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Transbronchial bullous volume reduction in COPD patients

Ahmed Sh. Mohamed [a], Dalia E. El-Sharawy [a,*], Mohamed M. Hefeda [b]

[a] Chest Department, Faculty of Medicine, Tanta University, Egypt
[b] Radiology Department, Faculty of Medicine, Tanta University, Egypt

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ABSTRACT

Introduction: COPD patients with advanced disease achieve minimal or no control despite proper medical therapy that necessitates more radical approach. The bullae accentuate the altered elastic properties of the emphysematous lung and contribute to the expiratory flow limitation.
Objective: The aim was to evaluate the therapeutic utility and safety of transbronchial volume reduction of emphysematous bullae in COPD patients.
Patients & methods: At the site of entry, the air from the bulla was aspirated slowly, and then 10 cm of autologous blood was instilled into the bulla before the needle was withdrawn. Clinical, functional & radiological assessment of bulla volume and the incidence of adverse events were evaluated.
Results: 12 male patients were enrolled in this study with mean age (±SD) 47 ± 5.6 years. The procedure was well tolerated and not associated with any serious complications. Improvements (clinically, functionally and radiologically) three months after the procedure were more obvious in patients with bullous volume <515 ml than in patients with bullous volume >515 ml.
Conclusions: Intra-bullous blood instillation could be an effective and safe volume reduction technique of emphysematous bullae.

Introduction

Chronic obstructive pulmonary disease is a widely recognized major health problem that will be the third leading cause of death by year 2030 [1].

COPD is a potentially preventable and treatable disease. Medical management of COPD largely relies on smoking cessation, bronchodilator therapy and anti-inflammatory drugs [2]. A large number of patients with advanced disease have been seen to deteriorate quite rapidly in their course or achieve minimal or no control. Management of such patients includes a more radical approach like lung transplantation or lung volume reduction surgeries [3].

The lung volume reduction in its initial conception hypothesized the reduction of that portion of the lung which is supposed to be physiologically nonfunctional. This portion of the lung might also physically compromise the function of normal lung tissue adjacent to it by compression [4].

The emphysematous bullae accentuate the altered elastic properties of the emphysematous lung and, therefore, contribute to the expiratory flow limitation. Also, it may rupture into the pleural cavity and cause a tension pneumothorax [5,6].

The operative approach for bullectomy is variable and is dependent on the anatomic details of the bullae using either a muscle-sparing thoracotomy or a video-assisted thoracoscopic surgery (VATS) [7].

The development of bronchoscopic techniques is an attempt to obtain the same results as surgery for lung volume reduction. Furthermore, bronchoscopic techniques could also be more suitable for patients who might not be good candidates for surgery [8,9].

Aim of the study

The aim of this study was to assess the therapeutic effectivity and safety of the transbronchial intra-bullous autologous blood instillation to induce bullous contraction.

Patients and methods

A total of twenty-eight COPD patients having emphysematous bullae were recruited from Chest Department, Tanta University

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* Corresponding author.
E-mail address: dalia-elsharawy@hotmail.com (D.E. El-Sharawy).

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Hospitals (August 2015–March 2016). Only twelve COPD patients had the typical inclusion and exclusion criteria as listed below. COPD was diagnosed on the basis of American Thoracic Society (ATS) guidelines [10,11].

Inclusion criteria; Emphysematous patients with large bullae (not less than 150 ml), not complicated (no infection, bleeding or pneumothorax) with normal pulmonary parenchyma around it and proximal in site (don't exceed the third generation of bronchi).

Exclusion criteria; **R**espiratory tract infection at least 4 weeks prior to the study, **M**ultiple bullae in one lung with destroyed lung parenchyma in-between, **P**ulmonary hypertension of >45 mmHg, **A**ny general medical conditions associated with a high risk for anesthesia or bronchoscopy and **B**leeding diathesis.

Assessment of Medical Research Council [MRC] dyspnea score [12], Chest X-ray (postero-anterior and lateral views), computed tomography (CT chest) to confirm and to delineate the anatomy of bulla, pulmonary function tests (PFT) and lung volumes by plethysmography (CareFusion 234 GmbH, Jaeger, Germany), Electrocardiogram (ECG), arterial blood gases (ABG) and coagulation profile were performed before the procedure.

Clinical, radiological and functional follow up; one week and three months after the procedure was done.

After the protocol was approved by the research ethics committee of Faculty of Medicine, Tanta University, a written informed consent was obtained from all patients.

Study procedure

A flexible bronchoscope was performed with (Pentax EPK-i5000, Tokyo, Japan) under topical anesthesia (2% xylocaine) and moderate sedation (7.48 ± 1.78 mg midazolam) within 10 days after CT examination. A trans-bronchial biopsy-needle 22gauge (ECHO-HD, 22-EBUS P, Echotip, Ultra, COOK, Ireland) was inserted through the working channel of the bronchoscopy into the affected segmental bronchus, reaching the site of entry (demarcated using sagittal and coronal CT reconstruction). Being inside the bulla was confirmed through the appearance of expiratory air bubbles inside a vertically held syringe (partially filled with water).

The radiologically pre-estimated volume of air was slowly aspirated (We estimated the volume of bulla according to the empirical formula of Lambert: Volume = L(Length) × W(Width) × H (Height) × 0.52) [13]. A maximal of 10 ml autologous blood was infused into the bulla with average of 8.55 ± 1.13 ml (The largest diameter of most giant bulla encountered in this study was 12 cm so this amount was suspected to cover all the entire wall of the collapsed bulla after aspiration of their inside air). The average procedure time was 19.75 ± 3.64 min.

Statistical analysis

Descriptive statistics (mean ± SD) and standard student '*t* test', test of significance of the difference between two means, were used for the statistical analysis. P value of less than 0.05 was considered to be significant. ROC-curve was used for detection of cut-off value of bullae's volume.

Results

Twelve male patients were incorporated into this study, with mean age (±SD) 47 ± 5.6 years. The mean pre-procedural functional parameters were: FEV1, 1.52 ± 0.27 L [58.77 ± 6.22% predicted]; FVC, 3.11 ± 0.17 L [70.77 ± 3.25% predicted]; RV, 5.19 ± 0.29L [212.92 ± 20.06% predicted]; TLC, 8.48 ± 0.87 L [125.17 ± 6.04% predicted] and RV/TLC ratio, 0.60 ± 0.04.

On CT scan, the number, distribution & volume of bullae (the volume of bulla was more precise measuring tool than its size due to difference in geometric shape of bulla from lung to lung using the empirical formula of Lambert [13]) were encountered in Table 1.

The procedure was well tolerated within average time of 19.75 ± 3.64 min and was not associated with any serious complications. All patients were discharged from the hospital on the same day.

No significant functional improvement was observed after one week later except in only two patient as regards FEV1 improved by 10.4% (239 ml), 8.3% (216 ml), FVC 12.1% (567 ml), 9.5% (398 ml)) & RV 11% (310 ml), 14% (360 ml) respectively.

Functional improvement was obvious after 3 months: mean FEV1, was improved to 1.65 ± 0.31 L [63.73 ± 8.00% predicted] (*P value 0.103)*; mean FVC, was improved significantly to 3.35 ± 0.22 L [76.13 ± 3.24% predicted] (*P value 0.001**); mean RV, was reduced to 4.96 ± 0.37 L [203.58 ± 22.99% predicted] (*P value 0.301*); mean TLC was reduced significantly to 7.86 ± 0.81 L [116.07 ± 7.73% predicted] (*P value 0.004**) and RV/TLC ratio, became 0.64 ± 0.07 (*P value 0.180*).

On analyzing the volume of bulla as an essential factor affecting the functional improvement, the results documented that bulla of volume less than 515 ml had significant functional improvement with the following parameters; mean FEV1, 67.99 ± 4.79% predicted which improved by +6.95% (*P value 0.023*); mean FVC, 77.29 ± 1.39% predicted which improved by +7.39% (*P value 0.001*); mean TLC, 111.40 ± 6.09% predicted reduced by −11.89% (*P value 0.003*) while mean RV, 191.86 ± 19.88% predicted reduced by −13.28% (*P value 0.239*) and RV/TLC became 0.64 ± 0.09 improved by 0.05 (*P value 0.241*) with no significance and these 7 patients were classified as (**Group I**). While bulla of volume more than 515 ml (5 patients) had functional improvement but with

Table 1
The number, distribution and volume of bullae (pre- & post-procedure).

	Patients	Number of bullae	Distribution	Volume (pre)	Volume (post)
Group I	1	1	Left upper lobe	320 ml	110 ml
	2	2	Right upper & left lower lobe	The nearest is upper one (410 ml)	180 ml
	3	1	Left lower lobe	380 ml	160 ml
	4	3	Right upper & lower lobes	The largest is lower one (390 ml)	150 ml
	5	1	Right upper lobe	250 ml	Less than 50 ml with linear density
	6	2	Left upper & lower lobe	The nearest is lower one (280 ml)	90 ml
	7	2	Left upper & right upper lobe	The left one is (430 ml)	200 ml
Group II	1	1	Right lower lobe	550 ml	380 ml
	2	2	Right upper lobe & left upper lobe	The nearest one is 720 ml	680 ml
	3	4	Scattered on right side	The nearest one is 680 ml	510 ml
	4	1	Right upper lobe	520 ml	370 ml
	5	2	Right upper lobe & small left lower one	610 ml	No change

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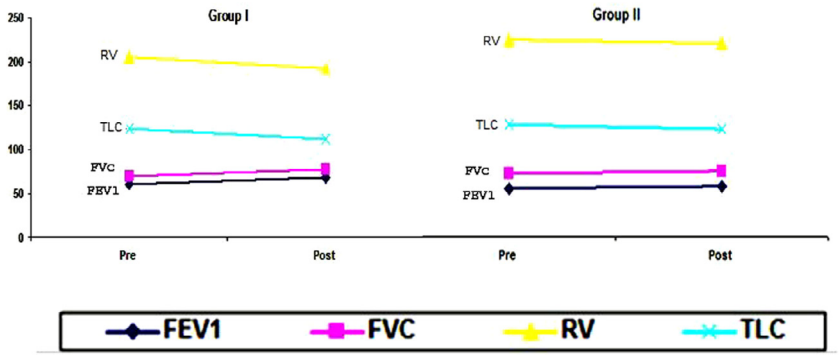

Figure 1. Diagram shows the functional parameters of Group I & Group II pre- & post-procedure.

Table 2
The functional parameters of bulla volume less than 515 ml (Group I) pre- & post-procedure.

Group I	Range		Mean ± S. D	t. test	p. value
FEV1	Pre	54.8–69.1	61.04 ± 5.13	6.849	0.023*
	Post	59.3–75.2	67.99 ± 4.79		
FVC	Pre	65.2–73.1	69.90 ± 2.59	44.341	0.001*
	Post	75.7–79.3	77.29 ± 1.39		
RV	Pre	181–236	205.14 ± 20.19	1.539	0.239
	Post	169–222	191.86 ± 19.88		
TLC	Pre	116–132	123.29 ± 5.71	14.188	0.003*
	Post	101.4–118	111.40 ± 6.09		
RV/TLC	Pre	0.52–0.65	0.59 ± 0.04	1.524	0.241
	Post	0.53–0.76	0.64 ± 0.09		

* Significant *P* value < 0.05.

Table 3
The functional parameters of bulla volume more than 515 ml (Group II) pre- & post-procedure.

Group II		Range	Mean ± S. D	t. test	p. value
FEV1	Pre	47.5–65.4	55.58 ± 6.72	0.219	0.652
	Post	49.2–70.1	57.78 ± 8.09		
FVC	Pre	67.1–76.7	71.98 ± 3.99	0.888	0.374
	Post	69.3–79.7	74.52 ± 4.52		
RV	Pre	200–240	223.80 ± 15.51	0.138	0.720
	Post	194–238	220.00 ± 16.84		
TLC	Pre	119–136	127.80 ± 6.06	2.502	0.152
	Post	118–127.1	122.62 ± 4.11		
RV/TLC	Pre	0.56–0.69	0.62 ± 0.05	0.318	0.588
	Post	0.55–0.68	0.64 ± 0.05		

no significant values: mean FEV1, 57.78 ± 8.09% predicted improved only by +2.2%; mean FVC, 74.52 ± 4.52% predicted improved by +2.54%; mean RV, 220.00 ± 16.84% predicted reduced by −3.8%; mean TLC, 122.62 ± 4.11% predicted reduced by −5.18% and RV/TLC became 0.64 ± 0.05 improved by 0.02 who were described as (**Group II**) as shown in Fig. 1. Only 1 patient in this group improved significantly (FEV1: +4.52%, FVC + 5.23%, RV: −9.8% & TLC: −11.2%) (Fig. 1, Tables 2& 3).

Also clinically; the MRC dyspnea scale in **group I** (7 patients) (3 months later) improved by 1 point in 4 patients and 2 points in 2 patients and no improvement in one patient. While in **group II** (5 patients) it improved by 1 point in only 2 patients and no improvement in 3 patients.

Radiologically; the mean volume of all bullae was reduced significantly from 461.67 ± 154.03 ml (range, 250–720 ml) to 290.00 ± 212.73 ml (range, 50–680 ml) *P value 0.034* "Table 1"). Volume changes at targeted sites seen in post-procedural CT scans were more noticed in group I than group II. In **group I**; images at 1 week post-procedural demonstrated a peripheral region of collapse at the site of blood injection with some infiltrates. By 3 months, this site transformed into a linear density indicating scar tissue formation with marked reduction of the diameter of bullae. While in **group II**, 2 patients' CT images at 1 week post-procedural demonstrated partial reduction in the bulla size by about one third of their baseline. By 3 months, there was no change in the bulla size compared with the previous; one patient experienced only mild reduction after 1 week becoming more obvious after 3 months but less than third of its baseline and 2 patients demonstrated no changes. (Figs. 2 & 3).

Discussion

Bullae are emphysematous spaces that contribute to increased lung volume and worsen the mechanical disadvantage of the inspiratory muscles by increasing the residual volume (RV) and RV/TLC ratio. Thus effective decompression of a large bulla or bullae is important to improve the lung function of affected patients and also to provide symptomatic relief [14,15].

A wide variety of surgical procedures have been used in the management of bullous emphysema, such as: intra-cavity drai-

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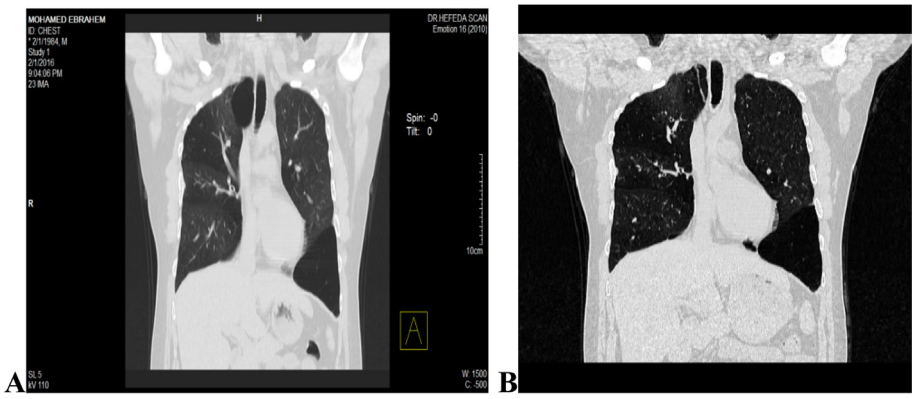

Figure 2. CT scan images from a group I patient before (A) and after (B) treatment with blood injection by 3 months. There is a localized linear density at the site of bronchoscopic treatment.

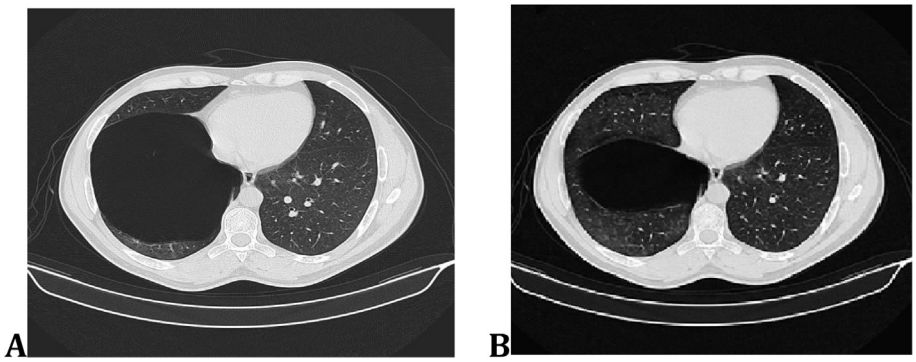

Figure 3. CT scan images from a group II patient before (A) and after (B) treatment with blood injection by 3 months. There is a partial reduction at the site of bronchoscopic treatment with about its third baseline volume.

nage, local excision of the bullae, placation, stapler resection and lobectomy. However, significant post-operative morbidity and a prolonged hospital stay were common problems [16].

Isolated decompression of bullae bronchoscopically has limited scope. So, in such study, we applied a new procedure using autologous blood to induce volume reduction of large bullae, based on blood potential bio-adhesive properties that could lead to collapse of emphysematous bulla by plugging and scarring [17,18].

In this study, bullae less than 515 ml were significantly reduced in their volume as documented radiologically with effective improvements in lung function and dyspnea scale 3 months after treatment. While in our experience with bullae more than 515 ml, there was less reduction in their volume with less impaction on pulmonary functions and dyspnea scale suggesting a size-related response pattern. Such result indicates that large bullae may not respond initially and need the maneuver to be repeated.

This study is in agreement with Kanoh et al. [19] who used in their study transbronchial intra-bullous autologous blood admixed with fibrinogen and thrombin that achieved significant reduction of emphysematous bullae with no re-expansion of the decompressed bulla, leading to marked functional and symptomatic relief.

Also, conceding with our study, the results of Zoumot et al. [20] who treated 5 patients with this minimally invasive approach as day-case procedure using moderate sedation. Three of the 5 patients had shrinkage of the bullae with significant and dramatic improvements in quality of life, exercise capacity and lung function.

The procedure was safe with no serious complications as pneumothorax, bronchopleural fistula, lung abscess or pneumonia. This could be due to proximal bullae selection with the precise demarcation of the point of entry under CT guiding.

Recommendation; considering the small number of cases enrolled in the study (only 12 cases) and the short period of follow up (3 months), future studies on a large scope and for sufficient time must be performed to standardize this technique as an acceptable therapeutic modality and to identify the best responders.

In conclusions, intra-bullous blood injection can be an effective, less invasive, and safe therapeutic approach for reduction of emphysematous bullae.

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