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ORIGINAL RESEARCH

Characterization of outcomes 1 year after endoscopic thermal vapor ablation for patients with heterogeneous emphysema

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Introduction: Endoscopic lung volume reduction has been developed as a therapeutic option for advanced emphysema. Six-month results following treatment with endoscopic thermal vapor ablation (InterVapor™; Uptake Medical, Tustin, CA) were described previously, and here we report observations from the 12-month assessment.

Methods: Two multicenter, international, single-arm trials of InterVapor (unilateral upper lobe treatment) in patients with upper lobe predominant emphysema were conducted. Inclusion criteria: forced expiratory volume in 1 second (FEV_1) 15%–45% predicted, residual volume > 150%, total lung capacity > 100%, 6-minute walk distance (6MWD) >140 m, and diffusing capacity for carbon monoxide > 20% predicted. Efficacy endpoints: spirometry, body plethysmography, lung volumes by high-resolution computed tomography, St George's Respiratory Questionnaire, modified Medical Research Council dyspnea scale, and 6MWD. All adverse events were collected and independently adjudicated.

Results: Forty four patients were treated at a mean (standard deviation) age of 63 (5.6) years, FEV_1 0.86 mL (0.25 mL) (n = 22 men and 22 women). Mean (standard deviation) changes from baseline at 12 months were: FEV_1 86.2 mL (173.8 mL), St George's Respiratory Questionnaire −11.0 (14.0) units, treated lobar volume from high-resolution computed tomography −751.8 mL (653.9 mL), residual volume −302.8 mL (775.6 mL), 6MWD 18.5 m (63.7 m), and modified Medical Research Council dyspnea scale score −0.83 (0.97) ($P < 0.05$ for all except 6MWD). Improvements were numerically larger at 6 versus 12 months. GOLD stage III and IV patients had similar outcomes at 6 months; however, improvements relative to baseline were numerically higher in GOLD stage IV patients. Larger improvements were observed in patients with higher heterogeneity. In total, 39 serious adverse events were reported in 23 patients with 10 events in 8 patients between 6 and 12 months.

Conclusion: Unilateral lobar InterVapor treatment of heterogeneous emphysema improved lung function and health outcomes 1 year following treatment. The magnitude of improvement was larger at 6 months compared to 12 months. Improvements relative to baseline continue to be exhibited at 12 months despite the expected disease related decline over time.

Clinical trials: NCT 01041586 and NCT 01102712

Keywords: emphysema, bronchoscopy, lung volume reduction, thermal energy

Introduction

Surgical removal of poorly functioning hyperinflated emphysematous lung results in long-term improvement in lung function, symptoms, exercise tolerance, and health-related quality of life in appropriately selected patients with emphysema.[1–5] Selection is based on a phenotype of patients characterized by severe and very severe emphysema, predominantly upper lobe heterogeneous disease, and physiological variables indicating

that the disease has not become end-stage.[3,4] While lung volume reduction surgery is beneficial to such patients, surgical intervention is only performed in a small number of presumably eligible patients.[6] In the United States, only 105 Medicare beneficiaries underwent lung volume reduction surgery in 2006.[6] Although various reasons have been proposed for this discrepancy, one prominent factor may be the short-term morbidity and mortality of this disease. Therefore, minimally invasive endoscopic techniques have been developed that are designed to induce lung volume reduction.[7–13]

The critical issue for any endoscopic approach appears to be identifying patients and phenotypes that will achieve meaningful lung volume reduction based on the assumption that reduced lobar volume (removal of tissue, ablation, or collapse) is the basis for clinical improvement. However, it is acknowledged that other mechanisms may contribute. Data from insertion of intrabronchial valves have documented improvement in 6-minute walk distance (6MWD) and the St George's Respiratory Questionnaire (SGRQ) in the absence of improvement in forced expiratory volume in 1 second (FEV_1).[14] The authors hypothesized that redirection of airflow between lobes may be an alternative mechanism of action.

InterVapor™ (Uptake Medical Corp., Tustin, CA) is a minimally invasive endoscopic technique in which thermal energy in the form of heated water vapor is directly administered to targeted regions of the lung.[15–17] The thermal energy leads to a short-term inflammatory response that is followed by healing with contraction fibrosis and atelectasis distal to fibrosed airways and subsequent lobar volume reduction.[15–17] A recently published single-arm clinical trial of InterVapor administered unilaterally in 44 patients with upper lobe predominant emphysema demonstrated significant lobar reduction, improved airflow, reduced hyperinflation, and improved health outcomes (dyspnea, exercise tolerance, and health-related quality of life) at 6 months.[17] Follow-up data from a 12-month visit was obtained that permits documentation of longer term safety and efficacy as well as exploration of subgroup analyses that may identify groups of patients that have differential responses.

Methods

Study design

The methodology has been described previously.[17] In brief, the data are based on two open-label, single-arm efficacy and safety clinical studies (clinical study protocols 0519 [NCT 01041586] and 0808 [NCT 01102712]) that evaluated unilateral InterVapor in the United States, Europe, and Australia. The clinical protocols have identical inclusion/exclusion criteria, efficacy variables, and adverse event collection, with the key differences being additional clinic visits (at 3 weeks and 2 months) and no high-resolution computed tomography (HRCT) at 12 months in protocol 0519. This analysis is from pooled data without the aforementioned information. Following treatment with InterVapor, subjects were asked to return to the clinic at weeks 1, 2, and 4, and at months 3, 6, and 12. The protocol was approved by local institutional review boards or ethics committees and all patients provided written informed consent prior to participation.

Study population

The key inclusion criteria were: upper lobe predominant emphysema determined from HRCT, aged 40 to 75 years, FEV_1 between 15% and 45% predicted, residual volume (RV) >150% predicted, total lung capacity > 100%, diffusing capacity for carbon monoxide > 20% predicted, 6MWD > 140 m, partial pressure of CO_2 < 55 mmHg and partial pressure of O_2 > 45 mmHg, nonsmoking ≥4 months, and recent participation in pulmonary rehabilitation. Key exclusion criteria were: known α-1-antitrypsin deficiency, clinically significant asthma, chronic bronchitis or bronchiectasis, recent pneumothorax, bullae > 1/3 of lobe, thoracotomy, left ventricular ejection fraction ≤ 40%, and pulmonary hypertension (peak systolic pulmonary artery pressure ≥ 45 mmHg or mean pulmonary artery pressure ≥ 35 mmHg).

Procedure

The InterVapor system delivers thermal energy to the airways of an upper lobe through the direct administration of heated water vapor. The system consists of a vapor generator, a catheter directed through a flexible bronchoscope, and a personalized procedure plan. The procedure plan was based on the calculated amount of energy (10 calories per gram of tissue) for each lung segment targeted for treatment. The amount of tissue was determined from software analysis (PW2 Software; VIDA Diagnostics Inc, Mountain View, CA) of a lung HRCT. Treatment time was between 3 and 10 seconds per airway treated. Selection of the lung targeted for treatment was based on the degree of heterogeneity and other anatomical factors. Further details of the procedure have been described previously.[17]

Outcomes

Efficacy measures assessed included lobar volume changes from HRCT, spirometry, body plethysmography, diffusing capacity for carbon monoxide, 6MWD, modified Medical Research Council dyspnea score, and the SGRQ.[18–20] Primary endpoint testing was prespecified at 6 months with the 12-month data providing supportive information. The primary efficacy endpoint was the proportion of patients having an improvement from baseline in $FEV_1 > 12\%$ or in SGRQ total score ≥ 4 units. The BODE (body mass index, obstruction, dyspnea, exercise) index was also calculated.[21]

All adverse events were reported throughout the trial with the primary diagnosis adjudicated by an independent physician.

Analysis

Descriptive statistics were performed for changes from baseline. Nominal *P* values were determined from paired *t*-tests. No correction for multiple comparisons was performed. Frequencies and percentages were calculated for categorical variables. No imputation was used for missing data. Post-hoc subgroup analyses were performed based on GOLD stage and heterogeneity index (HI). Patients were dichotomized based on low and high HI based on the median value. HI was calculated as the ratio of lower to upper lobe tissue mass to air volume.

Results

Twenty-four patients received treatment to the right upper lobe and 20 received treatment to the left upper lobe.[17] All procedures were completed successfully with no procedural complications. Data was not available for 4 patients at 6 months (2 missed visits, 1 withdrawn, 1 serious adverse event) and for 7 patients at 12 months (1 missed visit, 4 withdrawn, 2 serious adverse events).

Demographics

Fifty percent of patients were women, all were Caucasian, and the mean (standard deviation [SD]) age was 63.1 (5.6) years (Table 1). Lung function testing indicated GOLD stage III/IV disease and substantial gas trapping with hyperinflation. SGRQ and 6MWD were consistent with significant impairment. Fifteen patients (34.1%) had a history of chronic obstructive pulmonary disease (COPD) exacerbations requiring hospitalization in the 12 months prior to the procedure. Of these 15 patients, 12 had one event, one patient had two events, and two patients had three events. Maintenance respiratory medication use was consistent with treatment guidelines.[22]

Table 1 Baseline characteristics of 44 patients treated with InterVapor

Age (years)	63.1 (5.6)
Men (%)	50
Body mass index	25.3 (4.2)
Duration of COPD diagnosis (years)	7.3 (4.4)
Smoking history (pack-years)	56.2 (34.5)
BODE score	5.7 (1.5)
mMRC score	2.9 (0.7)
6MWD (m)	299.9 (77.0)
SGRQ total score	58.9 (14.0)
Pulmonary function	
FEV_1 (mL)	861 (253)
FEV_1 (% predicted)	31.4 (7.5)
FVC (% predicted)	72.6 (12.9)
TLC (% predicted)	138.9 (16.1)
RV (% predicted)	237.0 (50.1)
DLCO (% predicted)	34.8 (12.5)
PaO_2 (mmHg)	68.9 (12.1)
$PaCO_2$ (mmHg)	39.4 (7.2)
pH	7.43
Maintenance respiratory medications	
Tiotropium	95%
Long-acting beta-agonists	21%
Inhaled steroids	6%
Long-acting beta-agonist + inhaled steroid	70%
Theophyllines	23%
Oral steroids	16%
Supplemental oxygen	16%

Note: Values displayed as mean ± SD unless otherwise specified.

Abbreviations: COPD, chronic obstructive pulmonary disease; BODE, body mass index, obstruction, dyspnea, exercise; mMRC, modified Medical Research Council dyspnea scale; 6MWD, 6-minute walk distance; SGRQ, St George's Respiratory Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity for carbon monoxide; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide.

Efficacy

The primary endpoint was achieved in 84% of evaluable patients at 6 months with 78% of patients reaching the same endpoint at 12 months.

Physiologic

Significant reductions in upper lobar volume and increases in lower lobar volume were observed at 6 and 12 months ($P < 0.001$). Evaluable HRCT scans at 12 months were not available in 16 patients (10 excluded from protocol 0519, four withdrawn, one missed visit, and one serious adverse event). Data for those patients having both 6- and 12-month

HRCTs (n = 27) are presented in Figure 1, which indicates that lobar volume changes were stable.

The mean (SD) improvement in FEV_1 was 141 mL (166 mL; 17%) and 86 mL (174 mL; 10%) at 6- and 12-months, respectively ($P < 0.001$; Figure 2). At 6 months, 23 subjects (58%) had improvements ≥100 mL in FEV_1 with 22 subjects (55% of evaluable patients) having an increase ≥12%, and 20 (50%) having an increase ≥15%. At 12 months, 18 subjects (49%) had improvements ≥100 mL in FEV_1 with 17 subjects (46%) having an increase ≥12%, and 15 (41%) having an increase ≥15%. The mean (SD) improvement in RV was −406 mL (714 mL; 8%) and −303 mL (776 mL; 6%) at 6 and 12 months, respectively ($P < 0.001$; Figure 3). The pulmonary function results are displayed in Table 2.

Health-related quality of life

Significant improvements were demonstrated in the SGRQ total score with a change of −14 units at 6 months and −11 units at 12 months (Table 3). The total score improved by the minimal clinically important difference of four units[19] in 29 evaluable subjects (72.5%) at 6 months and 25 subjects (67.6%) at 12 months ($P < 0.001$).

Dyspnea, exercise, and BODE score

At 6 and 12 months, the mean (SD) improvement in 6MWD was 46.5 m (67.1 m) and 18.5 m (63.7 m), respectively ($P < 0.001$ at 6 months). The corresponding improvements (ie, reductions) in the modified Medical Research Council score were 0.90 (1.06) and 0.83 (0.97) units ($P < 0.001$). Twenty-five subjects (63%) reported an improvement of ≥1 unit at 6 months and 21 (58.3%) at 12 months, compared to baseline.

The mean (SD) improvement in the BODE index was 1.48 (1.75) and 1.25 (1.75) units at 6 and 12 months, respectively ($P < 0.001$). At 6 months after InterVapor treatment, 28 (70%) of the subjects had a decrease in BODE index, six (15%) had no change, and six (15%) had deteoriated. Corresponding 12 month values were 22 (61%), 8 (22%), and 6 (17%) units.

Subgroup analyses

Post-hoc subgroup analyses were performed based on GOLD stage III and GOLD stage IV disease severity and for patients based on HI (above and below median value of 1.6).

For GOLD stage, there were equal numbers of women in each group (11 each) with the mean age being similar. FEV_1 (% predicted) was 36.3% (4.9%) versus 26.5% (6.3%) with RV (% predicted) being 233% (46.4%) and 241% (54.4%) in GOLD stage III and IV groups, respectively. Mean HI was similar. Efficacy was observed at 6 and 12 months in both subgroups with findings similar at 6 months (Table 4). Twelve month efficacy was numerically higher in GOLD stage IV patients ($P > 0.05$ for comparisons between GOLD stages).

For HI, there were 9 and 13 women in the <1.6 and >1.6 groups with the mean age being similar. FEV_1 (% predicted) was 30.6% (7.3%) versus 32.1% (7.8%) with

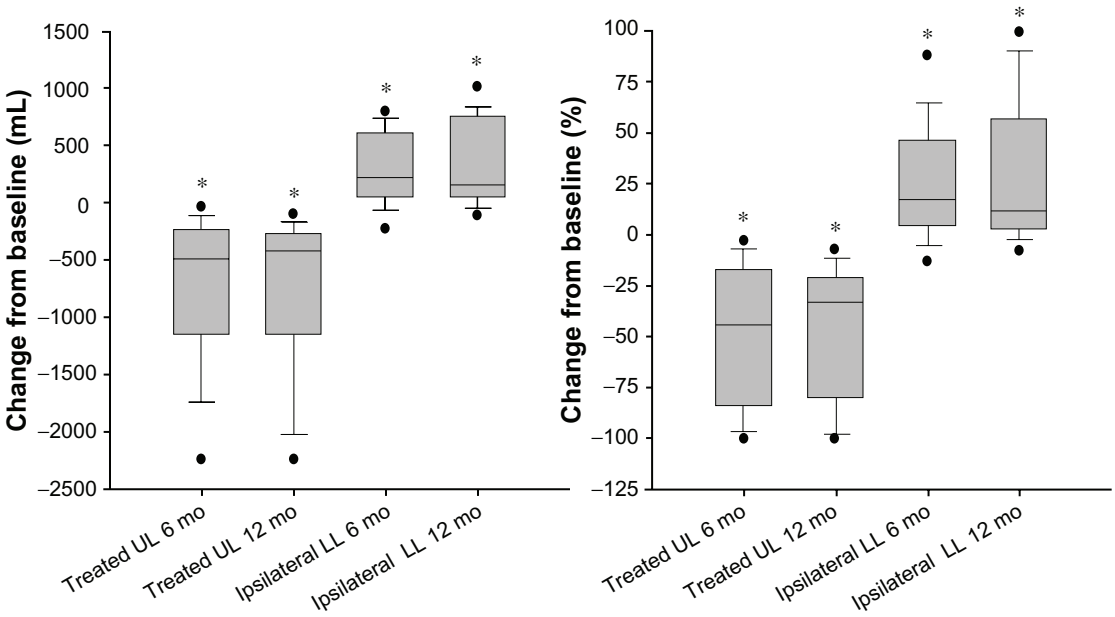

Figure 1 Change from baseline in treated upper lobe and ipsilateral lower lobe volumes 6 and 12 months after InterVapor treatment.
Note: *$P < 0.05$ vs baseline.
Abbreviations: UL, upper lobe; LL, lower lobe; mo, months.

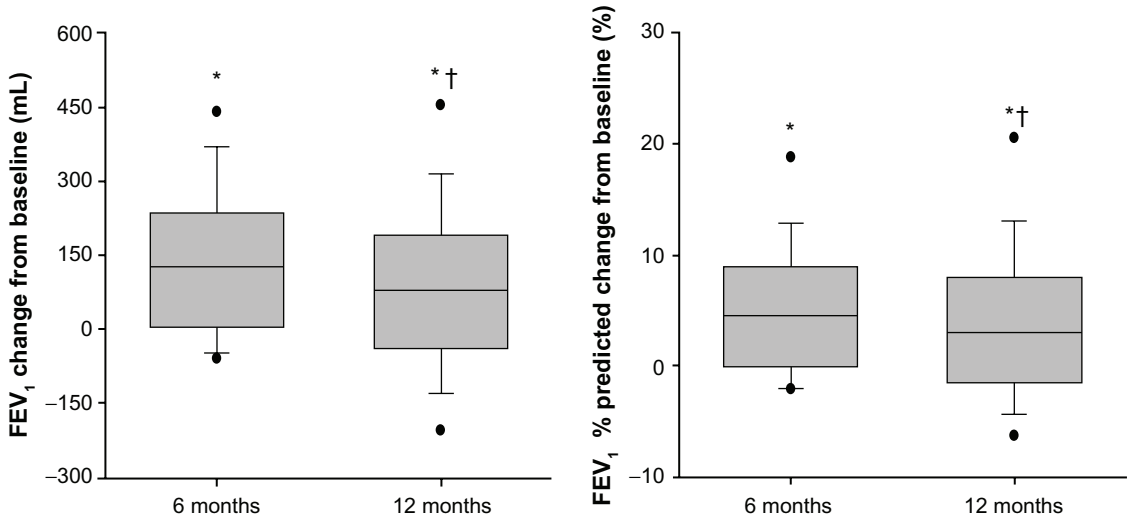

Figure 2 Change from baseline in FEV_1 (mL and % predicted) 6 and 12 months after InterVapor treatment.
Notes: *$P < 0.05$ vs baseline; †$P < 0.05$ 12 months vs 6 months.
Abbreviation: FEV_1, forced expiratory volume in 1 second.

RV (% predicted) being 228% (48%) versus 246% (51%) in HI < 1.6 and >1.6 groups, respectively. Efficacy was observed at 6 and 12 months in both subgroups with findings being overall higher in the higher HI group at 6 and 12 months (Table 5). The only between group differences associated with a nominal *P* value <0.05 were for lobar volume reduction and RV at both 6 and 12 months.

Safety

For the 12-month follow-up, 39 serious adverse events were reported in 23 patients (22 events were respiratory). The most common serious adverse event was COPD exacerbation. Events occurring within 6 months of treatment have been described previously.[17] Ten serious adverse events occurred beyond 180 days in eight patients (COPD exacerbation [n = 5], respiratory tract infection [n = 1], investigation of diabetes [n = 1], acute dyspnea [n = 1], cardiac insufficiency [n = 1], and right heart failure [n = 1]). One patient died 67 days post-treatment secondary to end-stage lung disease. A second death occurred 350 days post-treatment due to complications following lobectomy performed for aspergillus infection of the untreated lung. The numbers of patients with serious adverse events over 12 months by subgroup were as follows: GOLD III = 9, GOLD IV = 14, HI < 1.6 = 10,

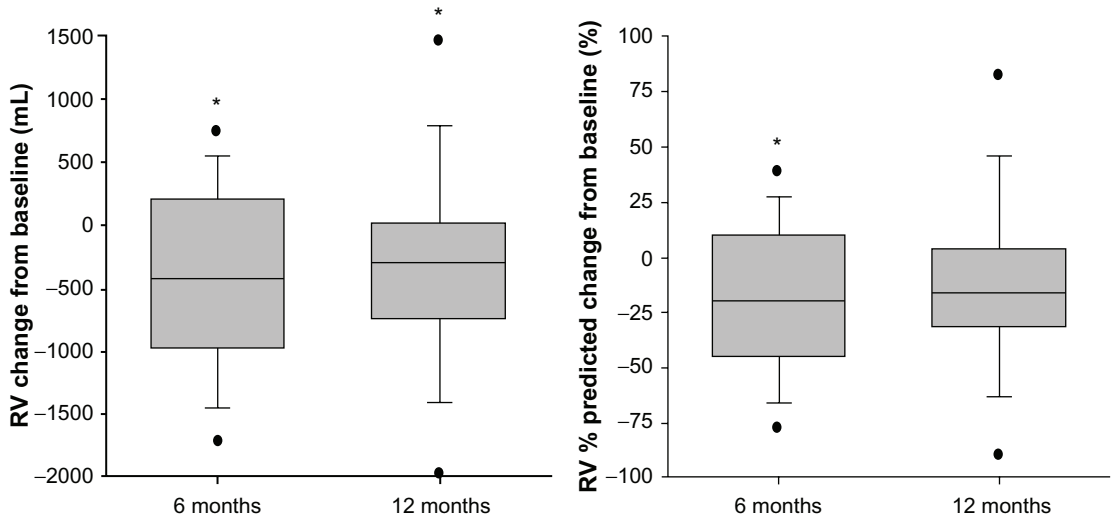

Figure 3 Change from baseline in RV (mL and % predicted) 6 and 12 months after InterVapor treatment.
Note: *$P < 0.05$ vs baseline.
Abbreviation: RV, residual volume.

Table 2 Change from baseline at 6 and 12 months in pulmonary function (absolute change and change in percent of predicted normal) following InterVapor

	Δ 6 months (n = 40)		Δ 12 months (n = 37)	
	Absolute	**% predicted**	**Absolute**	**% predicted**
FVC (mL)	271 (455)*	7.9 (12.2)*	249 (429)*	8.5 (13.4)*
FEV_1/FVC	0.02 (0.04)*	NA	0.00 (0.05)†	NA
TLC (mL)	–220 (445)*	–3 (8)*	–65 (532)†	–0.1 (11)†
FRC (mL)	–369 (615)*	–12 (20)*	–167 (624)†	–5 (21)†
IC (mL)	149 (403)*	NA	101 (495)	NA
RV/TLC	–0.03 (0.06)*	NA	–0.04 (0.07)	NA
DLCO (mL/min/mmHg)	0.32 (1.34)	1.5 (8.2)	0.46 (1.77)	1.2 (8.3)

Notes: Values presented as mean (SD); *$P < 0.05$ vs baseline; †$P < 0.05$ 12 months vs 6 months.
Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; FRC, functional residual capacity; IC, inspiratory capacity; RV, residual volume; DLCO, diffusing capacity for carbon monoxide; NA, not applicable.

HI > 1.6 = 13. During the first 30 days, the corresponding numbers of patients were 5, 6, 4, and 7.

Discussion

Several endoscopic options for inducing lung volume reduction have been developed for patients with severe and very severe emphysema.[7–17] InterVapor is one such technique and delivers thermal energy through heated water vapor directly to the airways via a bronchoscope.[15–17] At 6 months, a single-arm international clinical study of 44 patients demonstrated that InterVapor resulted in 48% lobar volume reduction, which was associated with reduced hyperinflation and improvements in airflow, dyspnea, exercise tolerance, and health-related quality of life.[17] Additional data from a 12-month follow-up visit indicates that improvements relative to baseline continued to be observed, with the magnitude of benefit less than that documented at 6 months. However, HRCT lobar volume reduction was stable over 12 months (46% at 12 months).

For patients with GOLD stage III and IV disease, improvements from baseline at 6 months were similar, while improvements at 12 months were more robust in GOLD stage IV patients. One explanation could be a ceiling effect where there is more "room" to improve in GOLD stage IV patients; however, this should have been apparent at 6 months. Another explanation may be related to differential contribution of small airways disease (obstructive bronchiolitis) versus emphysema, which might lead to GOLD stage III patients having more regions of the lung that can have compensatory hyperinflation. There may be more rapid equilibrium or changes in regional lung volumes when there is less severe disease relative to lungs with more uniformly severe disease. In terms of patient reported outcomes and exercise tolerance, it may be that improvements in ventilatory mechanics have a higher impact in GOLD stage IV patients relative to other factors such as nutritional, musculoskeletal, and cardiovascular disease. Other potential, but less likely, explanations include differences in regional perfusion and a more rapid FEV_1 decline in GOLD stage III versus stage IV patients. The above explanations are speculative and the caveat remains that the overall sample size within the two subgroups is relatively small and differences may simply be random.

Table 3 SGRQ total score and domains at baseline and change from baseline at 6 and 12 months following InterVapor

	6 months	Δ score	12 months	Δ score
Symptoms	43.2 (24.0)	–11.9 (21.8)*	48.5 (25.4)	–6.4 (25.4)
Activity	64.4 (20.4)	–14.7 (17.7)*	68.3 (19.6)	–10.3 (16.9)*†
Impact	32.1 (21.3)	–14.0 (16.1)*	33.0 (21.1)	–12.7 (13.2)*
Total	43.8 (19.5)	–14.0 (15.1)*	46.2 (19.2)	–11.0 (14.0)*

Notes: Values presented as mean (SD); *$P = 0.05$ vs baseline; †$P < 0.05$ 12 months vs 6 months.
Abbreviation: SGRQ, St George's Respiratory Questionnaire.

Regarding subgroup analyses, any differences in efficacy must be balanced by safety considerations. As part of the mechanism of action, patients receiving InterVapor may develop a temporary increase in symptoms with an infiltrate in the treated lobe. However, the current dataset indicates that there does not appear to be longer term safety issues. Any adverse events related to treatment should always be considered in the context of COPD morbidity and mortality, particularly in GOLD stage IV patients.[22,23]

The other major subgroup was based on the degree of heterogeneity. The calculations determining heterogeneity within the current trial are more objective than that used in the National Emphysema Treatment Trial, which utilized visual judgment with relatively broad categories.[3,4] Despite differences in methodology, the current findings that suggest larger responses with higher degrees of heterogeneity are consistent with the National Emphysema Treatment Trial results.[4] Furthermore, the findings are consistent with

Table 4 Changes in efficacy outcomes at 6 and 12 months according to GOLD stage III and GOLD stage IV disease severity

	Baseline	Δ 6 months	Δ 12 months
GOLD stage IV (n = 22)			
Lobar volume (mL)	1474 (484)	–690 (692)*	–772 (734)*
FEV_1 (mL)	715.9 (202.5)	142.0 (182.9)*	108.9 (182.25)*
RV (mL)	4970.5 (1033.7)	–302.0 (780.4)	–335.6 (908.3)
SGRQ total (units)	63.7 (11.9)	–17.4 (16.9)*	–12.7 (15.0)*
6MWD (m)	270.6 (65.8)	48.7 (78.5)*	25.6 (72.1)†
mMRC score	3.0 (0.7)	–0.8 (1.1)*	–0.9 (0.8)*
GOLD stage III (n = 22)			
Lobar volume (mL)	1503 (488)	–743 (565)*	–735 (601)*
FEV_1 (mL)	1005.5 (215.2)	139.5 (152.4)*	64.7 (167.5)†
RV (mL)	4989.6 (1114.0)	–510.0 (643.4)*	–270.0 (641.3)
SGRQ total (units)	54.1 (14.5)	–10.6 (12.7)*	–9.4 (13.1)*
6MWD (m)	329.3 (77.5)	44.4 (55.4)*	10.9 (54.5)
mMRC score	2.8 (0.8)	–1.0 (1.1)*	–0.7 (1.1)*

Notes: Values presented as mean (SD); *$P = 0.05$ vs baseline; †$P < 0.05$ 12 months vs 6 months.

Abbreviations: FEV_1, forced expiratory volume in 1 second; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; 6MWD, 6-minute walk distance; mMRC, modified Medical Research Council dyspnea scale.

efficacy observations from a large controlled trial with endobronchial valves.[12] The explanation for the apparent association with upper lobe predominant heterogeneity has not been adequately explained; however, heterogeneity is another phenotype that assists in assessment of patient candidacy for endoscopic lung volume reduction.

Table 5 Changes in efficacy outcomes at 6 and 12 months according to HI > 1.6 and HI < 1.6

	Baseline	Δ 6 months	Δ 12 months
HI > 1.6 (n = 22)			
Lobar volume (mL)	1630 (580)	–963 (704)†	–1078 (753)†
FEV_1 (mL)	870 (249)	183 (197)†	139 (200)*
RV (mL)	5053 (923)	–654 (738)*	–571 (837)*
SGRQ total (units)	55.9 (12.7)	–12.5 (17.0)*	–13.2 (13.6)†
6MWD (m)	297.0 (93.6)	48.4 (55.7)*	25.0 (59.8)
mMRC score	2.9 (0.8)	–1.2 (1.1)†	–1.0 (1.2)
HI < 1.6 (n = 22)			
Lobar volume (mL)	1347 (309)	–484 (431)	–426 (304)
FEV_1 (mL)	852 (262)	102 (125)*	36 (131)‡
RV (mL)	4907 (1202)	–182 (627)	–63 (645)
SGRQ total (units)	61.8 (14.9)	–15.3 (13.5)	–9.0 (14.4)*
6MWD (m)	302.9 (58.0)	44.8 (77.3)*	12.3 (68.3)‡
mMRC score	2.9 (0.7)	–0.7 (1.0)*	–0.7 (0.7)

Notes: Values presented as mean (SD); *$P = 0.05$ vs baseline; †$P < 0.05$ 12 months vs 6 months.

Abbreviations: HI, heterogeneity index; FEV_1, forced expiratory volume in 1 second; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; 6MWD, 6-minute walk distance; mMRC, modified Medical Research Council dyspnea scale.

A limitation in the current approach was the somewhat arbitrary HI threshold of 1.6, which was only based on dichotomizing patients using the median value, which might differ if the trial was repeated.

Although clear benefits are observed following InterVapor, a numerical difference in the magnitude of effectiveness was observed from 6 to 12 months. The histopathologic response with inflammation followed by contraction fibrosis is presumably stable over the 12-month observation period. HRCT data from the current study shows stability of lobar volume reduction in the treated lobe between 6 and 12 months. Clinical factors related to COPD are therefore the most likely explanations. A loss of lung function, health-related quality of life, and exercise tolerance is expected over time.[24,25] A recent randomized, double-blind, sham-controlled study of airway bypass in 315 patients with advanced emphysema demonstrated an annual loss of FEV_1 in the control population of approximately 40 mL (6% decline), which is consistent with other studies.[24–26] Assuming that a control population would have behaved similarly, a between-group difference (InterVapor vs control) of 86 + 40 = 126 mL would be anticipated at 12 months. Other possible factors include compensatory hyperinflation of the contralateral lung, exacerbations, and comorbidities. Additionally, as no visit was scheduled between 6 and 12 months, adherence to prescribed respiratory medications may have changed that could have led to worsening lung function. These hypotheses could be addressed with a control group. Nevertheless, all of the hypotheses would only contribute to underestimating the magnitude of benefit and not overstate the current observations. It is of interest to note that the mean improvement in BODE score remained above 1 at 12 months suggesting that a survival benefit might be anticipated.[21] A possible survival benefit has been described in a case series of patients who experienced atelectasis following lung volume reduction with endobronchial valves, which would be consistent with the above BODE data.[27]

Several limitations of the current study are acknowledged. The trial involves 44 patients and therefore has limited power to explore subgroups, yet the consistency of the results with all endpoints directionally positive, and with most of the efficacy endpoints associated with nominal *P* values less than 0.05, indicate the findings are not random. The other major limitation is the open nature design of the trial. However, an objective measure such as lobar volume reduction measured by HRCT would not change in a control group.

In summary, the current data provide longer term clinically relevant information about the effect of unilateral InterVapor in patients with severe and very severe predominantly upper lobe emphysema. Positive outcomes relative to baseline included lobar volume reduction along with improvements in physiology, dyspnea, and health-related quality of life. The magnitude of benefit was higher at 6 months compared to 12 months; however, serious adverse events diminished over time suggesting no long term safety concerns. The 12 month data substantiate the need for clinical trials in emphysema to follow patients beyond 6 months. Subgroup analyses identified patient populations that may have larger benefits that extend to the 12 month final observation period. Those subgroups include patients with more advanced disease (GOLD stage IV) and those with higher heterogeneity. Further studies including a control group would assist in confirming observations related to subgroups.

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