ORIGINAL ARTICLE

Endobronchial Valve Therapy in Patients with Homogeneous Emphysema

Results from the IMPACT Study

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Abstract

Rationale: Endobronchial valves (EBVs) have been successfully used in patients with severe heterogeneous emphysema to improve lung physiology. Limited available data suggest that EBVs are also effective in homogeneous emphysema.

Objectives: To evaluate the efficacy and safety of EBVs in patients with homogeneous emphysema with absence of collateral ventilation assessed with the Chartis system.

Methods: Prospective, multicenter, 1:1 randomized controlled trial of EBV plus standard of care (SoC) or SoC alone. Primary outcome was the percentage change in FEV_1 (liters) at 3 months relative to baseline in the EBV group versus the SoC group. Secondary outcomes included changes in FEV_1, St. George's Respiratory Questionnaire (SGRQ), 6-minute-walk distance (6MWD), and target lobe volume reduction.

Measurements and Main Results: Ninety-three subjects (age, 63.7 ± 6.1 yr [mean ± SD]; FEV_1, % predicted, 29.3 ± 6.5; residual volume, % predicted, 275.4 ± 59.4) were allocated to either the EBV group (n = 43) or the SoC group (n = 50). In the intention-to-treat population, at 3 months postprocedure, improvement in FEV_1 from baseline was 13.7 ± 28.2% in the EBV group and −3.2 ± 13.0% in the SoC group (mean between-group difference, 17.0%; $P = 0.0002$). Other variables demonstrated statistically and clinically significant changes from baseline to 3 months (EBV vs. SoC, respectively: SGRQ, −8.63 ± 11.25 vs. 1.01 ± 9.36; and 6MWD, 22.63 ± 66.63 m vs. −17.34 ± 52.8 m). Target lobe volume reduction at 3 months was −1,195 ± 683 ml ($P < 0.0001$). Of the EBV subjects, 97.2% achieved volume reduction in the target lobe ($P < 0.0001$). Procedure-related pneumothoraces occurred in 11 subjects (25.6%). Five subjects required removal/replacement of one or more valves. One subject experienced two valve migration events requiring removal/replacement of valves.

Conclusions: EBV in patients with homogeneous emphysema without collateral ventilation results in clinically meaningful benefits of improved lung function, exercise tolerance, and quality of life.

Keywords: homogeneous emphysema; endobronchial valve; collateral ventilation; lung volume reduction; lobar occlusion

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At a Glance Commentary

Scientific Knowledge on the Subject: Bronchoscopic lung volume reduction using one-way valves has been successfully used to cause lobar volume reduction in patients with severe heterogeneous emphysema by occluding the hyperinflated lobes with resultant improvements of lung function, exercise tolerance, and quality of life.

What This Study Adds to the Field: The present study is the first prospective, multicenter, randomized controlled clinical trial evaluating the efficacy and safety of bronchoscopically implanted one-way valves in patients with homogeneous emphysema distribution, demonstrating improvements in lung function, exercise tolerance, and quality of life in valve-treated patients.

Although lung volume reduction surgery (LVRS) can result in clinically meaningful improvements in pulmonary function, exercise capacity, and quality of life in patients with severe emphysema (1), it is offered only to a highly select group of patients with upper lobe–predominant emphysema and low exercise capacity and has not achieved widespread use in clinical practice (2–4). For patients with severe homogeneous emphysema, surgery is not an option, and other therapies, such as endoscopic coils, provide only modest lung function benefits (5–7).

Bronchoscopic lung volume reduction with one-way endobronchial valves (EBVs) has emerged as a potential treatment for patients with severe emphysema (8). Unidirectional EBVs are placed with the aim to occlude and collapse hyperinflated lung regions by allowing trapped air to escape from the targeted lobe while preventing air refill during inhalation (9). *Post hoc* analyses from earlier trials involving EBVs have revealed predictive factors that may help identify those patients who are most likely to benefit from this procedure. These characteristics include absence of significant collateral ventilation (CV) and complete occlusion of the targeted lobe after valve placement (10–12). Two randomized controlled trials (RCTs) in patients with severe emphysema have demonstrated improved clinical outcomes associated with EBV therapy in the absence of CV (13, 14). Although previous trials included predominantly patients with heterogeneous emphysema (10, 12, 13), subgroup analysis from a prospective single-center study (14) and pooled analysis from two RCTs (15) suggest that lung function and quality-of-life improvements are independent of the degree of emphysema heterogeneity.

The feasibility of EBV treatment in patients with severe homogeneous emphysema was initially demonstrated by Eberhardt and colleagues (16), but has not been tested in a prospective randomized trial. The IMPACT (Improving Patient Outcomes by Selective Implantation of the Zephyr EBV) study is the first prospective, multicenter, RCT evaluating the safety and efficacy of EBV therapy in patients with homogeneous emphysema and consistent assessment of CV.

Methods

Study Subjects

Eligible subjects were adults (≥40 yr of age), ex-smokers, diagnosed with severe emphysematous type of chronic obstructive pulmonary disease (COPD). Lung function parameters for inclusion included an FEV_1 (% predicted) of at least 15% and not more than 45% despite optimal medical management, TLC (% predicted) greater than 100, and residual volume (RV, % predicted) of at least 200. The complete list of inclusion/exclusion criteria is provided in the online supplement.

Computed tomographic (CT) quantitative analysis software (VIDA Diagnostics, Coralville, IA) was used to measure lobar volumes and emphysema destruction by lobe. Homogeneous emphysema was defined as a less than 15% difference in emphysema destruction score between target and ipsilateral lobes (12, 17), which was defined as the difference (in volume-weighted percent) between the density scores of the target lobe and the ipsilateral nontarget lobe at −910 Hounsfield units, using a high-resolution CT (HRCT) scan. In addition, a less than 20% difference in perfusion between right and left lungs, using perfusion scintigraphy, was required. Subjects were considered for treatment only when both criteria were met. The lobe with the highest emphysematous destruction on quantitative analysis by HRCT, the lowest perfusion score, and an absence of CV was chosen as the target lobe. The middle lobe was not allowed to be treated. Details on target lobe selection are provided in the online supplement.

Study Design

This randomized, controlled, one-way crossover study (NCT02025205) was conducted at eight sites in Austria (one site), Germany (six sites), and the Netherlands (one site) and was approved by the respective ethics committees at each site. All participating subjects provided written informed consent. Enrollment began in August 2014 and completed in January 2016. The 3-month follow-up for the primary end point was completed in April 2016. A data safety and monitoring board provided study oversight.

Subjects meeting all inclusion/exclusion criteria underwent a bronchoscopy procedure under conscious sedation or general anesthesia according to individual institutional sedation protocols. Collateral ventilation was measured with the Chartis system (Pulmonx Corp., Redwood City, CA) as previously described (18–20). If the primary target had collateral ventilation (CV positive), the secondary target was evaluated for CV status. Subjects who were CV positive in both target lobes were exited from the study. Subjects lacking collateral ventilation (CV negative) in the primary or secondary target lobe were randomized 1:1 to the EBV treatment group or the standard-of-care (SoC) control group. Randomization used a blocked design and concealed envelopes that were opened after CV-negative status had been established from the Chartis assessment (for further information, *see* the online supplement). On determination of the randomization assignment after the identification of CV-negative status for a target lobe, the bronchoscopy procedure for subjects randomized to the SoC group was terminated and subjects recovered appropriately per institutional standards. Subjects assigned to the EBV group underwent immediate placement of Zephyr endobronchial valves (Pulmonx Corp.) in all segments or subsegments of the target lobe with the intention of lobar occlusion. Additional procedural details and periprocedural medications are provided in the online supplement.

Follow-up

Subjects in the SoC group were hospitalized for at least 1 day postbronchoscopy and discharged to home. Subjects in the EBV group were hospitalized for a minimum of 2 days and discharged if there were no serious adverse events (SAEs) or complications. Patients were instructed to seek immediate medical attention in the event of symptoms related to a potential pneumothorax. EBV group subjects were evaluated at 30 days for pulmonary function and chest X-ray to verify procedural success. If subjects showed no evidence of functional benefits (i.e., $<$12% increase in FEV_1, and/or $<$10% reduction in RV) and/or signs of volume reduction on the follow-up chest X-ray, then a bronchoscopy was performed to confirm lobar occlusion or to exclude valve dysfunction or migration. If necessary, a valve replacement was performed. All subjects were evaluated at 3 months for vital signs, pulmonary function, target lobe volume reduction (TLVR) using HRCT (EBV group only), 6-minute-walk distance (6MWD), St. George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC) dyspnea index score, COPD Assessment Test (CAT) score, BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, and solicitation of adverse events. The 3-month evaluation visit for subjects with valve replacements was performed 3 months after valve removal/replacement.

Outcome Measures

The primary outcome was the percentage change in FEV_1 at 3 months relative to baseline in the EBV group, compared with the SoC group. Secondary outcomes included absolute change in FEV_1 at 3 months relative to baseline in the EBV group, compared with the SoC group; percentage of subjects in the EBV group achieving the minimal clinically important difference (MCID) for FEV_1 defined as an improvement of at least 15% (specified in the protocol) or an improvement of at least 100 ml and at least 12% (21, 22), RV (reduction equal to or less than $-$430 ml), 6MWD (improvement of $\geq$26 m), SGRQ score (reduction of $\geq$4 points), and mMRC dyspnea index score (reduction of $\geq$1 point) at 3 months, compared with the SoC group. The full list of outcome measures is provided in the online supplement. Although the prespecified primary end point was evaluated at 3 months, follow-up will continue out to 6 and 12 months postprocedure, with the SoC group subjects given the opportunity to crossover after the 6-month visit.

Adverse Events

Adverse events were actively solicited at each visit. Investigators attributed the severity of the adverse event and relatedness to EBV device/procedure. Pneumothorax, an anticipated SAE in some subjects after EBV placement, was managed per the Pneumothorax Management Recommendation outlined in the study protocol and published previously (23).

Statistical Analyses

The primary outcome (difference in FEV_1 percentage change at 3 mo relative to baseline between the two study groups) was analyzed by two-sample *t* test. The original sample size of 56 evaluable subjects was calculated on the basis of the VENT (Endobronchial Valve for Emphysema Palliation Trial) study (11), using a two-sided test with $\alpha = 0.05$, power = 0.80, a mean change of 17 versus 1.3%, and a SD of 23 versus 10 in the EBV and SoC groups, respectively, and an anticipated dropout rate of 20%. The sample size was adjusted while preparing for the preplanned interim analysis to 80 evaluable subjects, due to a random imbalance in both the EBV and SoC groups regarding the proportion of upper versus lower target lobes. The additional 24 subjects were added through stratified randomization to even out the skewness. However, because enrollment continued while the amendment for the change in randomization blocks was undergoing ethics committee review, there remained a difference in the sample sizes of the two groups. The difference in percentage and absolute change relative to baseline at 3 months between the two groups for the secondary outcome variables was analyzed by two-sample *t* test. The TLVR in the EBV group at 3 months relative to baseline was analyzed by one-sample *t* test. Adverse events were compared between groups by Fisher's exact test. The BODE index was analyzed by Wilcoxon signed-rank test. For the intention-to-treat (ITT) analyses, missing data were imputed by the most conservative approach of "last observation carried forward."

Results

Of the 183 subjects screened for inclusion, 93 subjects were randomized in the study with 50 subjects in the SoC group and 43 subjects in EBV group (Figure 1). Seventeen subjects were excluded for having CV-positive status as per their Chartis assessment. Four subjects in the EBV group and three subjects in the SoC group did not complete the 3-month follow-up assessment (details provided in Figure 1).

Baseline demographics and clinical characteristics were well matched between the EBV and SoC groups (Table 1; and *see* Table E1 in the online supplement). Enrolled subjects had severe airflow obstruction with a high symptom load and evidence of substantial hyperinflation on body plethysmography.

A median number of 4 valves per subject were implanted in the 43 subjects in the EBV group. The distribution of target lobes was 42% left lower lobe, 28% left upper lobe, 21% right lower lobe, and 9% right upper lobe. In 7 instances, the primary target was CV positive and valves were placed in the secondary target which was CV negative. The median postprocedure hospitalization stay was 6 days (range, 3–40 d) for the EBV group and 2 days (range, 1–6 d) for the SoC group.

In the EBV group, the change from baseline in TLVR on HRCT at 3 months was $-1{,}195 \pm 683$ ml (mean $\pm$ SD) compared with baseline ($P < 0.0001$). Of the EBV-treated subjects, 97.2% experienced a reduction in lobar volume in the target lobe ($P < 0.0001$) and 88.9% achieved a TLVR of at least 350 ml ($P < 0.0001$).

Primary End Point

For the ITT population, at 3 months postprocedure, there was an improvement from baseline in FEV_1 of 13.7 ± 28.2% (mean $\pm$ SD) in the EBV group, whereas in the SoC group, FEV_1 declined by 3.2 ± 13.0% with a mean difference between groups of 17.0% (95% confidence interval, 8.1–25.8%; $P = 0.0002$) (Figure 2). The mean difference between groups for the per protocol (PP) population was 19.3% in favor of the EBV group ($P = 0.0003$).

Secondary End Points

There were statistically significant differences in key secondary outcome measures between the EBV and SoC groups. The between-group difference was 120 ml for FEV_1 ($P < 0.0001$),

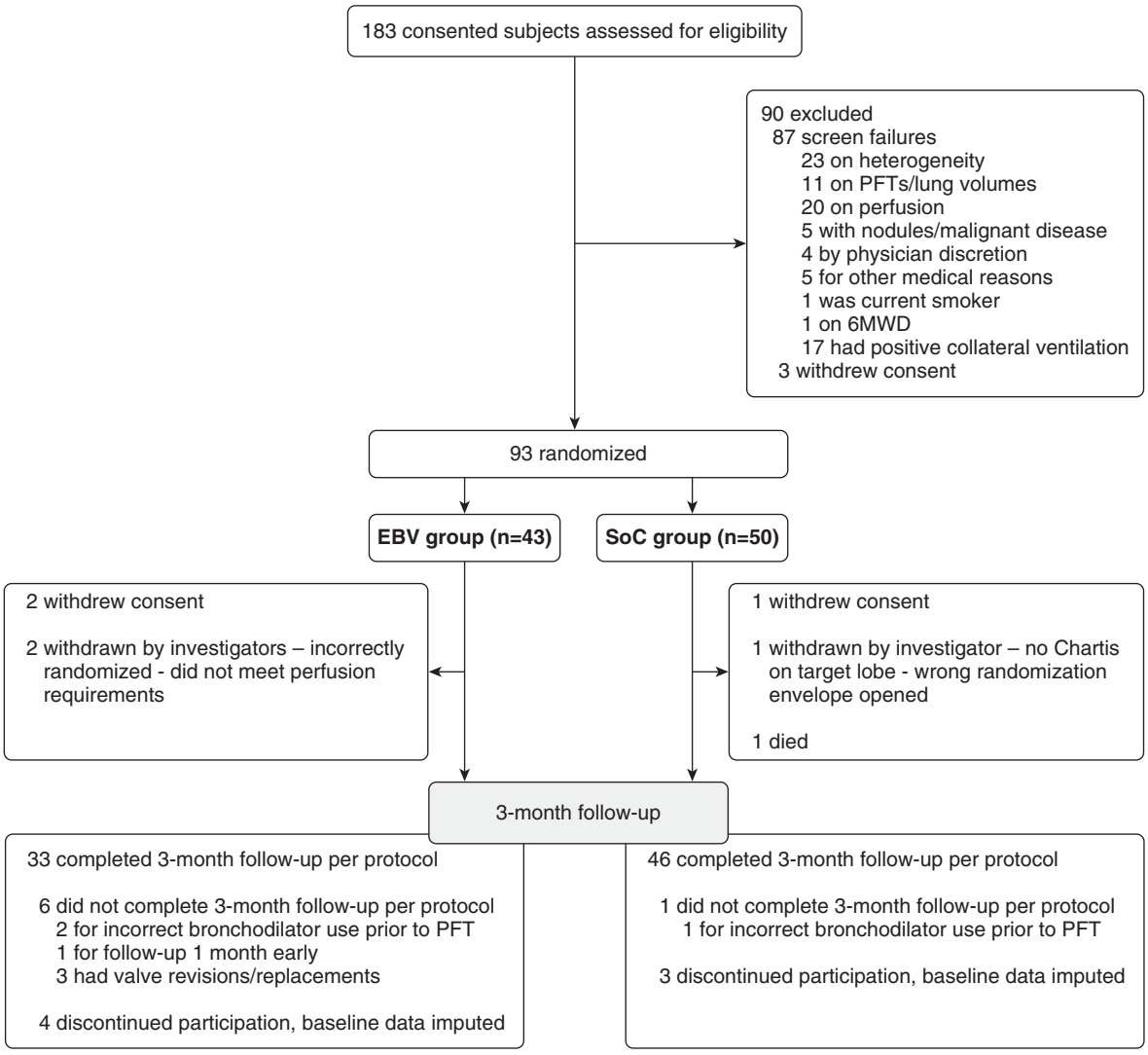

Figure 1. Subject disposition. Subjects who discontinued participation before 3-month follow-up: EBV group: subject 71007 (incorrect randomization; >20% in perfusion between left and right lung = exclusion criterion 9); subject 81016 (consent withdrawn); subject 81023 (consent withdrawn); subject 82005 (incorrect randomization; >20% in perfusion between left and right lung = exclusion criterion 9). SoC group: subject 81008 (consent withdrawn); subject 81021 (death, pneumonia); subject 81029 (incorrect randomization). EBV group ITT population includes 33 + 6 + 4 = 43 subjects; PP population includes 33 subjects. SoC group ITT population includes 46 + 1 + 3 = 50 subjects; SoC PP population includes 46 subjects. 6MWD = 6-minute-walk distance; EBV = endobronchial valve; ITT = intention to treat; PFTs = pulmonary function tests; PP = per protocol; SoC = standard of care.

9.6 points for SGRQ ($P < 0.0001$), 40 m for 6MWD ($P = 0.002$), and 480 ml for RV ($P = 0.011$) in favor of the EBV treatment group in the ITT analysis (Table 2 and Figure 3).

The absolute and percent changes in the EBV group at 3 months relative to baseline, compared with the SoC group for FEV_1, RV, SGRQ, 6MWD, mMRC, CAT, and the BODE index, are provided in Table E2. Results for the secondary outcomes at 3 months in the PP population are also provided in Table E3 and Table E4. Although there were small differences in FEV_1 outcome after EBV placement in the upper lobes compared with the lower lobes, the differences were not statistically significant (Table E5).

Table 3 displays the proportion of subjects with an MCID in key outcomes in the ITT population. Significantly more subjects in the EBV group (34.9%) than in the SoC group (4.0%) had a 15% or higher improvement in FEV_1 ($P = 0.0001$); for 6MWD, 50% of the EBV group compared with 14% of the SoC group had an improvement of 26 m or greater ($P = 0.0002$); and for the SGRQ, 56.8% of the EBV group compared with 25% of the SoC group had a decrease of 4 points or greater ($P = 0.0029$). MCID responder analysis in the PP population is presented in Table E6, Figure E1, and Figure E2 (ITT and PP populations, respectively).

Adverse Events

Over the 3-month period, respiratory-related SAEs occurred in 44.2% of the EBV group, as compared with 12% of the SoC group ($P < 0.001$) (Table 4). Twelve procedure-related pneumothoraces occurred in 11 subjects (25.6%). Seven occurred on the day of the procedure,

Table 1. Baseline Demographics and Clinical Characteristics: Intention-to-Treat Population

Variable	EBV Group (*n* = 43)	SoC Group (*n* = 50)	*P* Value (t *Test*)
Sex, male/female	20/23	16/34	NS
Age, yr	64.3 ± 6.3	63.2 ± 6.0	NS
BMI, kg/m^2	23.8 ± 4.4	22.6 ± 3.7	NS
Pack-year smoking history	41.5 ± 19.6	42.5 ± 22.0	NS
Clinical characteristics			
GOLD stage			
Stage III	16	22	NS
Stage IV	27	28	NS
Emphysema score of the target lobe at −910 HU*	68.0 ± 7.22	65.42 ± 7.06	NS
Volume-weighted heterogeneity index between target and ipsilateral lobe(s)†	6.88 ± 6.83	4.56 ± 6.30	NS
FEV_1, % predicted	28.4 ± 6.3	29.9 ± 6.6	NS
Residual volume, % predicted	277.3 ± 55.2	273.7 ± 63.4	NS
Total lung capacity, % predicted	144.9 ± 21.2	144.2 ± 17.6	NS
6MWD, m	308 ± 91	328 ± 93	NS
SGRQ total score‡	63.2 ± 13.7	59.34 ± 15.6	NS
mMRC dyspnea index score§	2.67 ± 0.75	2.42 ± 0.97	NS
CAT total score‖	23.4 ± 6.8	22.8 ± 5.9	NS
BODE index score¶	5.69 ± 1.4	5.22 ± 1.7	NS**

Definition of abbreviations: 6MWD = 6-minute-walk distance; BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; CAT = COPD Assessment Test; EBV = endobronchial valve; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield unit; mMRC = modified Medical Research Council; NS = not significant; SGRQ = St. George's Respiratory Questionnaire; SoC = standard of care.
Values represent means ± SD.
*Emphysema destruction score was assessed as the percentage of voxels of less than −910 HU on CT.
†Volume-weighted heterogeneity index was assessed as the difference in emphysema score between the target lobe and the ipsilateral lobe. A difference not exceeding 15% was defined as homogeneous.
‡SGRQ scores range from 0 to 100, with higher scores indicating worse quality of life.
§mMRC dyspnea scale scores range from 0 to 4, with higher scores indicating more severe dyspnea.
‖CAT scores range from 0 to 40, with higher scores indicating a more severe impact of COPD on a patient's life.
¶BODE index scores range from 0 to 10 based on a multidimensional scoring system to include FEV_1, body mass index, 6-minute-walk distance, and the mMRC dyspnea score. Higher scores denote a greater risk of mortality.
**Wilcoxon signed-rank test.

2 occurred on Day 1, and 1 each between Day 4 and Day 6, 1 week to 1 month, and 1 month to 3 months, respectively. All pneumothorax events involved hospitalization with a median hospital stay of 12 days (range, 7–39 d); all required insertion of a chest tube and five subjects required removal of one or more valves. Valves were later replaced in three subjects. One subject experienced two valve migration events requiring removal/replacement of the valves.

During this 3-month period, there was one death in the SoC group after pulmonary infection (nosocomial pneumonia), 54 days after being randomized; no deaths were reported for EBV subjects over this period. Detailed listings of respiratory and nonrespiratory adverse events are provided in Table E7 and Table E8, respectively.

Discussion

This is the first prospective, multicenter RCT of endobronchial valve therapy in patients with severe homogeneous emphysema and absence of collateral ventilation. We found statistically and clinically significant improvements in lung function, exercise capacity, and quality of life associated with EBV therapy compared with usual SoC. Nine of 10 subjects experienced target lobe volume reduction indicating effective occlusion of the target lobe after EBV placement. Significantly more patients in the EBV group had improvements that exceeded the MCIDs for FEV_1, SGRQ, RV, and 6MWD 3 months after valve treatment.

Although there are proven benefits of LVRS with respect to lung function, exercise capacity, and mortality in patients with (upper lobe–predominant) heterogeneous emphysema, LVRS in homogeneous emphysema has been performed with rather variable success (1, 24, 25). Indeed, results from the National Emphysema Treatment Trial (NETT) demonstrated increased mortality associated with LVRS in patients with homogeneous emphysema (1).

The principle of valve treatment is to block ventilation to the most emphysematous lung and induce atelectasis of the hyperinflated lobe. Previous studies, primarily targeting patients with heterogeneous emphysema without CV, have shown improvements in respiratory mechanics (26, 27), lung perfusion (28), cardiovascular function (29–31), and other key outcome measures (11, 13, 18, 32, 33). Similar to LVRS, successful valve treatment in patients with severe emphysema without CV has been associated with improved long-term survival rates in prospective case series (34, 35). Using a pooled analysis from two RCTs of EBV therapy we previously demonstrated clinical benefits independent of emphysema heterogeneity (15). The present study confirms these findings in patients with exclusively homogeneous emphysema, albeit functional improvements are of smaller magnitude than in heterogeneous patients (14). Fessler and Permutt (36) postulated that the single most important determinant of the

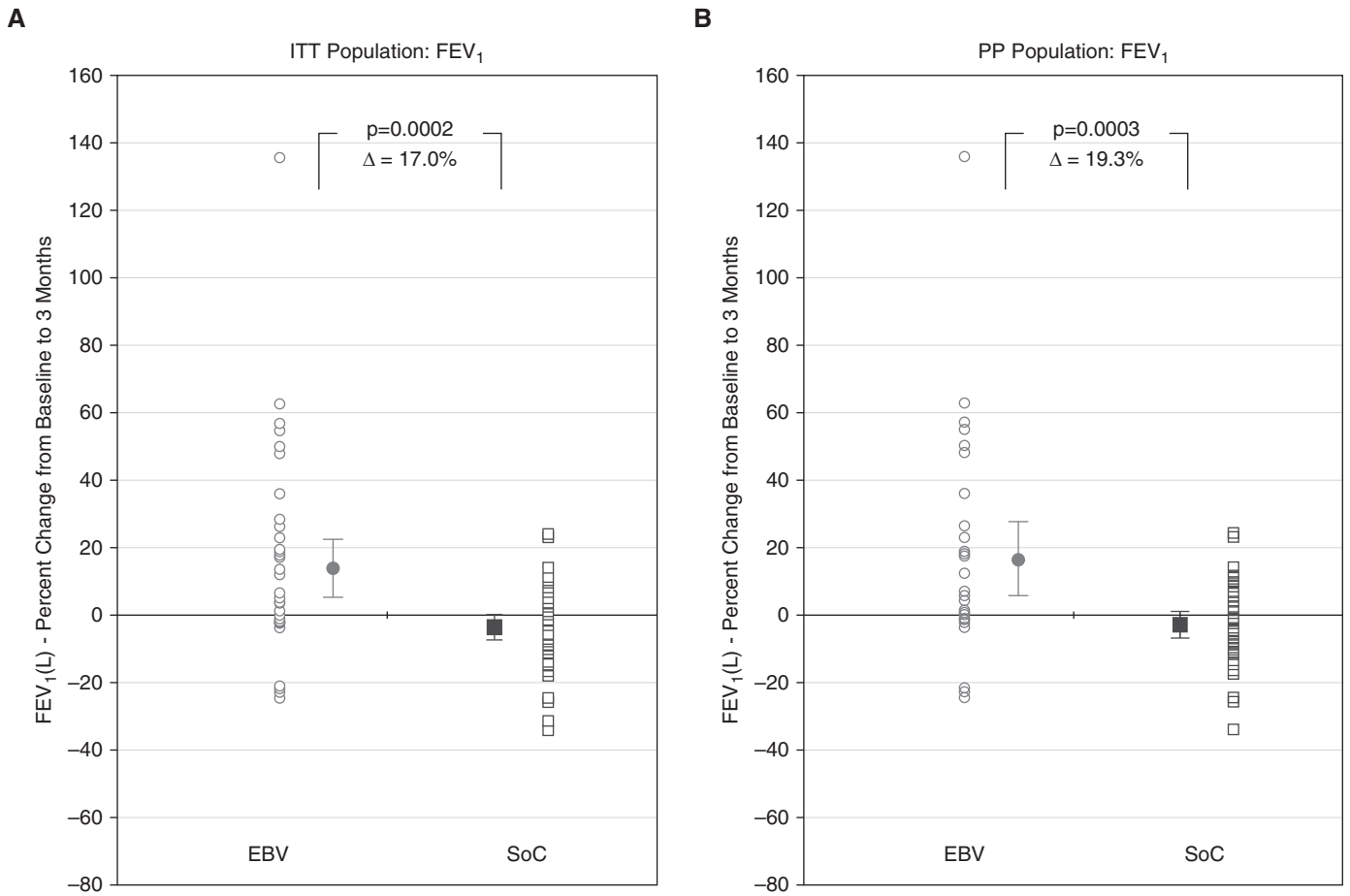

Figure 2. FEV_1: Percent change from baseline to 3 months (*A*, ITT; *B*, PP). Each *open symbol* represents individual subject data for EBV subjects (*open circles*) and SoC subjects (*open squares*). Mean values (*solid circles*, *solid squares*) and the 95% confidence intervals are presented. *P* values are by two-sample *t* test analysis. The percent change was calculated as (FEV_1 [L] at 3 mo − FEV_1 [L] at baseline)/(FEV_1 [L] at baseline) × 100. EBV = endobronchial valve; ITT = intention to treat; PP = per protocol; SoC = standard of care.

improvement in lung function, after LVRS, was the RV/TLC ratio. They hypothesized that if the reduction in FEV_1 was due to an increase in RV, then reducing RV by LVR should have a substantial effect on FEV_1. They also hypothesized that with significant hyperinflation, that is, RV/TLC levels of 0.6 and higher, LVRS in homogeneous subjects may become increasingly effective. In our current data set the mean RV/TLC at baseline was 0.68 and the mechanism of action of valves in homogeneous patients, based on the reduction of RV, is consistent with this hypothesis.

We speculate that EBV therapy, using the current algorithm of target lobe selection based on emphysema destruction scores and regional perfusion impairments, comes closest to removal of regions with high RV/TLC ratios, which has been related to lung function improvements in homogeneous emphysema (37). Indeed, a previous report suggested that low target lobe perfusion (i.e., perfusion in the target zone) was associated with improved exercise tolerance in patients with emphysema treated with valves (38). More recently, Thomsen and colleagues (39) extended these findings to indicate that, particularly in patients with low disease heterogeneity, low target lobe perfusion is crucial to predict clinical benefits.

Other endoscopic techniques aiming at reducing lung volumes in severe homogeneous emphysema are confined to either case series or subgroup analysis from a mixed emphysema population (6, 7, 40). A previous study of polymeric lung volume reduction in patients with severe emphysema similarly demonstrated improvements in FEV_1 for both homogeneous and heterogeneous emphysema; however, the effect size was greater in the latter group (40). More modest effects with respect to FEV_1 and 6MWD were also observed in subgroups of patients with homogeneous emphysema who underwent bilateral endobronchial coil therapy (6).

The positive outcomes associated with EBV therapy in homogeneous emphysema were accompanied by a higher incidence of serious adverse events (SAEs), predominantly pneumothoraces. Although a pneumothorax may be a surrogate of immediate technical and medium-term clinical success after EBV therapy (41), the benefits of this therapy need to be weighed carefully against the associated risk. A pneumothorax after EBV therapy is thought to be due to a rapid shift in lung volumes caused by the rupture of subpleural blebs or bullae of the adjacent

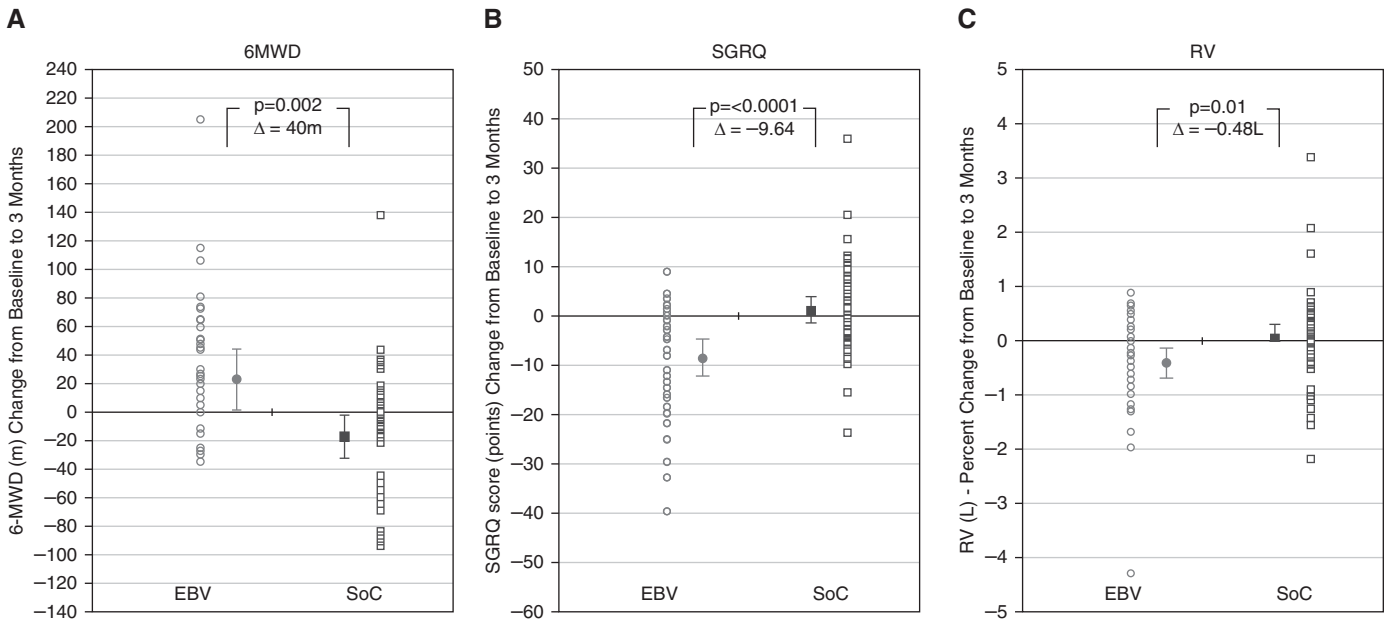

Figure 3. Changes from baseline to 3 months for (*A*) 6MWD, (*B*) SGRQ, and (*C*) RV for the ITT population. Each *open symbol* represents individual subject data for EBV subjects (*open circles*) and SoC subjects (*open squares*). Mean values (*solid circles*, *solid squares*) and the 95% confidence intervals are presented. *P* values are by two-sample *t* test analysis. 6MWD = 6-minute-walk distance; EBV = endobronchial valve; ITT = intention to treat; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SoC = standard of care.

untreated lobe and/or parenchymal rupture due to pleural adhesions (23). The observed frequency of pneumothorax in our study is similar to real-life data, ranging between 20 and 25% (32, 42). Consistent with a previous analysis from this group the majority of these events occurred within the first 48 hours (41), when the patients were still hospitalized. All the pneumothoraces were managed according to published recommendations, including clinical observation, chest tube placement, and/or valve removal to return the target lobe to its (hyperinflated) pretreatment state and promoting pneumothorax healing by reestablishing pleural contact (23). There were no patient deaths as a result of pneumothorax. However, given the chronic condition and declining state of these patients and limited therapeutic choices, patient preferences may need to be considered when evaluating the risks and associated benefit of this treatment option. Despite the considerable experience of investigators in this study, there was a low incidence of valve migration that required replacement of the valves. This could be readily accomplished because of the ease of removing the EBV valves.

We acknowledge some limitations of this study. First, there is no consensus regarding the definition of homogeneous emphysema. In the NETT, each lung was visually divided into thirds to define three apical to basal zones. Each zone was compared with the remaining two ipsilateral zones to evaluate heterogeneity (1). However, this method of visual scoring for emphysema severity does not necessarily follow anatomical lobar boundaries. Computerized quantitative measurement

Table 2. Absolute Change in Key Parameters from Baseline to 3 Months

Variable	EBV Group (*n*)	SoC Group (*n*)	ΔEBV − SoC [*Mean (95% CI)*]	*P* Value
FEV_1, L	0.10 ± 0.18 (43)	−0.02 ± 0.10 (50)	0.12 (0.06 to 0.18)	<0.0001
Residual volume, L	−0.42 ± 0.90 (43)	0.05 ± 0.87 (50)	−0.48 (−0.84 to −0.11)	0.0113*
6MWD, m	22.6 ± 66.6 (40)	−17.3 ± 52.8 (50)	40.0 (15.0 to 65.0)	0.002*
SGRQ total score, points	−8.63 ± 11.2 (37)	1.01 ± 9.3 (48)	−9.64 (−14.09 to −5.20)	<0.0001*
mMRC grade, points	−0.39 ± 1.00 (41)	0.18 ± 0.98 (50)	−0.57 (−0.98 to −0.16)	0.007*
CAT total score, points	−1.5 ± 5.6 (41)	−0.7 ± 3.7 (49)	−0.9 (−2.9 to 1.1)	0.374*
BODE index score	−0.7 ± 1.5 (39)	0.4 ± 1.1 (50)	−1.16 (−1.7 to −0.6)	<0.0001†

Definition of abbreviations: 6MWD = 6-minute-walk distance; BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; CAT = COPD Assessment Test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EBV = endobronchial valve; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire; SoC = standard of care.
Values represent means ± SD.
*Two-sample *t* test.
†Wilcoxon signed-rank test.

Table 3. Responders with Minimal Clinically Important Difference in Key Outcome Measures in Intention-to-Treat Population

Variable	EBV Group	SoC Group	*P* Value*
FEV_1 (L),† MCID ⩾ +15%	15/43 (34.9%)	2/50 (4.0%)	0.0001
FEV_1 (L),† MCID ⩾ +12%	17/43 (39.5%)	4/50 (8.0%)	0.0003
FEV_1 (L), MCID ⩾ 100 ml	16/43 (37.2%)	5/50 (10.0%)	0.002
RV (ml), MCID ⩽ −430 ml	19/43 (44.2%)	9/50 (18.0%)	0.006
SGRQ, MCID ⩽ −4 points	21/37 (56.8%)	12/48 (25.0%)	0.003
SGRQ, MCID ⩽ −8 points	17/37 (45.9%)	4/48 (8.3%)	<0.0001
6MWD, MCID ⩾ +26 m	20/40 (50.0%)	7/50 (14.0%)	0.0002
mMRC, MCID ⩽ −1 point	17/41 (41.5%)	7/50 (14.0%)	0.003

Definition of abbreviations: 6MWD = 6-minute-walk distance; EBV = endobronchial valve; MCID = minimal clinically important difference; mMRC = modified Medical Research Council; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SoC = standard of care.
*χ^2 test.
†FEV_1 responders were also evaluated using more conventional MCID thresholds of 10% and obtained similar results: greater than or equal to +10%: 40.5 versus 14.0% (EBV vs. SoC, respectively), $P = 0.004$.

tools have enabled more precise scoring of the lung, minimizing the variability seen during the radiologist-dependent visual scoring and allowing for a user-independent result (43). The definition of greater than 15% constituting heterogeneity and less than 15% equating to homogeneity was derived from the VENT trial (12), where patients had a median difference in emphysema score between the target and ipsilateral lobes of 15%. Future studies may need to confirm the usefulness of the target lobe selection algorithm implemented in the present trial. Second, the lack of a sham procedure might have influenced subjective measures, such as quality of life and symptom scores, with an unintentional bias. Indeed, the proportion of patients exceeding the MCID for the SGRQ in open-label (6) and sham-controlled (13) intervention studies in severe emphysema are as high as 28 and 46%, respectively. Using a more stringent cutoff of 8 points for the SGRQ, as proposed in the NETT (1), we observed a more pronounced difference between EBV-treated patients and control subjects. Thus, given the associated improvements in both airflow obstruction and lung volumes, together with the magnitude of SGRQ improvements reported here, there is a high likelihood of a true treatment-related effect. Third, standardized pulmonary rehabilitation was not performed as part of the pre- and/or postprocedural patient care, which may have contributed somewhat to a variable response in exercise testing results. However, there is no consensus whether pulmonary rehabilitation is needed for the minimally invasive endoscopic LVR procedures. In fact, a study from a real-life

Table 4. Respiratory Serious Adverse Events* during 3 Months of Follow-up

Adverse Event	Events (% Subjects)		*P* Value†
	EBV Group (*n* = 43)	SoC Group (*n* = 50)	
Total respiratory SAEs, n	26 (44.2%)	8 (12.0%)	<0.001
Pulmonary events			
Death	0	1 (2.0%)‡	
COPD exacerbation with hospitalization	10 (16.3%)	6 (12.0%)	NS
Dyspnea	1 (2.3%)	0	
Pneumonia	0	1 (2.0%)	
Respiratory distress	1 (2.3%)	0	
Pneumothorax	12 (25.6%)	0	<0.001
Resolved ⩽ 14 d after onset, with drainage§	8 (16.3%)	0	
Required temporary valve removal	2 (4.6%)	NA	
Required permanent valve removal because of recurrent pneumothorax	1 (2.3%)	NA	
Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax	2 (4.6%)	NA	
Other EBV-related events requiring valve replacement	3 (7.0%)	NA	
Valve migration	2 (4.6%)	NA	
Paralysis of the nervus recurrens	1 (2.3%)‖	NA	

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; EBV = endobronchial valve; NA = not applicable; NS = not significant; SAEs = serious adverse events; SoC = standard of care.
*Serious adverse events were events leading to death or to serious deterioration in health that resulted in a life-threatening illness or injury, a permanent impairment of a body structure or body function, hospitalization or prolongation of existing hospitalization, or medical or surgical intervention to prevent permanent impairment to body structure or body function.
†Fisher's exact test.
‡Subject died of respiratory failure subsequent to pneumonia.
§Drainage includes chest tube/drainage, thorax drainage, Bülau drainage, and pleural drainage.
‖Paralysis of nervus recurrens (nonrespiratory event).

clinical setting demonstrated best outcomes in patients with lowest exercise capacity in the absence of systematic pre- and/or postinterventional rehabilitation (44). Last, the present report provides short-term postprocedural primary outcome data at 3 months. Data from previous randomized controlled valve treatment trials indicate sustained benefits in key outcome measures throughout 6 months in the subgroup of patients with homogeneous emphysema (14, 15). Follow-up data from EBV-treated patients thus continue to be collected throughout 12 months and will be reported separately.

In conclusion, the present report demonstrates that EBV therapy in selected patients with homogeneous emphysema without collateral ventilation results in clinically meaningful benefits of improved lung function, exercise tolerance, and quality of life. Given the limited treatment options available for this particular patient population, most notably limitations beyond medical therapy, EBV therapy should be considered in these patients. ■

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