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Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous emphysema

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ABSTRACT: The need for a less invasive procedure than surgical lung volume reduction that can produce consistent improvements with reduced morbidity remains a medical goal in patients with emphysema. We sought to determine the effect of bronchoscopic thermal vapour ablation (BTVA) on lung volumes and outcomes in patients with emphysema.

44 patients with upper lobe-predominant emphysema were treated unilaterally with BTVA. Entry criteria included: age 40–75 yrs, forced expiratory volume in 1 s (FEV_1) 15–45% predicted, previous pulmonary rehabilitation and a heterogeneity index (tissue/air ratio of lower lobe/upper lobe) from high-resolution computed tomography (HRCT) $\geqslant$1.2. Changes in FEV_1, St George's Respiratory Questionnaire (SGRQ), 6-min walk distance (6MWD), modified Medical Research Council (mMRC) dyspnoea score, and hyperinflation were measured at baseline, and 3 and 6 months post-BTVA.

At 6 months, mean$\pm$SE FEV_1 improved by 141$\pm$26 mL ($p<0.001$) and residual volume was reduced by 406$\pm$113 mL ($p<0.0001$). SGRQ total score improved by 14.0$\pm$2.4 points ($p<0.001$), with 73% improving by $\geqslant$4 points. Improvements were observed in 6MWD (46.5$\pm$10.6 m) and mMRC dyspnoea score (0.9$\pm$0.2) ($p<0.001$ for both). Lower respiratory events (n=11) were the most common adverse event and occurred most often during the initial 30 days.

BTVA therapy results in clinically relevant improvements in lung function, quality of life and exercise tolerance in upper lobe predominant emphysema.

KEYWORDS: Bronchoscopy, emphysema, lung volume reduction, quality of life, spirometry

In lung volume reduction surgery (LVRS), ~20–25% of the lung is excised in order to improve the configuration of the thoracic cavity, improve elastic recoil, reduce neuromechanical dissociation and allow for improved lung inflation of the remaining and presumably better-preserved tissue [1–4]. In a randomised controlled trial of medical management compared with LVRS (National Emphysema Treatment Trial (NETT)), LVRS-treated patients obtained improvements in lung function, symptoms, exercise tolerance and quality of life relative to the medically treated group [4]. While long-term survival was improved, there was significant morbidity and mortality associated with surgery [4, 5]. The NETT study is considered as substantial evidence that benefits can be achieved with lung volume reduction (LVR) in patients with emphysema, particularly those with heterogeneous emphysema and upper lobe predominance [6, 7].

An effective alternative treatment to LVRS that is associated with an improved safety profile is an unmet medical need in the treatment of chronic obstructive pulmonary disease (COPD) patients with emphysema. Various minimally invasive bronchoscopic approaches are being investigated as a means to induce sustained LVR [8–14].

Bronchoscopic thermal vapour ablation (BTVA) uses heated water vapour to produce a thermal reaction leading to an initial localised inflammatory response followed by permanent fibrosis and atelectasis. The remodelling results in reductions in tissue and air volume of the targeted regions of the hyperinflated lung. An early preclinical animal study, including higher doses

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than those studied in humans, showed dose-dependent volume reduction. Minimal evidence of serious risk was observed. 19 out of 20 animals studied survived (the one death was due to pneumothorax) [15]. A preliminary study in 11 patients using a lower dose than the current protocol confirmed feasibility of unilateral BTVA with an acceptable safety profile; however, efficacy was modest and suggested that a higher dose would be justifiable [16]. The objective of the current study was to determine the efficacy and safety profile of BTVA at a higher dose in a larger cohort of COPD patients with emphysema.

MATERIALS AND METHODS

Study population

Patients were required to be between 40 and 75 yrs old with a forced expiratory volume in 1 s (FEV_1) between 15 and 45% predicted and have a diagnosis of heterogeneous emphysema with upper lobe predominance based on high-resolution computed tomography (HRCT). Using PW2 software (Vida Diagnostics Inc., Iowa City, IA, USA), a heterogeneity index was calculated based on the lower lobe to upper lobe tissue to air ratio. Heterogeneity was considered when the heterogeneity index exceeded 1.2. Other eligibility criteria are presented in table 1.

The protocol was approved by respective institutional review boards or ethics committees and all patients provided written informed consent prior to participation.

Study design

The study consisted of two virtually identical open-label, single-arm safety and efficacy clinical trials that evaluated unilateral BTVA. Trial 0519 (www.clinicaltrials.gov identifier number NCT01041586) was conduct in the USA (four sites, 10 patients), and trial 0519 (NCT01102712) was conducted in Europe (seven sites, 18 patients) and Australia (two sites, 16 patients). The main differences between the two protocols were the following additional measures in trial 0519: 1) HRCT scan and arterial blood gases at the 4-week clinic visit; and 2) clinic visits at 3 weeks and 2 months. Data are presented as pooled data.

Vapour dosing for each subject was calculated using a pre-defined algorithm based on quantification of tissue mass from the baseline HRCT, with an intended vapour dose of 10 $cal \cdot g^{-1}$ of lung tissue unilateral treatment. Subjects were treated with BTVA in a single procedural setting.

After treatment, subjects were required to be followed for 6 months for the primary end-points with post-procedure visits occurring weekly for weeks 1 and 2, and at months 1, 3 and 6. An additional visit was scheduled for month 12, but is not part of the current report. At 3 and 6 months following BTVA, subjects underwent pulmonary function testing, arterial blood gas measurement, questionnaires and the 6-min walk test [17]. During the 6-month visit, a follow-up bronchoscopy and HRCT were performed.

The primary end-point of this study was stated differently in each of the two protocols, with the occurrence of adverse events (serious and nonserious) being the primary outcome for the smaller 10-patient trial and FEV_1 and the St George's Respiratory Questionnaire (SGRQ) [18] as co-primary end-points for the 34-patient trial. Both protocols pre-specified that the primary end-points were to be tested from initiation of treatment through to completion of the 6-month follow-up period. The secondary end-points included post-procedure lobar volume (spirometry, body plethysmography and diffusion capacity of the lung for carbon monoxide), 6-min walk distance (6MWD), health-related quality of life as measured by the SGRQ (at visits other than 6 months) and dyspnoea as assessed by the modified Medical Research Council (mMRC) score [19].

Procedure

The BTVA system is comprised of a vapour generator and a vapour catheter, and has been previously described [16]. In brief, the vapour generator is an electronically controlled pressure vessel that generates and delivers precise amounts of energy (heated vapour) through the vapour catheter and into a targeted lung segment. The vapour catheter is composed of a

TABLE 1 Summary of key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age >40 yrs	Known α_1-antitrypsin deficiency
FEV_1 >15% and <45% pred	Evidence of either clinically significant asthma, chronic bronchitis or bronchiectasis
TLC >100% pred	$D_{L,CO}$ <20% pred
RV >150% pred	Post-rehabilitation 6MWD <140 m
mMRC dyspnoea score $\geqslant$2	Pneumothorax within previous 18 months
P_{a,CO_2} <55 mmHg, P_{a,O_2} >45 mmHg while breathing room air	Procedures involving thoracotomy
Nonsmoking for >4 months	Large bullae (>1/3 volume of lobe)
Recent completion of pulmonary rehabilitation	Left ventricular ejection fraction $\leqslant$40%
BMI $\geqslant$15 $kg \cdot m^{-2}$ or $\leqslant$35 $kg \cdot m^{-2}$	Stroke, unstable myocardial ischaemia or ICD
	Coagulopathy
	Pulmonary hypertension (peak systolic P_{pa} $\geqslant$45 mmHg or mean P_{pa} $\geqslant$35 mmHg
	Previous bronchoscopic LVR

FEV_1: forced expiratory volume in 1 s; % pred: % predicted; TLC: total lung capacity; RV: residual volume; mMRC: modified Medical Research Council; P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension; BMI: body mass index; $D_{L,CO}$: diffusing capacity of the lung for carbon dioxide; 6MWD: 6-min walking distance; ICD: implantable cardioverter-defibrillator; P_{pa}: pumonary arterial pressure; LVR: lung volume reduction.

TABLE 2 Baseline demographics and lung function of 44 patients treated with bronchoscopic thermal vapour ablation

Age yrs	63.1±5.6
Males %	50
BMI kg·m^{-2}	25.3±4.2
Duration of COPD diagnosis yrs	7.3±4.4
Smoking history pack-yrs	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$_1$ % pred	31.4±7.5
FVC % pred	72.6±12.9
TLC % pred	138.9±16.1
RV % pred	237.0±50.1
$D_{L,CO}$ % pred	34.8±12.5
P_{a,O_2} mmHg	68.9±12.1
P_{a,CO_2} mmHg	39.4±7.2
pH	7.43±0.03
Maintenance respiratory medications %	
Tiotropium	95
Long-acting β-agonists	21
Inhaled steroids	6
Long-acting β-agonist plus inhaled steroid	70
Theophyllines	23
Oral steroids	16
Supplemental oxygen	16

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; COPD: chronic obstructive pulmonary disease; BODE: BMI, airflow obstruction, dyspnoea and exercise capacity; mMRC: modified Medical Research Council; 6MWD: 6-min walk distance; SGRQ: St George's Respiratory Questionnaire; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; $D_{L,CO}$: diffusing capacity of the lung for carbon dioxide; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

flexible shaft and occlusion balloon located at the distal end. The BTVA procedure was performed in an operating room or bronchoscopy suite under general anaesthesia. During the procedure, the vapour catheter is introduced through the bronchoscope into the airway of the lung segment selected for treatment, where an occlusion balloon is then inflated and the pre-determined vapour dose (10 cal·g^{-1} tissue) is delivered to the targeted lung segments. Either the right upper lobe or left upper lobe (excluding the lingula) was treated.

Efficacy assessment

HRCT scans performed at full inspiration were obtained at pre-treatment, and at 3 and 6 months post-treatment. The total air volume of the target lobe was calculated at each time-point, and the change in air volume relative to pre-treatment (lobar volume reduction (LoVR)) was expressed as a percentage of pre-treatment volume. In addition to the efficacy end-points described in the study design section, the BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index was calculated [20].

Safety assessments

Subjects were monitored in the hospital for a minimum of 24 h following BTVA. After discharge, subjects returned to the study site for follow-up visits at 1, 2 and 4 weeks, and then at 3 and 6 months. Serious adverse events were defined as those that were either fatal, life-threatening, requiring or prolonging hospitalisation, or resulting in persistent or significant disability or incapacity. An independent physician adjudicated all adverse events. Laboratory tests during follow-up visits included complete blood count, biochemistry and nonspecific inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). Vital signs were recorded during each visit.

Analysis

The sample size was not determined *a priori* through a formal power calculation. Continuous variables were summarised over time in terms of mean, standard deviation and range. Categorical variables are summarised by frequencies and percentages. Changes from baseline were summarised with descriptive statistics (mean, median, range, standard deviation, standard error and 95% confidence intervals). Nominal p-values were determined from paired t-tests. No statistical correction was performed for multiple testing. As there are relatively few missing visits and a limited sample size, no imputation was used for missing data.

RESULTS

Unilateral BTVA treatment was administered to the right upper lobe (RUL) in 24 patients and to the left upper lobe (LUL) in 20 patients in a single procedure. Four patients did not complete 6 months of follow-up (one died 67 days post-BTVA, one withdrew consent and two missed visits).

Demographics

The mean±SD age of the population was 63.1±5.6 yrs, with 50% being male (table 2). Mean±SD FEV1 was 861±253 mL (31.4±7.5% pred) and residual volume (RV) was 237.0±50.1% pred (table 2). Maintenance pulmonary medication use was consistent with a population with severe disease (table 2).

Procedure

Treated unilateral lung volumes ranged from 805 to 2,842 mL and heterogeneity index ranged from 1.19 to 2.93 (mean 1.74). A total of 72 and 58 segments were treated in the RUL and LUL, respectively. The mean procedure time was 29 min (range 12–58 min). The procedure was well-tolerated by all subjects, with all subjects being discharged from hospital. No patients required mechanical ventilation beyond the procedure time.

Efficacy

The average lobe volume loss from baseline in the treated lobe was 717.6±78.8 mL at 3 months and 715.5±99.4 mL at 6 months ($p<0.001$), which represented a 48% reduction in lobar volume. HRCT scans were missing in two and five patients at 3 and 6 months, respectively. Differences in volumes from baseline to 3 and 6 months are shown in table 3. Volume differences at 6 months were similar to those determined at 3 months. The ipsilateral lower lobes increased

TABLE 3 Difference in volume from baseline to 3 and 6 months following bronchoscopic thermal vapour ablation

	Combined		Treated RUL		Treated LUL	
	3 months	6 months	3 months	6 months	3 months	6 months
Subjects	42	39	22	20	20	19
Treated upper lobe						
Volume mL	-722±607	-713±618	-705±617	-715±653	-740±611	-711±597
%	-48±32	-48±33	-46±34	-46±36	-51±30	-49±30
Ipsilateral RML or lingula						
Volume mL	28±101	57±84	38±97	59±87	16±107	55±84
%	9±29	16±25	11±21	16±24	7±36	17±27
Ipsilateral lower lobe						
Volume mL	275±239	279±303	286±235	299±287	263±250	258±326
%	23±22	24±27	24±23	25±26	22±23	22±29
Contralateral upper lobe						
Volume mL	42±129	6±140	65±135	19±152	17±119	-7±128
%	3±8	0±11	4±8	0±13	1±8	-1±9
Contralateral RML or lingula						
Volume mL	6±57	-12±52	7±65	-2±34	4±48	-21±65
%	4±17	-2±17	3±12	0±10	5±21	-4±22
Contralateral lower lobe						
Volume mL	79±150	-3±174	85±165	-21±162	72±133	16±187
%	5±11	-1±13	7±13	1±13	4±10	0±13

Data are presented as n or mean±SD. RUL: right upper lobe; LUL: left upper lobe; RML: right middle lobe.

in volume by 279±303 mL (24±27%) by 6 months. Two representative computed tomography scans are shown in figure 1. Compensatory hyperinflation of the contralateral lung was not observed (table 3).

Pulmonary function changes are illustrated in figure 2. The mean±SE improvement in FEV1 was 139.1±27.2 mL (17%) at 3 months and 140.8±26.3 mL (17%) at 6 months ($p<0.001$). 55% of subjects had an FEV1 improvement ⩾12% at 6 months and 58% of subjects had an improvement in FEV1 of ⩾100 mL. The average improvement in forced vital capacity at 6 months was 271.0±71.9 mL and RV was reduced by 406.0±112.9 mL at 6 months ($p<0.001$).

The mean±SE improvement in SGRQ total score was 11.0±2.3 and 14.0±2.4 points at 3 and 6 months, respectively ($p<0.001$; fig. 3). A total of 57% and 73% of subjects had a clinically meaningful improvement (decrease) in the SGRQ total score of ⩾4 points at 3 and 6 months, respectively. The largest difference was observed in the activity domain (14.7±2.8 points). Differences from baseline at 3 and 6 months in 6MWD and mMRC dyspnoea are shown in table 4. Dyspnoea (according to the mMRC index) improved by a mean of 0.9±0.2 points at 6 months ($p<0.001$) and by at least one point in 63% of subjects. The average change in 6MWD was 23.5±10.4 m ($p=0.029$) and 46.5±15.0 m ($p<0.001$) at 3 and 6 months, respectively. The BODE score declined by 1.36±0.27 and 1.4+0.27 points at 3 and 6 months, respectively ($p<0.001$ for both).

For the primary efficacy end-points of FEV1 and total SGRQ score, patients were analysed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. FEV1 improved by 120.4±30.7 mL in GOLD stage III ($p<0.001$) and 171.3±47.1 mL in GOLD stage IV ($p=0.002$) patients. Corresponding improvements in the SGRQ total score were 12.4±2.7 points ($p<0.001$) and 16.3±4.5 ($p=0.002$) points.

Safety

No adverse events were reported during the procedure. A total of 29 serious adverse events were reported in 19 subjects (table 5). 25 out of 29 events were respiratory in origin (exacerbation, n=9; pneumonia, n=6; lower respiratory tract infection, n=4; haemoptysis, n=3; end-stage COPD, n=1; inflammatory reaction, n=1; and *Pseudomonas* in sputum, n=1). One patient was reported to have a serious adverse event occurring within the first week, 10 patients had events with onset at between 9 and 30 days, nine patients at between 31 and 90 days and eight patients had events beyond 90 days. The event of end-stage COPD was fatal (67 days after BTVA following a re-admission for an exacerbation of COPD). Other than one patient, all respiratory events resolved with standard medical management. A total of 18 lower respiratory adverse events (other than haemoptysis), including both serious and nonserious events, occurred in 16 patients within the first 30 days. Of the events, nine, four and five were treated with antibiotics, steroids, or steroids plus antibiotics, respectively. The patients with these events had, on average, a higher degree of LoVR (HRCT available for 16 out of 18 patients) compared with the group average (69% *versus* 48%).

The inflammatory response in the targeted area was associated with varying reports of clinical symptoms ranging from either no symptoms or any combination of fatigue, fever, cough, sputum, dyspnoea and haemoptysis. The reaction appeared to

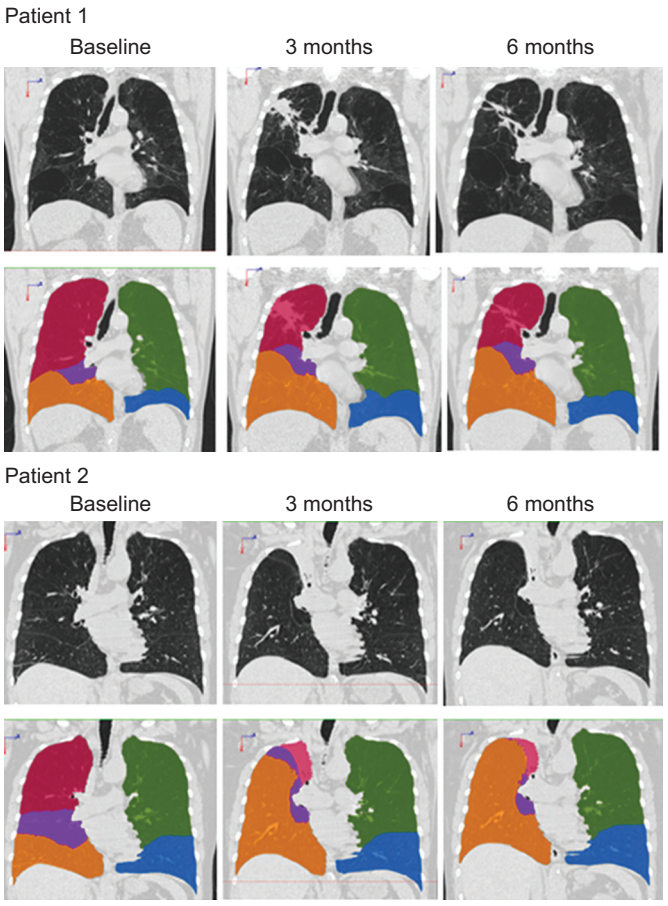

FIGURE 1. Representative coronal computed tomograms of lungs from two patients before (baseline) and after (3 and 6 months) treatment of right upper lobe using bronchoscopic thermal vapour ablation. The lower panel for each patient has each lobe colour coded to better illustrate the changes in lobar lung volumes. The red lobe represents the treated right upper lobe.

peak within the first 2–4 weeks and gradually resolved within 8–12 weeks following BTVA. Vital signs measured at clinic visits showed no overall change from baseline. Inflammatory markers were elevated during the first 4 weeks (table 6). No relevant changes in electrolytes, renal function or liver enzymes were observed.

DISCUSSION

BTVA therapy at a vapour dose of 10 cal·g^{-1} was administered unilaterally to one upper lobe in 44 patients with heterogeneous emphysema in a single-arm trial. The procedure was completed in all patients without procedure-related adverse events. After 6 months, HRCT measurement of lobar volume was reduced by 48%. Physiological changes included improvements in airflow and reductions with hyperinflation. These improvements were clinically relevant, as demonstrated by patient-reported outcomes of quality of life (reductions in the SGRQ and mMRC dyspnoea scores). Reduced symptoms were supported by more functional outcomes, such as improvements in exercise tolerance.

The short-term morbidity and associated costs of LVRS have led to investigations of minimally invasive approaches to achieve

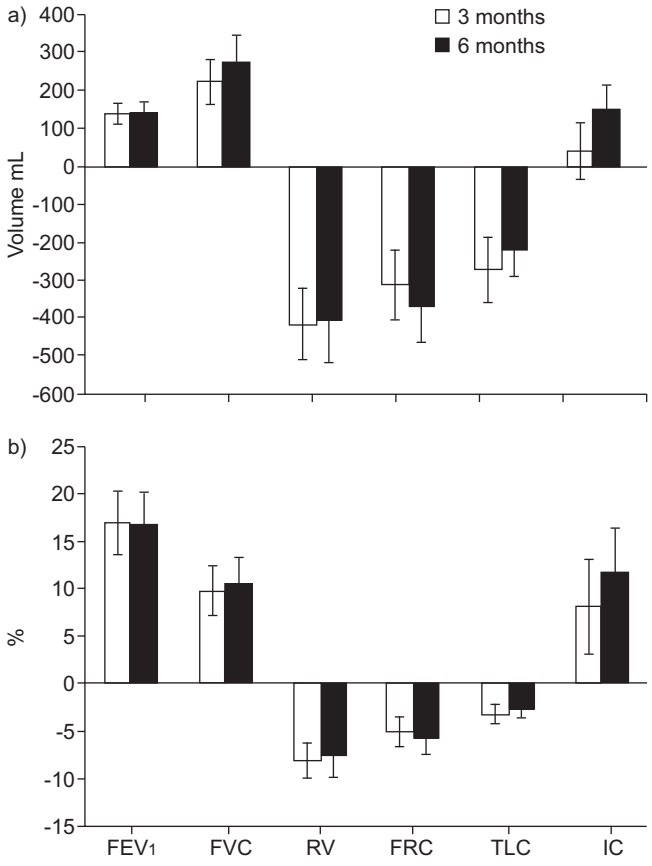

FIGURE 2. Difference from baseline (mean±SE) in pulmonary function expressed as a) volume and b) percentage at 3 and 6 months following bronchoscopic thermal vapour ablation in 44 patients. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity; IC: inspiratory capacity.

clinically relevant changes with reduced morbidity, which may also benefit a broader population of emphysema patients [1–5, 21]. Several bronchoscopic approaches to LVR have been evaluated over the last few years. Implantation of multiple

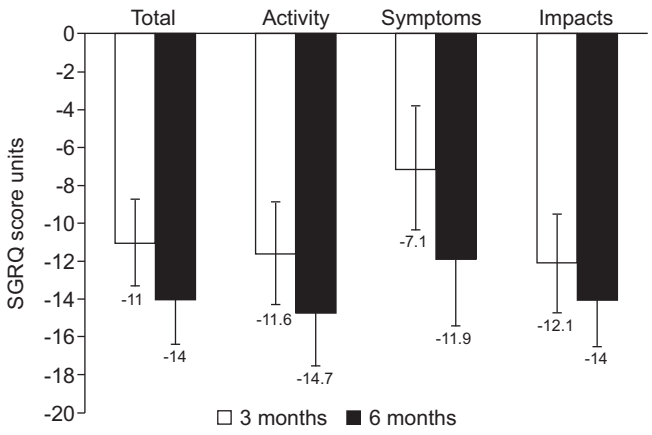

FIGURE 3. Differences from baseline to 3 and 6 months (mean±SE) in the St George's Respiratory Questionnaire (SGRQ) total score and the activity, symptoms and impact domains following bronchoscopic thermal vapour ablation in 44 patients.

TABLE 4 Differences from baseline to 3 and 6 months in 6-min walk distance (6MWD) and modified Medical Research Council (mMRC) dyspnoea scores in 44 patients receiving bronchoscopic thermal vapour ablation

	6MWD m		mMRC score points	
	3 months	6 months	3 months	6 months
Absolute	332.7±16.0	352.7±17.4	2.07±0.14	1.93±0.16
Change from baseline	23.5±10.4	46.5±10.6	-0.79±0.16	-0.90±0.17
p-value	0.029	<0.001	<0.001	<0.001

Data are presented as mean±SE, unless otherwise indicated.

one-way endobronchial valves has been explored in single-centre and larger multicentre studies [8–14]. Results indicate that endobronchial valves offer modest improvements in pulmonary function (increase in FEV1 6.8%) and health-related quality of life (improvement in total SGRQ score 3.4 points) [13]. The lower improvement relative to studies of LVRS is most likely to be attributable to inter-lobar collateral ventilation, a common finding, which will limit lobar collapse despite occlusion of the major airways [13]. Exploration of techniques that provide high levels of improvement despite the presence of inter-lobar collateral ventilation would represent an advance relative to valve techniques. Nevertheless, it appears that bronchoscopic approaches are able to reduce lung volumes and produce symptomatic benefit [14].

BTVA produces a thermal reaction within targeted regions of diseased hyperinflated lung and is not anticipated to be affected by collateral ventilation [15]. The system consists of a reusable vapour generator with a disposable vapour catheter, which delivers heated water vapour through a bronchoscope channel to targeted upper lobe emphysematous lung regions. A localised inflammatory reaction (LIR) within the treated lobe is expected following BTVA. Radiographically, the treated area will typically show infiltrates that could be indistinguishable from pneumonia. The response may be asymptomatic or accompanied by any of the symptoms of fatigue, fever, cough, sputum, dyspnoea and haemoptysis. The reaction appears to peak within the first 2–4 weeks and gradually resolves within 8–12 weeks of BTVA. Improvements in the group mean FEV1 relative to baseline were observed at 1 month. The need for treatment (*i.e.* antibiotics and/or steroids) has not been established, but has been prescribed based on individual investigator clinical decisions.

The LIR appears to be responsible for the early reporting of exacerbations and ''pneumonia'', given the similarity or symptoms and radiographic findings. Future studies will need to explore whether early intervention with standard medical therapy with the onset of symptoms may reduce the need for hospitalisation for those patients who have a higher degree of symptoms. Additionally, it may be possible to stage the procedure such that an overall lower amount of thermal energy is applied each time. Nevertheless, all patients who had an LIR were discharged from hospital. One of the 44 treated patients died from end-stage COPD at 67 days post-procedure. The safety observations must be put into context with the anticipated efficacy (*i.e.* benefit–risk balance) and with the expected natural course of COPD patients with lung function averaging 31% pred of normal [4, 13, 22, 23].

The LIR in the affected areas is followed by a healing period. The healing and repair process is characterised by fibrosis of the airways and parenchyma (*i.e.* remodelling of the architecture of the lung) [15]. LVR from BTVA treatment is accomplished *via* the fibrosis along with atelectasis that occurs distally in the treated region. The LVR of diseased hyperinflated lung regions after BTVA treatment is expected to increase elastic recoil by reducing the most compliant areas of lung, decompressing areas of healthy lung allowing for alveolar recruitment and improving the mechanical positioning of the respiratory muscles. The aforementioned changes are most likely to be responsible for the positive clinical outcomes.

It is recognised that conclusions must be tempered by the relatively small sample size and single-arm, open trial design. Future studies will need to consider incorporation of a control

TABLE 5 Number of serious adverse events and occurrence relative to bronchoscopic thermal vapour ablation treatment within 6 months of treatment

Event	Total observed	⩽48 h	>48 h ⩽30 days	>30 days ⩽90 days	>90 days ⩽180 days
End-stage COPD	1	0	0	1	0
COPD exacerbation	9	0	2	5	2
Gastro-oesophageal reflux	1	0	0	1	0
Haemoptysis	3	0	1	1	1
Pneumonia	6	0	4	1	1
Post-treatment inflammation reaction	1	0	1	0	0
Respiratory tract infection	5	0	3	0	2
Right upper quadrant abdominal pain	1	0	0	0	1
Urinary retention	1	0	0	0	1
Ventricular fibrillation	1	0	0	1	0
Total events	29	0	11	10	8

Data are presented as n. COPD: chronic obstructive pulmonary disease.

TABLE 6 Change in nonspecific inflammatory markers following bronchoscopic thermal vapour ablation

Parameter	Baseline	Change from baseline				
		Week 1	Week 2	Week 4	Month 3	Month 6
WBC $\times 10^9$ cells·L^{-1}	8.10±2.30	1.51±2.56	3.53±3.42	2.60±4.0	1.28±2.86	0.62±2.47
Neutrophils $\times 10^9$ cells·L^{-1}	5.30±2.14	1.42±2.14	3.36±3.26	2.35±3.86	1.05±2.23	0.42±2.66
ESR mm·h^{-1}	13.5±12.1	15.3±11.3	22.8±23.9	27.0±28.7	7.11±14.36	4.50 ±14.6
CRP mg·L^{-1}	0.62±0.67	1.70±4.78	8.10±21.2	9.71±38.4	1.11±5.07	0.67±2.78

Data are presented as mean±SD. WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

arm. Optimally, the control arm should include a sham procedure. Nevertheless, the changes from baseline in the current study showed consistent efficacy across multiple endpoints that demonstrated improvements in physiology, symptoms, exercise tolerance and health-related quality of life with nominal p-values <0.05. It must be recognised that this patient population with GOLD stage III and IV disease remained symptomatic at study entry with significant impairments in health-related quality of life despite previous participation in pulmonary rehabilitation and prescription of pharmacotherapy.

Another potential limitation is the wider-spread applicability given that only patients with upper lobe predominant emphysema were studied. Additional studies should therefore be directed to those patients with lower lobe disease to evaluate the overall benefit–risk. The NETT data suggest that improvements in the BODE score may be associated with improved survival [24]. Whether this observation can be extended to BTVA (a decrease of 1.4 points over 6 months) will require longer term follow-up.

In summary, patients with heterogeneous emphysema with upper lobe predominance may achieve clinically important improvements in physiology, quality of life and exercise tolerance following a single session of unilateral BTVA. The procedure is well tolerated, with all patients being discharged from hospital. An expected inflammatory response can be managed with standard care with the reasonable expectation of resolution over a few weeks and continued improvement. Given the efficacy data demonstrated to date, BTVA has a favourable benefit–risk in COPD patients with heterogeneous emphysema. Future studies are needed to corroborate the findings with larger sample sizes and a control arm.

SUPPORT STATEMENT

This study was funded by Uptake Medical Corp.

CLINICAL TRIAL

This study is registered at www.clinicaltrials.gov with identifier numbers NCT01041586 and NCT01102712.

STATEMENT OF INTEREST

Statements of interest for G. Snell, F.J.F. Herth, M.H. Gotfried, A. Valipour, S. Kesten and A. Ernst, and for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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