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Lung Volume Reduction Coil Treatment in Chronic Obstructive Pulmonary Disease Patients with Homogeneous Emphysema: A Prospective Feasibility Trial

Karin Klooster[a] Nick H.T. ten Hacken[a] Ina Franz[b] Huib A.M. Kerstjens[a]
Eva M. van Rikxoort[c] Dirk-Jan Slebos[a]

Departments of [a]Pulmonary Diseases and [b]Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, and [c]Department of Radiology, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands

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Key Words
Chronic obstructive pulmonary disease · Emphysema · Bronchoscopy · Lung volume reduction · Airway resistance · Hyperinflation

Abstract
Background: In patients with heterogeneous emphysema, surgical and bronchoscopic lung volume reduction (LVR) treatments are available. However, for patients with homogeneous emphysema these treatments are hardly investigated and seem less effective. Bronchoscopic LVR coil treatment has been shown to be effective in patients with heterogeneous emphysema, but this treatment has not been exclusively investigated in homogeneous emphysema. ***Objectives:*** The aim of this study was to investigate the safety and efficacy of LVR coil treatment in patients with homogeneous emphysema. ***Methods:*** In this single-arm, open-label study, patients received a maximum of 12 LVR coils (PneumRx Inc., Mountain View, Calif., USA) in each upper lobe in two sequential procedures. Tests were performed at baseline and at 6 months. The primary endpoint was the improvement from baseline in 6-min walking distance (6MWD) after treatment. ***Results:*** Ten patients with severe airway obstruction and hyperinflation were treated. A median of 11 (range 10–12) coils were placed in each lung. Two chronic obstructive pulmonary disease exacerbations and one small pneumothorax were recorded as serious adverse events. At 6 months, 6MWD had improved from 289 to 350 m ($p = 0.005$); forced vital capacity from 2.17 to 2.55 liters ($p = 0.047$); residual volume from 5.04 to 4.44 liters ($p = 0.007$) and St. George's Respiratory Questionnaire from 63 to 48 points ($p = 0.028$). ***Conclusion:*** LVR coil treatment in homogeneous patients improves hyperinflation, airway resistance, exercise capacity and quality of life with an acceptable safety profile. The benefit of LVR coil treatment is not limited to patients with heterogeneous emphysema, and patients with homogenous emphysema can benefit as well.

KARGER

E-Mail karger@karger.com
www.karger.com/res

Karin Klooster
Department of Pulmonary diseases, AA11, University Medical Center Groningen
PO Box 30001
NL–9700 RB Groningen (The Netherlands)
E-Mail k.klooster@.umcg.nl

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide and it will become the third leading cause of death by 2020 [1]. COPD is characterized by a spectrum of small airway abnormalities (the 'bronchitic' component) and lung parenchymal destruction (the 'emphysema' component). Parenchymal destruction of the lung reduces the protective elastic recoil forces on the airways leading to increased airway collapsibility. This emphysema component may contribute importantly to the airflow limitation due to the narrowed and obliterated small airways in COPD [2]. These combined pathophysiological effects may result over time in clinically important air trapping and hyperinflation. Lung hyperinflation correlates with important patient-related outcomes, such as dyspnea, exercise performance, physical activity and quality of life [2]. In patients with severe COPD, the currently available pharmacological treatment options have only limited effectiveness. For patients with the emphysematous COPD phenotype, surgical and bronchoscopic therapeutic interventions exert an effect through reducing hyperinflation [3]. However, until now only patients with severe emphysema and a heterogeneous distribution have been selected for surgical or bronchoscopic interventions. The National Emphysema Treatment Trial showed that lung volume reduction (LVR) surgery improved quality of life, pulmonary function and exercise tolerance, especially in patients with predominant upper lobe emphysema [4]. Over the past years a number of new minimally invasive bronchoscopic LVR modalities have been investigated, these being mainly effective in patients with heterogeneous emphysema. Endobronchial one-way valve placement has shown to be of benefit especially in a small subgroup of patients with heterogeneous emphysema [5, 6]. Using a lung sealant for emphysema, upper lobe target sites have a greater treatment response in heterogeneous emphysema when compared to homogeneous disease [7]. We recently showed that LVR coil treatment in patients with upper lobe heterogeneous emphysema improved quality of life, hyperinflation and exercise capacity [8]. One major randomized sham-controlled trial investigating the use of bronchoscopic airway bypass, dedicated to patients with homogeneous emphysema, showed short-term but no sustainable benefit [9]. To date, there is no solid evidence for the efficacy of bronchoscopic LVR treatment in patients with exclusively homogeneous emphysema defined by strict computed tomography (CT) criteria. Therefore, we investigated the safety and efficacy of LVR coil treatment in patients with homogeneous emphysema.

Table 1. Study inclusion and exclusion criteria

Main inclusion criteria
– >35 years of age
– CT scan indicating homogeneous emphysema
– Post-bronchodilator FEV_1 ≤35% predicted
– Post-bronchodilator FVC ≤90% predicted
– TLC >120% predicted
– RV >225% predicted
– RV/TLC >60%
– Dyspnea score >1 on mMRC scale of 0–4
– Stopped smoking for a minimum of 6 months prior to procedure
– Signed informed consent
Main exclusion criteria
– DLCO <20% predicted
– History of recurrent clinically significant respiratory infection
– Uncontrolled pulmonary hypertension defined by right ventricular pressure >50 mm Hg
– Inability to walk >140 m (150 yards) in 6 min
– Evidence of other disease that may compromise survival, such as lung cancer, etc.
– Clinically significant bronchiectasis
– Giant bullae >1/3 lung volume
– Previous LVR surgery, lung transplant or lobectomy
– >20 mg prednisone (or equivalent) daily
– Antiplatelet agent which cannot be weaned off prior to procedure

Methods

Patients and Study Design

This study was a prospective, open-label, single-center cohort trial for patients with severe emphysema and a homogeneous distribution assessed on chest tomography. All patients were on optimal medication and completed a rehabilitation program. The main inclusion and exclusion criteria are shown in table 1. The protocol included a 6-month follow-up after the first treatment. This study was approved by the University Medical Center of Groningen medical ethics committee (NL36612.042.11). The trial is registered with ClinicalTrials.gov (No. NCT01421082). All study patients gave written informed consent.

LVR Coils and the LVR Coil Procedure

The LVR coil is an implantable, shape-memory Nitinol device. The system (RePneu®, Lung Volume Reduction Coil System, PneumRx Inc., Mountain View, Calif., USA) consists of a single-patient use delivery system with a cartridge, catheter, guide wire, forceps and coils (fig. 1). These self-actuating coils are delivered via the bronchoscope into the airway in a straight configuration and recover to a non-straight pre-determined shape upon deployment. The coil is available in 3 lengths (100, 125 and 150 mm) to accommodate different airway lengths. The distal and proximal ends of the coil are designed to reside in subsegmental airways. In this study, the bronchoscopy was

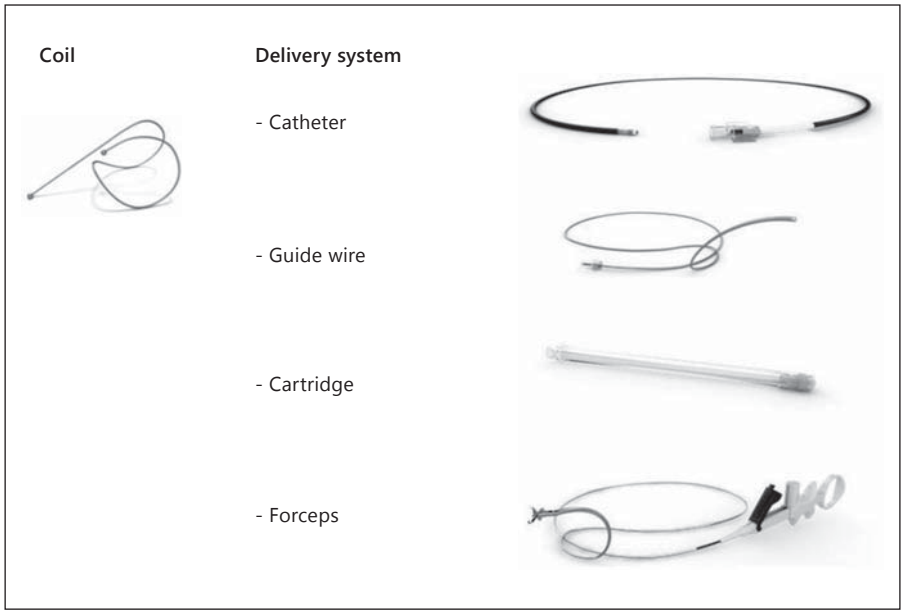

Fig. 1. Components of the RePneu Lung Volume Reduction Coil System.

performed under general anesthesia using a 9.0-mm endotracheal flexible tube and flexible bronchoscope (BF180; Olympus, Hamburg, Germany; 2.8-mm working channel, 6.0-mm outer diameter), and coil deployment was completed under fluoroscopic guidance. Following recovery from anesthesia, patients stayed in the hospital overnight for observation. The LVR coil procedure in this study was performed as described previously [8], with placement of a maximum of twelve LVR coils per upper lobe and by using a standardized segmental treatment algorithm independent of specific CT findings. During the first procedure the coils were placed into the right upper lobe (RB2-RB1-RB3) and 2 months later during the second procedure the coils were placed into the left upper lobe (LB1/2-LB3-LB4, leaving LB5 untreated because of its proximity to the heart). Patients received as per our standard interventional bronchoscopy prophylactic regimen a 5-day course of prednisolone (25 mg once daily), starting 2 days before the procedure, and a 5-day course of azitromycin (250 mg once daily), starting on the procedure day.

Follow-Up

Safety was assessed by recording all the adverse events that occurred. Adverse events were divided into those occurring in the first 30 days after each LVR coil treatment, the period which we regarded to be related to the actual procedure (labeled as the recovery period), and those occurring in the 31 days between procedure 1 and procedure 2, and the 31 days from procedure 2 to the 6-month follow-up after procedure 1 (labeled as the follow-up period). At baseline and the final 6-month follow-up we performed a high-resolution volume CT scan, measured quality of life using the St. George's Respiratory Questionnaire (SGRQ) [10], assessed the health status of COPD patients using the Clinical COPD Questionnaire (CCQ) [11] and measured the disability of our patients with the modified Medical Research Council dyspnea scale (mMRC) [12]. We performed pulmonary function testing (spirometry, body-plethysmography and diffusion capacity using a Jaeger MasterScreen™ Body Plethysmograph) and impulse oscillometry according to the ATS/ERS guidelines [13, 14] and using reference values from workers of the European Community for Steel and Coal [15]. The 6-min walking distance (6MWD) test was done according to ATS recommendations [16], and was prospectively chosen as the primary endpoint. Besides the conventional body plethysmography pressure/volume loops, we also obtained resistance/volume graphs using an automated conversion program (CareFusion Corporation) [17]. The resistance/volume graph gives information about the combination of the within breath course of the dependency of absolute lung volume on airway resistance.

CT Scan Qualifications and Analysis

The chest CT scan slice thickness was 1.0 mm, made at 120 kV/210 mAs. All quantifications were performed with CIRRUS Lung 13.10 (http://cirrus.diagnijmegen.nl; Diagnostic Image Analysis Group, Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany) [18–20]. The lungs and lobes were automatically segmented and visually inspected. Emphysema severity was computed as an emphysema score, i.e. the percentage of voxels below –950 Hounsfield units, and this score was computed for the entire lung and per lung lobe. The airways were excluded to ensure that only lung parenchyma was analyzed. Patients were considered to be homogeneous and eligible when the difference in destruction between ipsilateral lobes was less than 15% using this analysis for both lungs.

Statistics

Safety is reported descriptively. The other results are presented as medians and range. The Wilcoxon signed-rank test was used to assess the statistical significance of changes from baseline. A p value of <0.05 was considered statistically significant. IBM SPSS Statistics 20 was used for all analyses.

Results

Patients

We screened 11 patients between November 2011 and July 2012. One patient was not eligible due to a residual volume (RV) percent predicted value of 195%. Ten patients were treated bilaterally in two sequential procedures (see table 2 for demographics and baseline characteristics).

The median emphysema CT destruction scores of the treated patients expressed as the percentage relative area of destruction below –950 Hounsfield units for the right lung were: upper lung 39% (range 34–51) and lower lung 33% (range 26–53), and for the left lung were: upper lung 37% (range 29–47) and lower lung 35% (range 24–49).

LVR Coil Procedure

In 10 patients we performed 20 procedures in which a total of 227 LVR coils were placed, with a median of 11 (range 10–12) coils positioned in 33 (range 22–55) min per lung. No periprocedural technical events occurred, and all coils were placed as planned. Of the 227 coils placed in this study, none had to be replaced or removed (see table 3 for all procedural results). The median hospital stay after the procedure was 1 night (range 1–4).

Safety

No adverse events occurred due to anesthesia in these patients with severe COPD. After the procedure, we observed only one small 2-cm apical pneumothorax which spontaneously resolved without a chest tube. No other serious adverse events occurred in the first 30 days following each procedure (defined as the recovery period). During the follow-up period (31 days after procedure 1 to procedure 2, and 31 days after procedure 2 to 6 months after procedure 1) two serious adverse events were reported due to COPD exacerbations requiring hospitalization. All the adverse events in this study were managed with standard care and no life-threatening events occurred. All adverse events are listed in table 4.

Efficacy

Comparing the 6-month follow-up results to baseline revealed that bilateral LVR coil treatment had resulted in a significant improvement in exercise performance as measured by an increase in 6MWD from 289 to 350 m ($p = 0.005$). Quality of life also showed significant improvements as measured by a change in SGRQ total score from 63 to 48 points ($p = 0.028$) and by a change in CCQ score from 3.0 to 2.3 points ($p = 0.007$). There was also a significant improvement in lung volumes, with forced vital capacity (FVC) improving from 2.17 to 2.55 liters ($p = 0.047$) and RV from 5.04 to 4.44 liters ($p = 0.007$). Airway resistance (Raw) changed significantly with a decrease in Raw from 0.82 to 0.62 kPa/l/s ($p = 0.009$). CT scan analysis showed a significant decrease in lung volume in the treated upper lobes from 3,204 to 2,941 ml ($p = 0.037$), while in non-treated lower lobes there was no change in lung volumes (3,496–3,489 ml,

Table 2. Patient demographics and baseline characteristics (n = 10)

Age, years	54 (44–66)
Female/male	9/1
Pack years, n	40 (25–60)
BMI, kg/m^2	22.4 (16.2–28.7)
FEV_1, % predicted	22 (19–31)
FVC, % predicted	69 (52–89)
FEV_1/FVC, %	29 (19–38)
TLC, % predicted	141 (121–182)
RV, % predicted	253 (217–375)
RV/TLC	0.68 (0.61–0.74)
Raw, % predicted	272 (180–403)
DLCO, % predicted	31 (23–42)
$PaCO_2$, kPa	5.9 (4.4–6.9)
PaO_2, kPa	9.2 (7.3–10.6)
Patients on home oxygen, n	6
6MWD, m	289 (160–485)
mMRC	2.5 (2–4)
SGRQ total score	63 (45–79)
CCQ	3.0 (1.9–3.8)

Values in parentheses are the range. FEV_1 = Forced expiratoiry volume in 1 s; DLCO = carbon monoxide diffusion capacity; $PaCO_2$ = arterial carbon dioxide pressure; PaO_2 = arterial oxygen pressure.

Table 3. LVR coil procedural results

Procedures, n	20
Procedure time, min	33 (22–55)
Post-procedure hospital stay, days	1 (1–4)
Coils per procedure, n	11 (10–12)
Total coils implanted	227
Upper right lobe	113
Upper left lobe	114
Length of coils used	
100 mm	123
125 mm	104
150 mm	0

Values in parentheses are the range.

p = 0.646). All baseline and 6-month follow-up results are shown in table 5.

Seventy percent of the patients responded by more than the minimal clinically important difference (MCID) for 6MWD, RV [21], SGRQ [22] and CCQ [11] (table 6). Individual patient data at baseline and follow-up for 6MWD, SGRQ, RV and Raw are shown in figure 2.

Table 4. Investigator-reported serious adverse events and adverse events

	Recovery period	Follow-up period
Serious adverse events		
Pneumothorax	1	0
COPD exacerbation requiring hospitalization	0	2
Pneumonia	0	0
Respiratory failure	0	0
Death	0	0
Adverse events		
Slight hemoptysis (<5 ml)	5	0
Chest discomfort (non-cardiac)	6	0
COPD exacerbation	3	5
Dyspnea	0	1
Bronchitis	1	0
Hypertension	0	1
Hypermenorrhea	0	1

The recovery period is defined ≤30 days after each LVR-coil procedure. The follow-up period is defined as 31 days post-procedure 1 to pre-procedure 2, and 31 days post-procedure 2 to the 6-month follow-up after procedure 1.

Discussion

In this trial we demonstrated for the first time prospectively the feasibility and safety of LVR coil treatment specifically in patients with severe COPD and homogeneous emphysema. Despite the small sample size of this study, LVR coil treatment significantly improved hyperinflation, exercise tolerance and quality of life, with 70% of the patients responding by at least the MCID.

In this severely diseased group of patients it was safe to perform the LVR coil procedure under general anesthesia. To minimize the anesthesiology time and reduce the risk of bilateral procedure-induced complications, we performed the LVR coil treatment in two consecutive procedures 8 weeks apart. No anesthesia-related events occurred. The adverse events profile seen with the LVR coil treatment appears acceptable as only one small apical pneumothorax not needing chest tube drainage occurred directly after the procedure, whereas two COPD exacerbations were recorded as serious adverse event during the follow-up. Beforehand, one would expect extra coughing and sputum production after implanting more than 20 coils in diseased airways. However, the symptoms score assessed with the SGRQ demonstrated a significant reduction.

In patients with severe emphysema, only patients with a heterogeneous disease distribution have so far been seen as the proper candidates for effective treatment by both LVR surgery [4] and a number of bronchoscopic LVR modalities, such as endobronchial one-way valve placement [5], thermal vapor ablation [23] and using lung sealant [24]. In patients with homogeneous emphysema all these procedures showed limited efficacy.

The first clinical pilot LVR coil study, using a maximum of 6 coils per lobe, suggested that patients with homogeneous emphysema might not benefit as well as patients with heterogeneous emphysema [25]. In the second LVR coil study only patients with heterogeneous emphysema were included and treated with a new generation coil, with the number of coils implanted in the lobe increased [8]. In our study we now show a high responder efficacy rate in patients with homogeneous emphysema. These results are also supported by recently published randomized controlled trial data (RESET trial) where both heterogeneous as well as homogeneous emphysema patients had improved quality of life, exercise tolerance and hyperinflation at 3 months after LVR coil treatment compared to controls [26]. Future prospective randomized controlled trial data will have to confirm our findings. Currently, two larger (n = 315 and n = 100) randomized controlled trials using LVR coils in both heterogeneous and homogeneous populations are underway (NCT01608490 and NCT01822795).

In our study, we observed a significant decrease in airway resistance as measured by body plethysmography and by forced oscillation after bilateral LVR coil treatment. Beforehand, one might expect that implantation of coils inside the airways would obstruct airflow and increase airway resistance. Apparently, the mechanical properties of the lung are improved by the treatment and, importantly, our study also suggests that the lung parenchyma in subjects with homogeneous emphysema is healthy enough to transfer the elastic recoil forces to the airways. The effects of our coil treatment on airway patency were substantial since we found significant im-

Table 5. Baseline and 6-month follow-up results (20 bilateral LVR coil treatments in 10 patients)

	Baseline	6-Month follow-up	p value
6MWD, m	289 (160–485)	350 (192–520)	0.005
FEV_1, l	0.58 (0.45–0.93)	0.69 (0.56–1.02)	0.102
FVC, l	2.17 (1.82–3.17)	2.55 (1.81–3.67)	0.047
ITGV, l	6.02 (5.28–7.19)	5.84 (4.63–7.13)	0.009
TLC, l	7.48 (6.46–9.08)	7.36 (5.97–9.09)	0.037
RV, l	5.04 (4.14–6.57)	4.44 (3.57–5.68)	0.007
RV, % predicted	253 (217–375)	231 (172–325)	0.007
RV/TLC, %	68 (61–74)	60 (55–67)	0.005
Raw, kPa/l/s	0.82 (0.54–1.21)	0.62 (0.43–0.91)	0.009
R5-R20, kPa/l/s	0.28 (0.21–0.64)	0.27 (0.14–0.44)	0.043
SGRQ total, points	63 (45–79)	48 (25–68)	0.028
SGRQ symptoms, points	63 (13–79)	36 (2–69)	0.017
SGRQ activity, points	89 (72–100)	79 (35–93)	0.018
SGRQ impacts, points	44 (16–71)	32 (14–64)	0.074
CCQ, points	3.0 (1.9–3.8)	2.3 (1.4–3.0)	0.007
mMRC, points	2.5 (2–4)	2.0 (1–4)	0.16
CT volume RUL, ml	1,514 (1,096–1,700)	1,399 (1,126–1,702)	0.053
CT volume LUL, ml	1,685 (1,157–1,901)	1,547 (1,218–1,868)	0.037
CT volume treated lobes, ml	3,204 (2,253–3,601)	2,941 (2,344–3,570)	0.037
CT volume untreated lobes, ml	3,496 (2,172–4,262)	3,489 (2,071–4,244)	0.646

Median values are presented with range in parentheses. FEV_1 = Forced expiratory volume in 1 s; R5 = airway resistance at 5 Hz; R20 = proximal resistance at 20 Hz; RUL = right upper lobe; LUL = left upper lobe.

Table 6. Responder rates at 6 months after LVR coil treatment using MCID for RV, 6MWD, SGRQ and CCQ

Variable	MCID	Reference	Responder rate at 6 months, %
RV	≥0.43 liters	[21]	70
6MWD	≥26 m	[29, 30]	70
6MWD	≥48 m	[31]	50
SGRQ	≥4 points	[22]	70
SGRQ	≥8 points		70
CCQ	≥0.4 points	[11]	80

Values are given as the percentage of patients responding.

provements in airway resistance, despite the fact that improved residual volumes lead to reduced airway patency and, thus, underestimation of improved airway resistance. To illustrate this we took the example of 2 patients before and after treatment (fig. 3) and plotted 'resistance/volume' graphs. The interpretation of body-plethysmography measurement is traditionally based on the results of the lung volumes and the airway resistance. The graphic presentation of the airway resistance is normally displayed as pressure/volume loops. Important intra-breath information incorporating inhomogeneity of ventilation, expiratory flow limitation or airways closure is not presented in this form. When combining the 'traditional' airways resistance (Raw) loop and the intra-thoracic gas volume (ITGV) graphs, the resistance/volume graph can be determined. The maneuver of the body-plethysmographic measurement is not changed and there are no additional efforts or maneuvers necessary for the patient. The resistance/volume graph just gives additional information about the volume-dependent airway resistance dur-

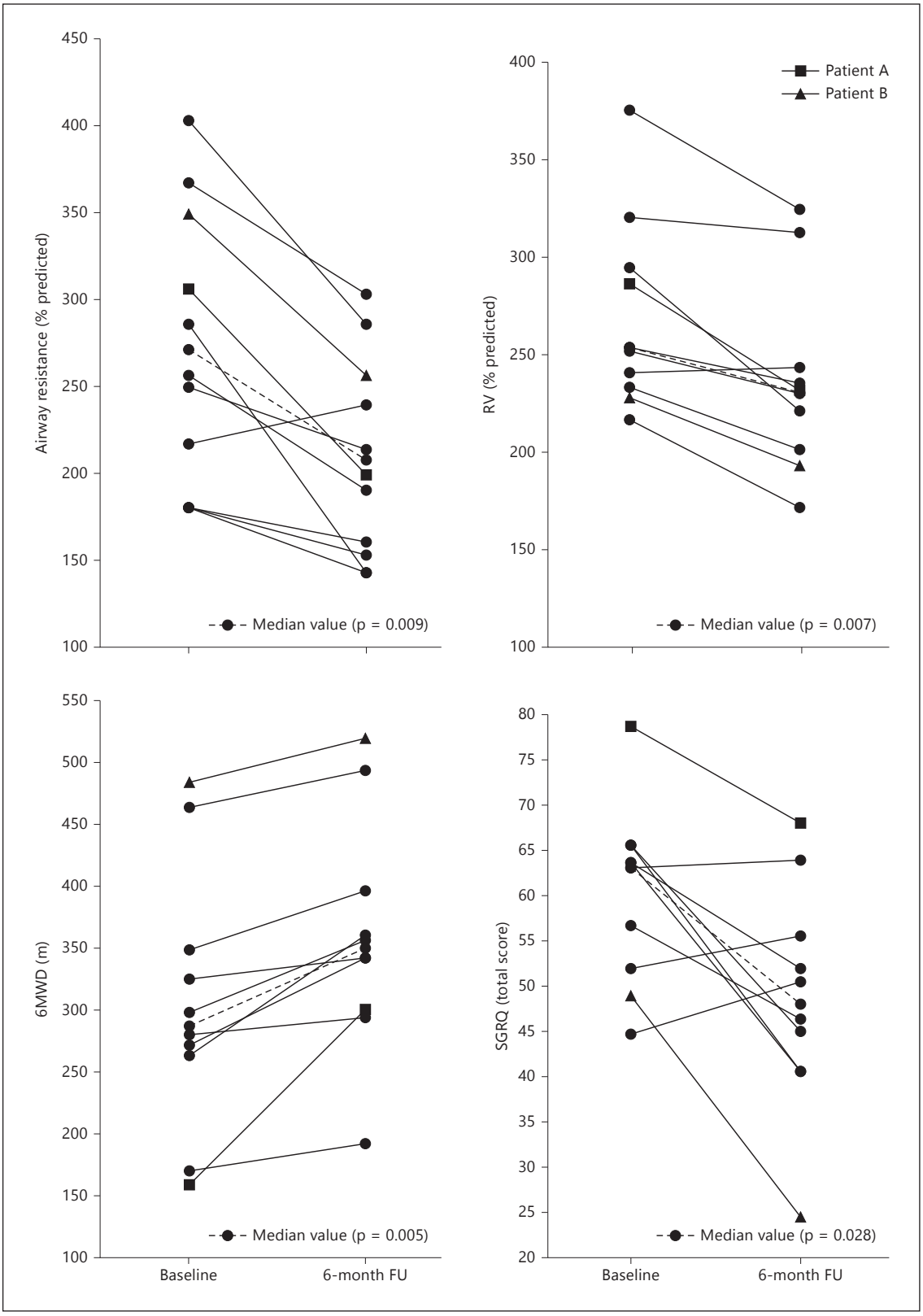

Fig. 2. Individual patient data at baseline and at 6-month follow-up (FU) for 6MWD, SGRQ, RV and Raw (patients A and B are shown in more detail in figure 3).

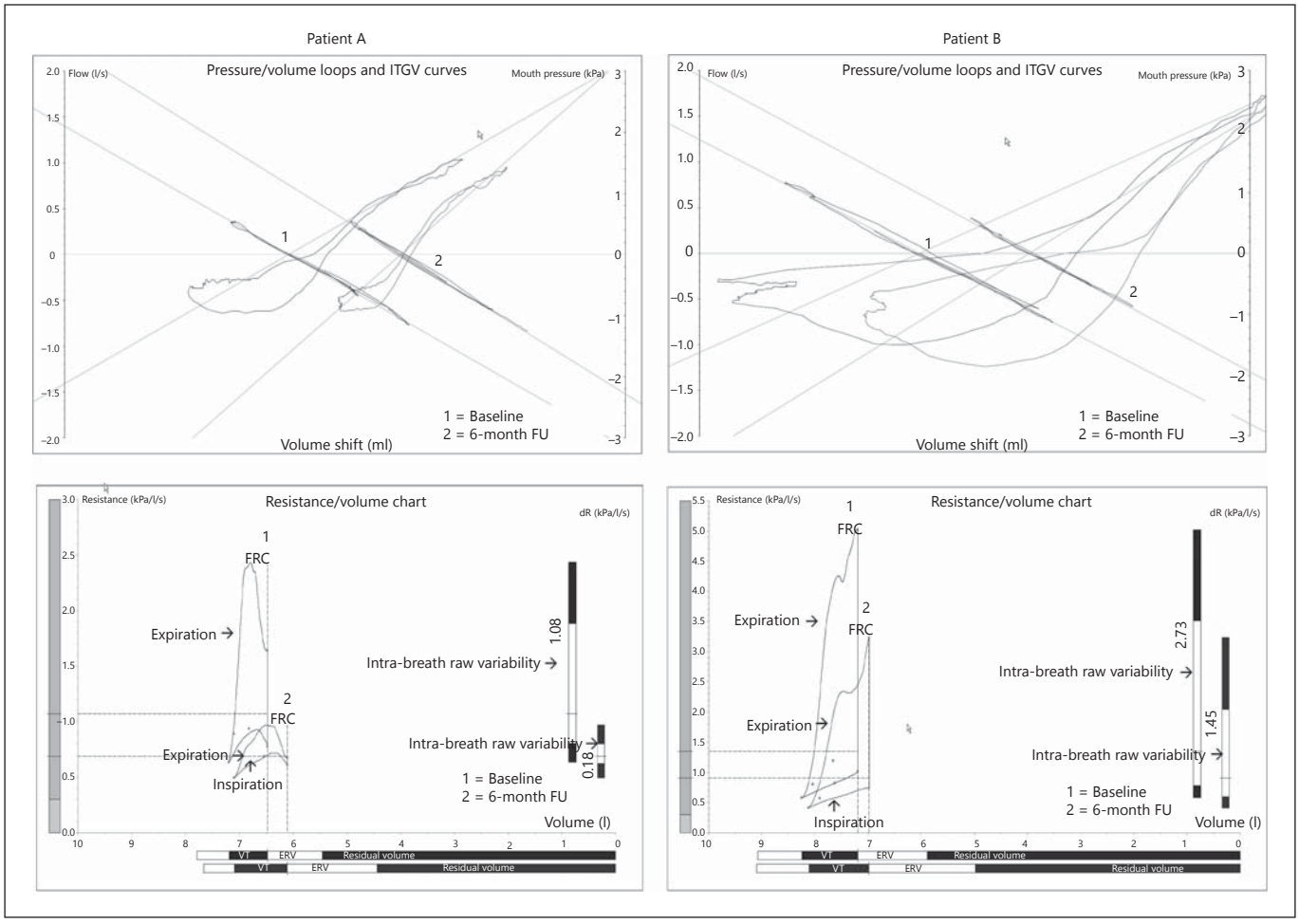

Fig. 3. Pressure/volume loops and resistance/volume graphs of 2 patients as an illustrative example of changing lung mechanical properties at baseline and 6 months after LVR coil treatment. The resistance/volume graph presents the single breath course of airway resistance, dependent on absolute lung volume. VT = Tidal volume (liters); FRC = functional reserve volume (liters); ERV = expiratory reserve volume (liters).

ing a breathing cycle, and can be very useful for any differences before and after treatment. Nevertheless, the mechanisms of action of the LVR coil are not fully understood and additional studies are needed to learn more about the lung compliance, elastic recoil and diaphragm function before and after LVR coil treatment.

Total lung capacity (TLC) was both measured by body-plethysmography as well as inspiratory high-resolution CT scans (HRCT). TLC measured by body-plethysmography appeared to be higher compared to TLC measured by HRCT. However, the decrease in TLC at the 6-month follow-up using HRCT analysis appears to be greater than the TLC measured by body-plethysmography.

It is difficult to explain these subtle differences. It is known in COPD patients that TLC can be up to 2 liters greater than the TLC measured by HRCT, especially in patients with severe COPD [27]. Also, the measurement of TLC by body-plethysmography is not without errors, particularly in severe COPD, and the same applies to TLC measurement by HRCT.

A limitation of our cohort study is that the design cannot correct for potential placebo effects, which is especially important for the questionnaire data (SGRQ, mMRC and CCQ). However, in other published uncontrolled LVR device trials using a bilateral intra-bronchial valve placement in patients with severe emphysema, no significant changes were observed in 6MWD or pulmonary function parameters despite this bronchoscopic treatment [28]. Also, the EASE trial data showed no placebo effect for 6MWD, pulmonary function parameters and quality

of life questionnaires in a randomized sham-controlled intervention trial design using the airway bypass approach [9]. Although a contribution from a placebo effect cannot be excluded, in our opinion the magnitude of the current effect size exceeds any potential placebo effect.

In conclusion, LVR coil treatment in patients with homogeneous emphysema is a promising bronchoscopic technique. The procedure is safe and feasible. There is a high responder rate and patients have demonstrated clinically meaningful improvements in exercise capacity, pulmonary function and quality of life at 6 months of follow-up.

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