1 - FEV_1)/FEV_1$, where $NFEV_1$ and FEV_1 are absolute values of forced expiratory volume in 1 second (litres) as measured by the standard method and the NCM (see above).

Statistical analysis

STATA version 7 (College Station, TX, USA) was used for statistical data analysis. Demographic and baseline lung function data were analysed by descriptive statistics and presented as means and standard deviation. The paired Student's t test was used to evaluate the effect of LVRS on

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Table 1 Lung mechanics in 27 subjects before and 6 months after LVRS

Parameter	Baseline	After LVRS	p value
PEF (l/s)	2.9 (0.83)	3.3 (1.7)	>0.2
TP_{peak} (cm H_2O)	128 (73)	130 (56)	>0.42
TLC (l)	9.7 (1.3)	8.8 (1.1)	<0.003
RV (l)	6.5 (1.2)	5.3 (1.3)	<0.001
RV/TLC (%)	67 (7)	59 (9)	<0.001
Rle (cm H_2O/l/s)	26 (17.9)	19 (13.7)	<0.01
Rli (cm H_2O/l/s)	5 (2.2)	4 (2.4)	>0.11
Coefficient P_{el} (cm H_2O/l)	1.15 (0.49)	1.59 (0.81)	<0.005
FVC (l)	2.35 (0.75)	2.87 (0.79)	<0.005
FEV_1 (l)	0.87 (0.24)	1.07 (0.38)	<0.005
FEV_1 (% predicted)	26 (8)	31 (11)	0.005
$NFEV_1$ (l)	1.44 (0.37)	1.53 (0.48)	>0.15
$DFEV_1$ (% change from baseline)	74 (52)	48 (27)	<0.05

PEF, peak expiratory flow; TP_{peak}, peak transpulmonary pressure during a forced expiratory manoeuvre; TLC, total lung capacity; RV, residual volume; RV/TLC, RV/TLC ratio; Rle, expiratory lung resistance; Rli, inspiratory lung resistance; coefficient P_{el}, elastic recoil pressure at TLC/TLC; FVC, forced expiratory vital capacity; FEV_1, forced expired volume in the first second of forced expired manoeuvre; $NFEV_1$, FEV_1 obtained using no compression method; $DFEV_1$, $(NFEV_1 - FEV_1)/FEV_1$.

Table 2 Baseline lung mechanics in 27 subjects undergoing LVRS according to their FEV_1 response to the surgery

Parameter	FEV₁ groups		p value
	Responders	Non-responders	
PEF (l/s)	2.96 (0.26)	2.93 (0.19)	>0.91
TP_{peak} (cm H_2O)	148 (19.5)	92 (27.1)	0.11
TLC (l)	9.4 (1.4)	9.8 (0.8)	>0.44
RV (l)	6.2 (1.3)	6.5 (1.1)	>0.59
RV/TLC (%)	66 (6)	66 (8)	>0.90
Rle (cm H_2O/l/s)	26 (19.4)	25 (17.0)	>0.94
Rli (cm H_2O/l/s)	5 (2.6)	5 (1.8)	>0.80
Coefficient P_{el} (cm H_2O/l)	1.14 (0.35)	1.14 (0.47)	>0.99
FVC (l)	2.2 (0.60)	2.5 (0.89)	>0.24
FEV_1 (l)	0.84 (0.26)	0.90 (0.23)	>0.50
$NFEV_1$ (l)	1.56 (0.39)	1.30 (0.31)	0.06
FEV_1/FVC (%)	39 (7.5)	38 (8.2)	>0.73
$DFEV_1$ (% change from baseline)	98 (58)	48 (30)	0.01

PEF, peak expiratory flow; TP_{peak}, peak transpulmonary pressure during a forced expiratory manoeuvre; TLC, total lung capacity; RV, residual volume; RV/TLC, RV/TLC ratio; Rle, expiratory lung resistance; Rli, inspiratory lung resistance; coefficient P_{el}, elastic recoil pressure at TLC/TLC; FVC, forced expiratory vital capacity; FEV_1, forced expired volume in the first second of forced expired manoeuvre; $NFEV_1$, FEV_1 obtained using no compression method; $DFEV_1$, $(NFEV_1 - FEV_1)/FEV_1$.

different lung function parameters (table 1). The relationships between the TGC and other parameters of lung function were evaluated by stepwise multiple regression analysis. A p value of <0.05 was considered an acceptable level of significance. To identify predictors of FEV_1 improvement with LVRS a stepwise multiple regression analysis was used (p value entrance and removal criteria of 0.2 and 0.4, respectively). The results of the analysis are reported as p values, β coefficients, and adjusted R^2.

The subjects were also grouped according to their FEV_1 response into responders (improvement in FEV_1 of 200 ml and 12% from baseline) and non-responders. An unpaired Student's t test was used to compare the baseline lung function parameters between the two groups (table 2). Logistic regression analysis was used to identify the predictors of response.
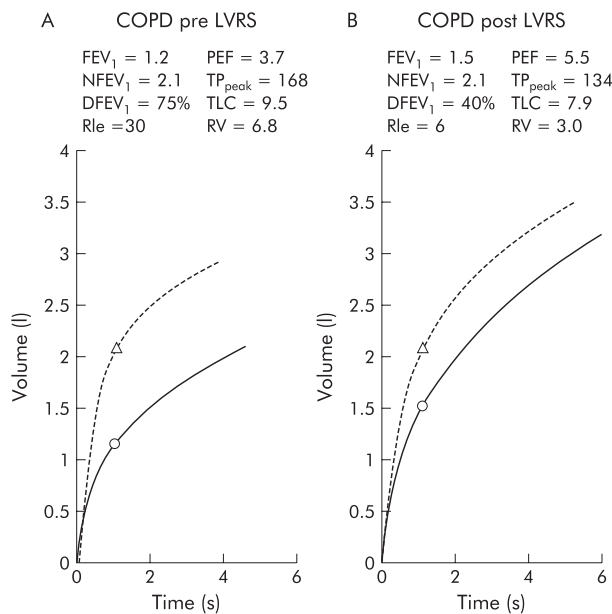

Figure 2 Improvement in FEV_1 with LVRS correlates with baseline TGC. There is a strong association between baseline $DFEV_1$ and improvement in FEV_1. A large TGC at baseline linearly predicted a greater improvement in FEV_1 with surgery. Linear regression line and 95% confidence interval lines are also shown.

RESULTS

The baseline and post LVRS pulmonary function data of the 27 study subjects are shown in table 1. All the subjects were male with a mean (SD) age of 63 (7) years, and all suffered from severe emphysema. At baseline the subjects had severe expiratory flow limitation as indicated by high Rle, low FEV_1, and low PEF. In addition, they suffered from significant hyperinflation as indicated by high TLC, RV, and RV/TLC ratio. They also produced very high intrathoracic pressure during the forced manoeuvres as shown by high peak transpulmonary pressure (TP_{peak}). The profile of the patients in our study is similar to published data from other LVRS trials.[8 9 12]

$NFEV_1$ was significantly higher than FEV_1 at baseline (p<0.0001) and the mean (SD) $DFEV_1$ was 74 (52)% at baseline. In multiple regression analysis, baseline $DFEV_1$ was significantly predicted by baseline TP_{peak} (p<0.0001, β coefficient = 0.006), RV/TLC ratio (p<0.02, β coefficient = 2.545) and Rle (p = 0.07, β coefficient = 0.007; $R^2 = 0.83$). Lung mechanics data before and 6 months after LVRS in one patient with COPD are shown in fig 1. In this patient FEV_1 increased by 25% from baseline after LVRS whereas $NFEV_1$ did not change, so the $DFEV_1$ was reduced. The subject's effort was not appreciably different as shown by similar TP_{peak} measurements at baseline and follow up.

Figure 1 Effect of LVRS on thoracic gas compression (TGC) in a representative patient with COPD. Solid black line shows FEV_1 and dotted line shows $NFEV_1$ (A) at baseline and (B) 6 months after surgery. $DFEV_1$ fell from 75% to 40% with LVRS. These data show that LVRS has a considerable effect on TGC.
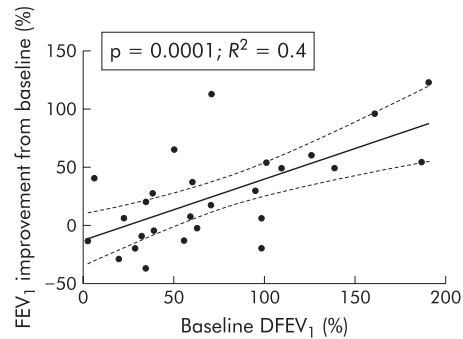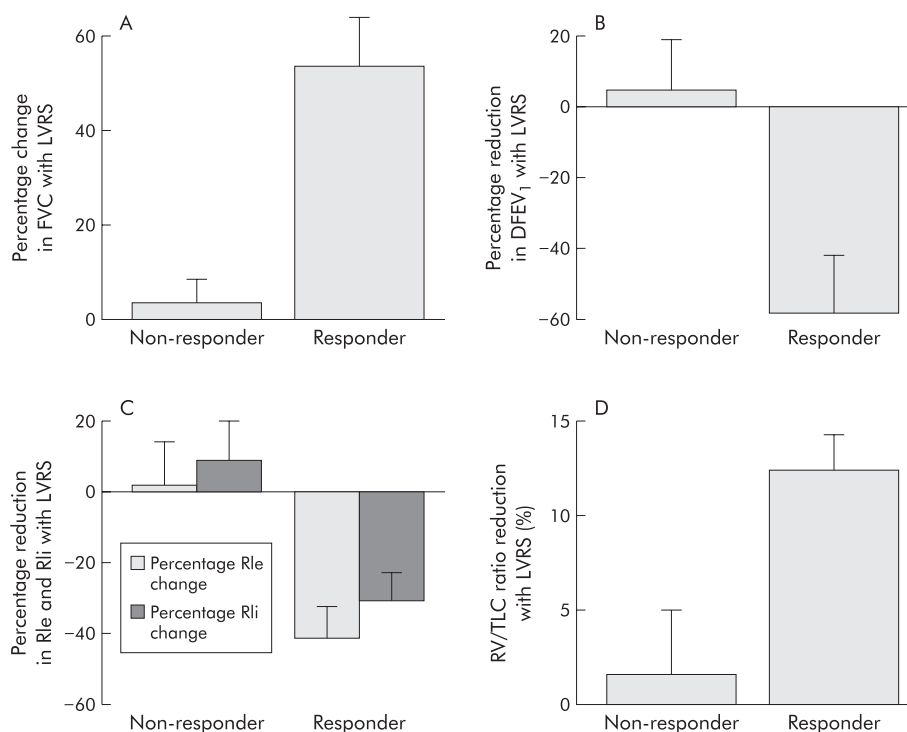
Figure 3 Changes in lung function in LVRS responders and non-responders. Compared with non-responders, responders showed (A) a significantly greater improvement in FVC; (B) a significantly diminished TGC; (C) reduced expiratory and inspiratory lung resistances; and (D) a greater reduction in the RV/TLC ratio.

DFEV$_1$ decreased significantly after LVRS (p<0.05). In stepwise multiple regression analysis, changes in TP$_{peak}$ and Rle significantly predicted the change in DFEV$_1$ (TP$_{peak}$: p = 0.0001, β coefficient 0.005; Rle: p = 0.01, β coefficient −0.023; R^2 = 0.68). Other parameters including change in TLC, RV, and RV/TLC were not significantly predictive of the change in DFEV$_1$ with the surgery.

LVRS in this cohort resulted in a significant improvement in FEV$_1$ and elastic recoil pressure and a significant reduction in Rli, Rle, TLC, RV, and RV/TLC (table 1). In linear regression analysis the improvement in FEV$_1$ with LVRS was significantly correlated with the reduction in Rle (p<0.02, R^2 = 0.17, β coefficient −0.015 (95% CI −0.028 to −0.003)), Rli (p<0.002, R^2 = 0.35, β coefficient −0.103 (95% CI −0.159 to −0.048)), DFEV$_1$ (p<0.0001, R^2 = 0.58, β coefficient 0.557 (95% CI 0.368 to 0.746)), RV/TLC (p<0.03, R^2 = 0.14, β coefficient −1.569 (95% −2.965 to −0.17)), and TP$_{peak}$ (p<0.05, R^2 = 0.28, β coefficient 0.003 (95% CI 0.001 to 0.005)). In stepwise multiple regression analysis the improvement in FEV$_1$ was predicted by the change in DFEV$_1$ (p<0.0001, β coefficient 0.451 (95% CI 0.237 to 0.665)) and Rli (p = 0.07, β coefficient −0.046 (95% CI −0.096 to −0.004) with adjusted R^2 = 0.62.

Table 2 shows the baseline lung mechanics data for the FEV$_1$ responders and non-responders after LVRS. DFEV$_1$ at baseline differed significantly between the two groups (p = 0.01). In linear regression analysis using FEV$_1$ as a continuous variable, baseline DFEV$_1$ was predictive of the improvement in FEV$_1$ with LVRS (p<0.0001, R^2 = 0.4, β coefficient 0.523 (95% CI 0.271 to 0.776)). The TP$_{peak}$ was different in the two groups but this difference did not reach statistical significance. Data showing an association between baseline DFEV$_1$ and FEV$_1$ improvement from baseline with LVRS are shown in fig 2. The baseline TGC strongly predicted FEV$_1$ improvement with LVRS.

A comparison of the change in lung function parameters with LVRS between FEV$_1$ responders and non-responders is shown in fig 3. The improvement in FVC with LVRS was significantly higher in FEV$_1$ responders (fig 3A) and TGC was reduced more with LVRS in FEV$_1$ responders (fig 3B). A similar pattern was seen for expiratory and inspiratory resistances (fig 3C) and RV/TLC ratio (fig 3D).

DISCUSSION

In this cohort of subjects with severe airflow limitation due to emphysema, TGC was large. TGC is appreciably higher in subjects with COPD than in normal subjects.[22] Lung resistance, the subjects' effort, and lung volume significantly predicted the magnitude of TGC. LVRS reduced TGC mainly as a result of improvement in lung resistance. The most striking result of our study is that a reduction in TGC was predictive of an improvement in FEV$_1$ with LVRS. Furthermore, baseline TGC significantly predicted FEV$_1$ improvement with the surgery. The lung function characteristics of our patients were similar to those enrolled in other LVRS studies including the National Emphysema Treatment Trial.[8]

Previous studies have shown that TGC is influenced by expiratory flow limitation, lung volume, and subject's effort.[6 7] Our subjects had a large lung volume and increased lung resistance, and generated a significant degree of positive intrathoracic pressure during forced expiratory manoeuvres. In our study the expiratory lung resistance and the effort significantly predicted the magnitude of TGC.

Several studies have reported an improvement in expiratory flow and FEV$_1$ and a reduction in hyperinflation with LVRS.[8 10 11] The improvements in FEV$_1$ and lung resistance observed in our study were similar to those reported by others.[8 10 11] Furthermore, although both TLC and RV were reduced, RV decreased more than TLC. This resulted in a

reduction in hyperinflation and increased FVC with the surgery (table 1). The intrathoracic pressure generated during the forced manoeuvres did not appreciably change with LVRS. In contrast, TGC diminished with improvement in expiratory flow and reduction in hyperinflation. However, according to regression analysis, only reduced lung resistance with LVRS significantly predicted the reduction in TGC. Lung volumes remained high after LVRS, and this may explain the lack of effect of lung volume change on TGC in our study.

Our data support the role of TGC reduction in FEV_1 improvement with LVRS. Absolute lung volume is a major determinant of maximal expiratory flow, especially in lung volumes below 75% of TLC.[24] TGC exerts a negative effect on forced expiratory flow by reducing the lung volume and thus diminishing the retractive forces applied by the lung parenchyma on the small airways. For example, submaximal effort during forced expiratory manoeuvres in subjects with expiratory flow limitation result in higher FEV_1.[6] This effect is due to lower TGC. Our analysis showed that half of the improvement in FEV_1 with LVRS can be explained by the reduction in TGC.

In our study the baseline TGC predicted the improvement in FEV_1 with LVRS. The baseline TGC, as reflected by $DFEV_1$, was higher in responders than in non-responders. One of the most striking results of our study is that the baseline TGC alone can predict 40% of the improvement in FEV_1 with LVRS. TGC is influenced by a number of factors. A large absolute lung volume and RV/TLC ratio are associated with higher TGC. Furthermore, increased airway resistance and a large expiratory effort are required to produce a significant TGC. Although not statistically different, the maximum intrathoracic pressure generated in the responders appeared to be higher than in the non-responders. This may indicate that patients with higher TGC have more preserved expiratory muscle function. Ramírez-Sarmiento and others showed that deterioration in expiratory muscle strength and endurance were associated with parallel impairments in other respiratory muscle groups.[25][26] The ability to generate a higher transpulmonary pressure during a forced manoeuvre may therefore indirectly affect the function of the respiratory muscles. Furthermore, the mismatch between the size of the lungs and the chest in patients with emphysema is an important factor in causing flow limitation.[12] The magnitude of gas compression therefore reflects the patient characteristics which may influence the response to LVRS.

In summary, in our cohort of patients with severe COPD, LVRS reduced TGC and this reduction partially explained the improvement in FEV_1. Our data suggest that baseline TGC might predict the FEV_1 response to LVRS, but further studies are needed to confirm this finding.

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