

Endoscopic Lung Volume Reduction: Review of the EMPROVE and LIBERATE trials

Khaled M. Nada, MD, and Shawn Nishi, MD

Abstract

Endoscopic lung volume reduction is now included in the guidelines for treatment in severe chronic obstructive pulmonary disease. Since December 2018, 2 valve systems have been approved by the US Food and Drug Administration (FDA). To date, there is no head-to-head trial comparing both valve systems and no clear benefit of one over the other. This article provides an overview of the two largest prospective trials performed with the FDA-approved valve systems.

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Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States; it is associated with significant disability and reduced quality of life, and it is the primary contributor to deaths from chronic respiratory diseases.^{1,2} Severe COPD is characterized by reduced lung elastic recoil and expiratory flow limitation with progressive air trapping and hyperinflation manifested by increases in residual volume (RV) and total lung capacity (TLC) on pulmonary function testing.³ The increased static and dynamic lung volumes put the diaphragm and intercostal muscles at a mechanical disadvantage, increase intrathoracic pressure, and decrease cardiac filling; they are also associated with shortness-of-breath symptoms and functional capacity better than the spirometric indices of the disease.^{4,5}

Treatment of COPD centers around tobacco cessation, immunization, pulmonary rehabilitation, and medication management. In patients with severe COPD, predominant upper lobe emphysema, and decreased exercise capacity, lung volume reduction surgery (LVRS) has been shown to improve survival, dyspnea, and quality of life.⁶ LVRS alleviates the increased static and dynamic lung volumes which mechanically handicaps the diaphragm and intercostal muscles, and it can reduce the intrathoracic pressure hindering cardiac filling.^{4,5} However, because of the perioperative morbidity associated with the procedure, most patients are not eligible for LVRS because

of either the distribution of emphysema or multiple medical comorbidities, placing them at high surgical risk.^{7,8}

Endoscopic lung volume reduction (ELVR) techniques have emerged as a promising minimally invasive treatment option that provides benefits comparable to LVRS with the advantage of being less morbid.⁹ Initial methods including endobronchial plugs and blockers, nitinol coils, biologic lung volume reduction, airway bypass procedures, and thermal airway ablation have failed to provide consistent benefits, and they are currently not approved by the US Food and Drug Administration (FDA).¹⁰⁻¹²

Two endobronchial valves—the Olympus Spiration Valve System and the Pulmonx Zephyr Endobronchial Valve—have been recently approved by the FDA for ELVR. There is no head-to-head trial to compare both valves, but both have shown improvements in radiologic, spirometric, and patient-centered outcomes. We provide an overview of the Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE) and the Evaluation of the Spiration Valve System for Emphysema to Improve Lung Function (EMPROVE) trials, the two largest prospective trials performed with the Zephyr and the Spiration valves, respectively, in terms of patient selection, outcomes, and adverse events.

From the Department of Internal Medicine, Division of Pulmonary Critical Care & Sleep Medicine, The University of Texas Medical Branch, Galveston, TX.

TABLE 1. Comparison of Inclusion Criteria^a

Criteria	LIBERATE trial	EMPROVE trial
Demographics		
Age (years)	40-75	≥40
Tobacco status	Tobacco free for at least 4 months before screening interview	
BMI (kg/m ²)	<35	>15
Bronchitis phenotype	<4 tablespoons per day sputum production	
Number of exacerbations with hospitalization	≤1 (12 months before screening)	None 3 months before screening
Steroids (daily mg of prednisone or equivalent)	≤20	≤15
PR	Completed in last 6 months or maintenance phase, 20 visits after valve placement	Completed within 2 years or PR if "likely to clinically benefit from PR"
Cardiac		
Ejection fraction	≥45% within 3 months of screening	
Pulmonary hypertension	sPAP < 45 mm Hg without evidence of cor pulmonale	Not "severe by clinical evaluation"
Pulmonary testing		
FEV1 post-bronchodilator	15%-45% of predicted	≤45% predicted
TLC	>100% predicted	≥100% predicted
RV	≥175% predicted	≥150% of predicted
DLCO	≥20% predicted	NR
MMRC	NR	mMRC ≥ 2
6MWT distance (m)	100-450	≥140
PaCO ₂ (mm Hg)	<50 on room air (Denver < 55)	
PaO ₂ (mm Hg)	>45 on room air (Denver > 30)	
Lobar selection criteria		
Collateral ventilation determination	Chartis (CV-) ^b	QCT fissure integrity ≥90%
Emphysema (% voxels by HU cutoff)	≥50% using -910 HU	≥40 using -920 HU
Heterogeneity ^c	≥15%	≥10%
RML	Possible target	Not a target

^aBMI = body mass index; CV = collateral ventilation; DLCO = diffusion capacity for carbon monoxide; EMPROVE = Evaluation of the Spiration Valve System for Emphysema to Improve Lung Function; FEV1 = forced expiratory volume in 1 second; HU = Hounsfield unit; LIBERATE = Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema; MMRC = Modified Medical Research Council dyspnea scale; NR = not reported; PR = pulmonary rehabilitation; QCT = quantitative computed tomography; RML = right middle lobe; RV = residual volume; sPAP = systolic pulmonary artery pressure; TLC = total lung capacity; 6MWT = 6-minute walk test.

^bSubjects randomized after CV-Chartis assessment.

^cDetermined by the absolute difference in percent of emphysema destruction between the target and the ipsilateral lobe.

RESULTS

Tables 1 and 2 compare inclusion criteria and baseline patient characteristics between the two trials. The LIBERATE trial randomized 190 patients in a 2:1 ratio comparing Zephyr ELVR to standard of care (SOC) maximal medical therapy. Patients had severe emphysema (defined by quantitative computed tomography [CT] as the percent of voxels <-910 HU at a >50% threshold), hyperinflation (defined as TLC > 100% predicted) with air trapping (defined as RV > 175% predicted) and heterogeneous emphysema with ≥15%

difference between the target and ipsilateral lobes emphysema assessment. The primary endpoint was the percentage of subjects in the EBV group at 1 year after the procedure who had an improvement in the post-bronchodilation forced expiratory volume in 1 second (FEV1) ≥15% compared with the percentage of subjects achieving this improvement in the SOC group.

The EMPROVE trial randomized 174 patients in a 2:1 ratio comparing the Spiration Valve System ELVR with SOC. Patients with hyperinflation (defined as TLC > 100%

TABLE 2. Comparison of Patient Baseline Characteristics^a

Baseline characteristic	LIBERATE trial ^b		EMPROVE trial ^c	
	SoC	EBV	SoC	EBV
Patients, n	62	128	59	113
Enrollment	October 13 to September 16, 24 sites		October 13 to May 7, 41 sites	
COPD stage, n (%) ^d				
III	16 (25.8)	54 (42.2)	NR	NR
IV	46 (74.2)	74 (57.8)	NR	NR
FEV1 (L), mean ± SD	0.75 ± 0.22	0.76 ± 0.25	0.792 ± 0.260	0.825 ± 0.264
FEV1 (% predicted), mean ± SD	26.2 ± 6.28	28.0 ± 7.45	28.5 ± 8.5	30.8 ± 8.1
FVC (L), mean ± SD	2.63 ± 0.79	2.60 ± 0.86	2.63 ± 0.76	2.49 ± 0.75
FVC (% predicted), mean ± SD	68.5 ± 13.59	71.2 ± 15.99	70.5 ± 16.7	70.2 ± 16.5
RV (L), mean ± SD	4.76 ± 0.90	4.71 ± 1.05	4.85 ± 1.20	4.57 ± 1.25
RV (% predicted), mean ± SD	224.6 ± 38.86	224.5 ± 42.45	213.4 ± 49.3	207.5 ± 45.0
TLC (L), mean ± SD	7.63 ± 1.37	7.54 ± 1.59	7.65 ± 1.43	7.22 ± 1.53
TLC (% predicted), mean ± SD	130.2 ± 12.44	133.5 ± 21.17	128.2 ± 17.0	126.5 ± 14.5
DLCO (% predicted), mean ± SD	33.1 ± 9.84	34.6 ± 11.34	NR	NR
PaO ₂ (mm Hg)	67.8 ± 11.72	68.7 ± 11.62	68.0 ± 11.6	67.9 ± 10.2
PaCO ₂ (mm Hg), mean ± SD	41.3 ± 5.33	40.1 ± 4.91	40.9 ± 6.0	40.2 ± 5.7
6MWD (m), mean ± SD	302 ± 79	311 ± 81	306.9 ± 104.2	303.5 ± 84.6
SGRQ, mean ± SD	53.10 ± 14.14	55.15 ± 14.08	54.6 ± 13.6	57.2 ± 14.8
MMRC (points), mean ± SD	2.2 ± 0.83	2.4 ± 0.97	2.7 ± 0.6	2.7 ± 0.7
CAT (points), mean ± SD	19.3 ± 6.35	19.2 ± 6.32	20.0 ± 6.3	21.8 ± 6.8
Pulmonary rehabilitation (%) [pre, post]	100, 100	100, 100	100, 30.5	100, 34.5
Target lobe volume (L), mean ± SD	NR	NR	1.82 ± 0.46	1.84 ± 0.60
Emphysema target lobe severity (%), mean ± SD ^e	70.9 ± 8.77	70.9 ± 8.52	61.6 ± 11.6	63.6 ± 10.1
Emphysema heterogeneity (%), mean ± SD ^f	26.1 ± 9.81	25.5 ± 9.85	23.3 ± 11.6	25.3 ± 12.0

^a6MWD = 6-minute walk distance; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; DLCO = diffusion capacity for carbon monoxide; EBV = endobronchial valve; EMPROVE = Evaluation of the Spiration Valve System for Emphysema to Improve Lung Function; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LIBERATE = Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema; MMRC = Modified Medical Research Council dyspnea scale; NR = not reported; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SOC = standard of care; TLC = total lung capacity.

^bSubjects randomized after Chartis CV-exam confirmed.

^cSubjects randomized after quantitative computed tomography confirmed fissure integrity >90%.

^dStage III = FEV1, 30-50% predicted; stage IV = FEV1 < 30% predicted.

^eQuantitative computed tomography software measuring percent of voxels <−910 HU (StratX software) for LIBERATE or <−920 HU (SeleCT software) for EMPROVE.

^fDifference in the percentage of emphysema between the target and ipsilateral lobes.

predicted), air trapping (RV > 150% predicted), and heterogeneous emphysema on CT (defined as emphysema destruction score of >40% using <−920 HU threshold) with an absolute difference of ≥10% between the target and ipsilateral lobes. The primary endpoint was the mean change in FEV1 after bronchodilation from baseline to 6 months between treatment and SOC groups.

Both studies showed FEV1 improvement, reduction of hyperinflation (TLC and RV/TLC ratio), improved dyspnea (assessed by

MMRC scale and St. George's Respiratory Questionnaire), 6-minute walk distance, and quality of life in patients treated with ELVR compared with SOC.

The left upper lobe followed by the left lower lobe were the most frequent targeted lobes in both trials. However, in contrast to the EMPROVE trial where the right middle lobe was not a target for valve placement, up to 7% of patients in the LIBERATE trial had a combined target of the right upper and middle lobes. Collateral ventilation assessment

TABLE 3. Comparison of Outcomes^{a,b}

Outcome Measured	LIBERATE trial			EMPROVE trial		
	Control	EBV	diff T-C	Control	EBV	diff T-C
Patients, n	62	128		59	113	
Procedure						
Mean procedure time, minutes (range)	NA	29 (4-123)		NA	24.3 (9-73)	
Valves (average number per patient)	NA	4		NA	3.83	
Mean and median hospitalization days (range)	NA	NR		NA	3.83, 1 (1-95)	
Efficacy						
Change in lung function from baseline, L (%)						
TLV reduction, 6 mo	NA	NR	—	NA	-0.97 ± 0.74	-0.97
TLV reduction, 12 mo	NA	-1.142 ± 0.702	-1.142	NA	NR	—
FEV ₁ , 6 mo	—	+18% ^c	—	-0.002 ± 0.098	0.099 ± 0.154	0.101
FEV ₁ , 12mo (% change from baseline)	-0.003 ± 0.194 (-0.80 ± 26.94)	0.104 ± 0.200 (17.16 ± 27.93)	0.106 (17.96)	-0.032 ± 0.114	0.067 ± 0.167	0.099
RV, 6 mo	NR	NR	—	-0.04 ± 0.58	-0.40 ± 0.85	-0.36
RV, 12 mo	0.03 ± 0.66	-0.49 ± 0.83	-0.522	NR	NR	
FVC, 0 to 6 mo	NR	NR	—	-0.098 ± 0.252	0.147 ± 0.485	0.245
FVC, 0 to 12 mo	NR	NR	—	-0.103 ± 0.369	0.097 ± 0.536	0.2
Change in exercise, m						
6MWD, 6 mo	—	+39 ^c	—	-11.3 ± 51.4	-4.4 ± 76.7	6.9 ^d
6MWD, 12 mo	-26.33 ± 81.50	12.98 ± 81.54	39.31 (14.64-63.98)	NR	NR	—
Change in patient-centered outcomes						
SGRQ total score, 0-6 mo	—	-7.1 ^c	—	4.8 ± 10.6	-8.1 ± 17.1	-13.0
SGRQ total score, 0-12 mo	-0.50 ± 15.50	-7.55 ± 15.71	-7.05 (-11.84 to -2.27)	3.7 ± 10.9	-5.8 ± 16.8	-9.5
mMRC change, 0-6 mo	—	-0.8 ^c	—	0.0 ± 0.6	-0.6 ± 1.0	-0.6
mMRC change, 0-12 mo	0.3 ± 1.03	-0.5 ± 1.17	-0.8 (-0.4 to -1.1)	0.2 ± 0.6	-0.6 ± 1.1	-0.9
CAT change, 0-6 mo	NR	NR	—	1.6 ± 5.3	-3.0 ± 7.8	-4.3
CAT change, 0-12 mo	NR	NR	—	3.0 ± 5.7	-2.3 ± 8.1	-5.3
Responder rates ^e						
FEV ₁ ≥ 15%						
6 months, n/N (%)	12.3%	49.6%	37.30%	5/50 (10%)	39/106 (36.8%)	25.70%
12 months, n/N (%)	16.8%	47.7%	31%	2/39 (5.1%)	32/86 (37.2%)	30.40%
RV ≥ 310 reduction						
45 days, %	22	66.4	44	NR	NR	—
6 months, n/N (%)	NR	NR	—	16/50 (32%)	53/105 (50.5%)	18.50%
12 months, %	22.4	61.6	39.2	NR	NR	—
TLV (≥350-L reduction)						
45 days	NA	79.1%	—	NA	—	—
6 months, n/N	NA	NR	—	NA	76/102 (74.5%)	—
12 months	NA	84.2%	—	NA	NR	—

Continued on next page

TABLE 3. Continued

Outcome Measured	LIBERATE trial			EMPROVE trial		
	Control	EBV	diff T-C	Control	EBV	diff T-C
Responder rates ^e , continued						
Lobar atelectasis complete by imaging	NA	NR	—	NA	40%, 6 months	—
6MWD ≥ 25 m, 6 mo (%)	27.2	39.4	12.2	22.9	32.4	9.5
6MWD ≥ 25 m, 12 mo (%)	19.6	41.8	22.2	NR	NR	—
SGRQ ≥ 4-point reduction						
6 months, n/N (%)	36.5%	55.7%	19.2%	9/50 (18%)	57/105 (54.3%)	36.3%
12 months, n/N (%)	30.2%	56.2%	26%	9/41 (22%)	48/95 (50.5%)	28.5%
MMRC ≥ 1-point reduction						
6 months, n/N (%)	21.1%	46.5%	25.4%	9/50 (18%)	57/107 (53.3%)	35.3%
12 months, n/N (%)	18.6%	47.8%	29.2%	3/41 (7.3%)	46/94 (48.9%)	41.6%

^a6MWD = 6-minute walk distance; CAT = chronic obstructive pulmonary disease assessment test; EBV = endobronchial valve; EMPROVE = Evaluation of the Spiration Valve System for Emphysema to Improve Lung Function; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LIBERATE = Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema; MMRC = Modified Medical Research Council dyspnea scale; NA = not applicable; NR = not reported; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; TLV = total lung volume.

^bData are presented as median (range) or mean change, unless otherwise stated.

^cIntention to treat analysis.

^dNot statistically significant.

^ePercentage of patients who reached the earlier established minimal important difference reported at 45 days and 12 months for the LIBERATE trial; reported at 6 months and 12 months for the EMPROVE trial.

TABLE 4. Adverse Events^a

Events	LIBERATE trial (%)			EMPROVE trial (%)		
	Control	EBV	diff T-C	Control	EBV	diff T-C
Safety composite adverse events ^b						
45 days	4.8	35.2	30.4	NR	NR	NR
6 months	NR	NR	NR	11.9	31.0	19.1
12 months	30.6	33.6	3 ^c	10.6	21.4	10.7 ^c
Pneumothorax						
<45 days	NA	30.5	—	NA	24.8	—
12 months	NA	34	—	NA	31	—
COPD exacerbation						
Short-term ^d	4.8	7.8	3 ^c	10.2	16.8	6.6 ^c
Long-term ^e	30.6	23	7.6 ^c	8.5	13.6	5.1 ^c
Pneumonia						
Short-term ^d	0	0.8	0.8 ^c	1.7	7.1	5.4 ^c
Long-term ^e	8.1	5.7	2.4 ^c	2.1	7.8	5.6 ^c
Valve removal owing to pneumothorax	NA	12% of subjects	—	NA	9.7% of total number of valves	—
Valve removal owing to any cause n(% of subjects)/total number reimplanted	NA	18 (14.1%)/10 (7.8%)	—	NA	9.7%, 4.4%	—
Re-bronchoscopy for valve adjustment, n (% of subjects)	NA	8.6 (n = 11)	—	NA	0	—
Device migration rate	NA	0.6	—	NA	0	—
Device expectoration rate	NA	0.4	—	NA	0	—
Deaths						
<6 mo						
All cause	0	3.1 (n = 4)	—	1.7 (n = 1)	5.3 (n = 6)	— ^c
Procedure related	—	3.1 (n = 4)	—	0	0.88 (n = 1)	— ^c
6-12 mo						
All cause	1.6 (n = 1)	0.8 (n = 1)	—	6.4 (n = 3)	3.9 (n = 4)	— ^c
Procedure related	0	0	—	0	0.88 (n = 1)	— ^c

^aCOPD = chronic obstructive pulmonary disease; EBV = endobronchial valve; EMPROVE = Evaluation of the Spiration Valve System for Emphysema to Improve Lung Function; LIBERATE = Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema; NA = not applicable; NR = not reported.

^bFor the EMPROVE trial, this includes death, pneumothorax requiring intervention or >7-d air leak, COPD exacerbation, pneumonia, and respiratory failure. For the LIBERATE trial, this includes death, pneumothorax, COPD exacerbation, pneumonia, respiratory failure and arrhythmia.

^cNot statistically significant.

^dShort-term: 0-45 days (LIBERATE) and 0-6 months (EMPROVE) from valve implantation.

^eLong-term: 45 days to 12 months (LIBERATE) and 6 to 12 months (EMPROVE) from valve implantation.

was indirectly assessed using quantitative CT to evaluate fissure integrity in EMPROVE, whereas in the LIBERATE trial, fissure integrity was confirmed with physiologic assessment intraoperatively using the Chartist system.

Efficacy of ELVR treatment was assessed with follow-up quantitative CT, functional testing, and surveys on patient-centered outcomes (Table 3). Minimal clinically important differences (MCIDs) were defined as target

lung volume reduction (TLVR) ≥ 350 mL and RV decrease ≥ 310 mL. TLVR was met for 75% of the treated patients at 6 months in the EMPROVE trial compared to the LIBERATE trial where 79% and 84% of patients met the TLVR criteria at 45 days and 12 months, respectively. Half of treated subjects in the EMPROVE trial and 66.4% in the LIBERATE trial met RV improvement MCID. Of note, 11 patients (8.5%) in the LIBERATE trial underwent secondary valve adjustments,

whereas no valve adjustments were reported in the EMPROVE trial. Overall, more patients in the LIBERATE trial met the MCID for the 6-minute walk test (>25-m improvement); in contrast, there was no statistically significant difference in the 6-minute walk performance between the treatment and control arms in the EMPROVE trial.

The incidence of pneumothorax and number of complex pneumothorax events were higher in LIBERATE (34.4% and 38, respectively) compared with EMPROVE (27.4% and 18, respectively). However, “complex” defined by trial differed. In LIBERATE, this was any event requiring chest tube placement, whereas in EMPROVE, an event was considered complex only if the patient required surgical intervention or had a persistent air leak for longer than 7 days. In both trials, there was higher mortality in the treatment arm, but the results were not statistically significant.

On the long-term follow-up, ELVR versus SOC groups in LIBERATE had a lower incidence of COPD exacerbation (23% vs 30.6%, respectively) and pneumonia (5.7% vs 8.1%, respectively) versus patients treated in EMPROVE who had a higher incidence of COPD exacerbation (13.6% vs. 8.5%) and higher incidence of pneumonia (7.8% vs. 2.1%, respectively). A comparison between the adverse events in both trials is outlined in [Table 4](#).

DISCUSSION

LVRS is shown to improve lung function and patient-centered outcomes in carefully selected patients with advanced emphysema refractory to maximal medical therapy. Benefit is mainly derived by reduction in functional residual capacity with subsequent improvement in the mechanical function of the diaphragm and intercostal muscles, decreased intrathoracic pressure, and improved cardiac filling.⁴

The National Emphysema Treatment Trial (NETT) is the largest randomized trial for LVRS; it compared LVRS and maximal medical therapy in 1218 patients with advanced emphysema. The authors of the NETT concluded that overall LVRS was associated with improved exercise capacity compared with medical therapy. However, there was no mortality benefit. The subgroup analysis

identified a group of patients as “high risk” with significant increase in mortality after LVRS; this subgroup of patients had a FEV1 \leq 20% predicted with either homogeneous emphysema or DLCO \leq 20% predicted.⁶

Another subgroup of patients with predominant upper lobe emphysema and decreased baseline exercise capacity seemed to achieve the most benefit from LVRS with reduction in long-term mortality and sustained improvement in exercise capacity. Although there was an increase in 90-day mortality after LVRS in patients with non-upper-lobe emphysema, but there was no increase in long-term mortality.⁶

Results from the NETT trial indicate many limitations with LVRS; the procedure is contraindicated in patients with homogeneous emphysema and patients with distorted surgical anatomy (eg, prior pleurodesis). In addition, because of the invasive nature of the procedure, patients with multiple medical comorbidities are often considered nonsurgical candidates.

Over the past decade, endoscopic lung volume reduction (ELVR) via bronchial valve implantation was developed as a minimally invasive procedure to achieve benefits of LVRS with less perioperative morbidity and mortality. The Zephyr valve was initially developed and investigated by the VENT trial in 2007.¹³ Four additional randomized controlled trials (RCTs)—STELVIO,¹⁴ IMPACT,¹⁵ TRANSFORM,¹⁶ and LIBERATE¹⁷—have been published with a total of 448 patients, showing comparable significant and clinically relevant improvements in lung function, exercise capacity, physical activity, dyspnea severity, and quality of life. The Spiration valve system was developed in 2008 and investigated in 2 RCTs (REACH and EMPROVE),^{8,18,19} totaling 378 patients and demonstrating the benefit of ELVR compared with SOC.

The direct comparison of LVRS and ELVR is currently being investigated in the CELEB trial (ISRCTN19684749).²⁰ However, the majority of our current ELVR candidates are ineligible for surgery because of factors such as homogeneous emphysema, lower lobe predominant disease, comorbidity, operability, age, or patient preferences.

Crucial factors for ELVR treatment success are the presence of an emphysematous treatment target lobe, fully occluded lobe after intervention, and the absence of interlobar collateral ventilation, which can be assessed with quantitative CT or intraoperatively with the Chartis system.

The Chartis pulmonary assessment system is an invasive, catheter-based measurement that is performed bronchoscopically, usually in the same setting before endobronchial valve placement. The catheter's balloon inflates and allows sealing of a lung compartment with measurement of air pressure and flow from the sealed compartment. Persistence of flow after 5 minutes of balloon inflation suggests the presence of collateral ventilation. False-negative collateral ventilation assessment has been reported in a subset of patients and is attributed to either collapse of the bronchial wall distal to the inflated balloon or the presence of large collateral channels leading to reverse airflow and causing air to escape from the target lobe to the adjacent lobe after balloon inflation. Furthermore, the Chartis measurement is technically complicated in patients with difficult anatomy, coughing, or mucous clogging at the tip of the Chartis catheter.^{21,22}

The more novel quantitative CT technique now offers a noninvasive assessment of collateral ventilation based on the interlobar fissure integrity. Recent data suggest the exclusion of patients with less than 80% fissure integrity on quantitative CT and EBV implantation in patients with more than 95% fissure integrity on quantitative CT, limiting the role of the Chartis assessment to the subset of patients with 80%-95% fissure integrity.^{23,24}

Pulmonary rehabilitation is a core component in the management of COPD leading to improvement in the 6-minute walk distance and quality of life.²⁵ However, it is both underused because of inadequate awareness and knowledge of benefits among professionals, and underprovisioned with only 831 pulmonary rehabilitation centers available for approximately 24 million patients with COPD in the United States.²⁶

In the LIBERATE trial, all patients were mandated to complete a supervised pulmonary rehabilitation program before

randomization with continued participation after valve placement. In contrast, pulmonary rehabilitation participation within 2 years before randomization was encouraged in the EMPROVE trial, but continued participation after therapy was not required. This might contribute to the better performance in the 6-minute walk test in patients treated with the Zephyr compared with the Spiration valve. The optimal timing of pulmonary rehabilitation in patients treated with ELVR is currently being investigated in the SOLVE trial (NCT03474471).²⁷

Pneumothorax is the main adverse event of ELVR; the highest risk is in the first 3 days after the procedure and is mainly related to acute reduction in lung volume by valve therapy, triggering rapid ipsilateral nontargeted lobe expansion, which is often recognized as an indicator of successful target lobe occlusion. The higher heterogeneity requirement in the LIBERATE trial might have led to treatment of the less diseased lobes with expansion of the more diseased lobes and contributed to the higher number of pneumothorax events reported in the LIBERATE trial. In fact, there was a higher chance of a complex pneumothorax in patients who were not treated in the most diseased lobe and in patients with nontreated contralateral lobe destruction score greater than 60%.¹⁷

CONCLUSION

In patients with COPD and hyperinflation, ELVR lowers TLC and RV, resulting in improved exercise capacity and quality of life. The reported improvement in the same indices in the standard of care groups in both trials reinforces the importance of concomitant medical therapy.

The Zephyr and Spiration valves currently approved by the FDA for ELVR are effective in achieving benefits in patients with heterogeneous emphysema, but there is no clear benefit of one over the other, and we believe that a head-to-head trial is needed to elucidate any superiority if present. However, only the Zephyr valve was evaluated in patients with homogeneous emphysema, and it is the only FDA-approved valve for this group of patients.¹⁵


There are not enough data to determine the appropriate criteria for destruction scores and heterogeneity, which we believe will affect the rates of pneumothorax and treatment success. The trials mentioned different destruction scores with different Hounsfield unit thresholds, and they did not have the same inclusion criteria in regard to the heterogeneity requirement or the diffusion capacity for carbon monoxide. The LIBERATE trial used the same cutoff mentioned in the NETT trial and excluded patients with diffusion capacity for carbon monoxide less than 20% predicted, although this was not mentioned as an exclusion criterion in the EMPROVE trial. We believe that patient selection and exclusion criteria require further exploration.

Abbreviations and Acronyms: COPD = chronic obstructive pulmonary disease; CT = computed tomography; ELVR = endoscopic lung volume reduction; EMPROVE = Evaluation of the Spiration Valve System for Emphysema to Improve Lung Function; FDA = US Food and Drug Administration; FEV1 = expiratory volume in 1 second; LIBERATE = Lung Function Improvement After Bronchoscopic Lung Volume Reduction With Pulmonx Endobronchial Valves Used in Treatment of Emphysema; LVRS = lung volume reduction surgery; MCID = minimal clinically important difference; NETT = National Emphysema Treatment Trial; RV = residual volume; SOC = standard of care; TLC = total lung capacity; TLVR = target lung volume reduction

Potential Competing Interests: Dr Nishi is a PulmonX clinical faculty expert for panel discussions and workshops.

Correspondence: Address to Khaled M. Nada, MD, 301 University Blvd, Galveston, TX 77555 (kmnada@utmb.edu; Twitter: @khaled_sharkawy).

ORCID

Khaled M. Nada:  <https://orcid.org/0000-0001-7740-3973>; Shawn Nishi:  <https://orcid.org/0000-0002-7510-2664>

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