

Assessment of lung functions using impulse oscillometry before and after bronchoscopic lung volume reduction with histoacryl gel

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Background Many forms of bronchoscopic lung volume reduction were introduced as a treatment for patients with emphysema surpassing the surgical management and its fatality. Biological bronchoscopic lung volume reduction (BBLVR) proved to be a safe and competent solution inducing collapse of the emphysematous segment(s). Impulse oscillometry (IOS) constitutes an effortless but underused surrogate to spirometry in assessment of pulmonary function. Therefore, the aim of this study was to evaluate the use of IOS before and after BBLVR with histoacryl gel in comparison with spirometry among patients with emphysema.

Patients and methods A prospective comparative follow-up study was performed at Kobry El-Kobba Military Hospital. A total of 30 patients with radiological evidence of heterogenous emphysema or emphysematous bullae were enrolled during the period from July 2014 to April 2015. BBLVR was accomplished by the instillation of the histoacryl gel into the affected segment(s) using standard technique. Clinical, radiological, and functional assessments were done before and 4 weeks after the procedure.

Results After BBLVR, the following outcome was measured: 6-min walk test, partial pressure of O₂ in arterial blood, forced expiratory volume in the first second, resistance at 5 Hz, resistance at 20 Hz, and reactance at 5 Hz. They improved with statistical significance among all the patients. There was

a negative correlation between forced vital capacity and resistance at 5 Hz in the heterogenous emphysema group ($\rho=0.47$ and $P<0.025$); however, the forced expiratory volume at first second showed positive correlation with reactance at 5 Hz in emphysematous bullae group ($\rho=0.82$ and $P<0.023$).

Conclusion BBLVR with histoacryl gel is associated with improvement in exercise capacity and lung functions. IOS provided comprehensive assessment of the pulmonary functions, which was in good correlation with spirometry.

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Keywords: biological bronchoscopic lung volume reduction, heterogenous emphysema and emphysematous bullae, impulse oscillometry, spirometry

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Introduction

Although many patients are receiving intensive treatment in different forms including respiratory rehabilitation, still emphysema is considered a crippling permanent disease. Therefore, the pursuit to improve the quality of life among patients with emphysema was the focus of countless and diverse researches [1].

Following the work of Cooper *et al.* [2], surgical lung volume reduction was introduced for patients with severe heterogenous emphysema. The National Emphysema Treatment Trial started to enroll patients with emphysema in a large-scale randomized trial to test the efficacy of the surgical lung volume reduction and recommended specific selection criteria for these patients and defined the high-risk groups [3].

Bronchoscopic lung volume reduction (BLVR) started to emerge after the striking results of the National Emphysema Treatment Trial where the mortality was ~5% and postoperative complications were more than 50%. The new bronchoscopic technique was less invasive, sometimes reversible, and generated lower

costs. Many methods used the endobronchial valves, foam seal, and coils, which were involved in the BLVR [4,5]. Biological bronchoscope lung volume reduction (BBLVR) proved to be a safe and efficient procedure. The injected material induces inflammatory reaction converting the unhealthy emphysematous segment to a collapsed one [6].

Spirometry has been used widely in clinical practice as well as in researches for the diagnosis and assessment of chronic obstructive pulmonary diseases (COPD). Nevertheless, the test requires the patient's collaboration and is effort dependent [7].

Impulse oscillometry system (IOS) was presented to resolve the preceding problem. It is a simple noninvasive method that does not depend on the patient's effort [8]. The measurement of airflow resistance during normal breathing requires no

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maximal forced expiratory efforts and does not subject patients to bronchoprovocation from forced expiration. Resistance is distributed between large airways and smaller more peripheral airways, with distinct patterns attributable to each. This technique is applied when the patient is breathing normally [9].

This study aimed to compare the scarcely used IOS with the standardly used spirometry in the assessment of patients with emphysema before and after BLVR using histoacryl glue.

Patients and methods

Patients

This prospective comparative follow-up study was carried out at Kobry El-Kobba Military Chest Hospital during the period from July 2014 to April 2015. A total of 30 patients with COPD who presented to the outpatient clinic or inpatients with the clinical or radiographic evidence of emphysema were enrolled. In preparation for BBLVR, detailed medical history, clinical examination, modified Borg scale of dyspnea (MBSD) [10], 6-min walk test (6MWT) [11], laboratory analysis, ECG, echocardiography, spirometry (Cardiotouch 3000s; Bionet America Inc.) [12], and IOS (Master screen IOS 2011; Erich Jaeger GmbH, Friedberg, Germany) [13] were done.

All the included patients were older than 40 years with persistent moderate to severe dyspnea by MBSD [10]. They had predominately upper lobe heterogenous emphysema or localized bulla by high-resolution computed tomography (HRCT) of the chest as determined by radiology consultants. By spirometry [12], forced expiratory volume at first second (FEV1) to forced vital capacity (FVC) ratio was less than 70% and FEV1 was less than 45% predicted.

Patients with FEV1 less than 20%, patients with arterial partial pressure of carbon dioxide (PaCO_2) more than 55 mmHg, patients with any contraindications for fiberoptic bronchoscope (FOB), patients with other pulmonary diseases, patients with emphysematous bulla more than one-third of the lung, and/or patients who underwent LVRS were excluded.

Procedure

BBLVR was carried out under local anesthesia or conscious sedation in the outpatient endoscope suite, using standard technique of injecting histoacryl blue gel (*N*-butyl-2-cyanoacrylate) into the affected segment(s) of one or both lungs, separated by 2-week interval. The

therapeutic wide channel video-bronchoscope (Pentax EB-1575K; Tokyo, Japan) was used to explore the chosen segment(s) selected by HRCT before procedure. Good suction was applied to remove air and secretions. A single lumen catheter (medical grade Pebax construction, OF 1.85 mm) is introduced through the bronchoscopic channel to reach the targeted segment with its tip 2 cm beyond the FOB. Histoacryl 2 ml (B. Braun Melsungen AG, Germany) diluted in 0.6 lipiodol is injected rapidly until filling of the segment. Wedging of the FOB is ensured from the start of the procedure till 1 min after to avoid back flow and allow complete in-situ polymerization, and any traces are removed using forceps. The process is then repeated in other segments of the targeted lobe(s) [14].

Follow-up

Clinical, functional, and radiological evaluation of the patients after 4 weeks of the BBLVR procedure was done using MBSD to assess dyspnea [10], 6MWT [11], spirometry (FEV1, FVC, FEV1/FVC, maximum mid-expiratory flow, and maximum mid-expiratory flow 50) [12], IOS [resistance at 5 Hz (R5), resistance at 20 Hz (R20), and reactance at 5 Hz (X5)] [13], arterial blood gas [pH, PaCO_2 , partial pressure of O_2 in arterial blood (PaO_2), HCO_3 , and SaO_2], and HRCT of the chest.

Statistical analysis

Descriptive and analytical statistics were done using IBM SPSS for Windows, version 22 [15].

The study was approved by the Ethics Committee of Faculty of Medicine, Ain Shams University. A detailed consent was approved and signed by all the willing participants.

Results

The study included 30 male patients with a mean age of 63 ± 7.7 years, smoking index of 22 ± 2.75 pack/years, modified Borg scale of 4 ± 1 , and a 6MWT of 237.13 ± 40.6 . Based on the HRCT of the chest, seven (23.3%) patients had single upper lobe emphysematous bullae, whereas 23 (76%) patients displayed heterogenous upper lobe emphysema, of which 13 (56%) had unilateral and 10 (43%) had bilateral presentation. Later during the radiological follow-up 4 weeks after BBLVR, 13 (43.3%) patients developed atelectasis in the CXR as well as HRCT.

Using the Mann-Whitney-Wilcoxon tests to compare the clinical and functional parameters of the patients

before and after the procedure, there was a highly significant statistical difference ($P<0.001$) regarding the 6MWT and PaO_2 in all the patients. The dyspnea improved when assessed with the modified Borg Scale after BBLVR but with no statistical significance (Table 1).

From Table 2, it can be concluded that after BLVR, the FVC, R5, and R20 improved in both groups, whereas FEV1 improved only in the patients with emphysematous bullae.

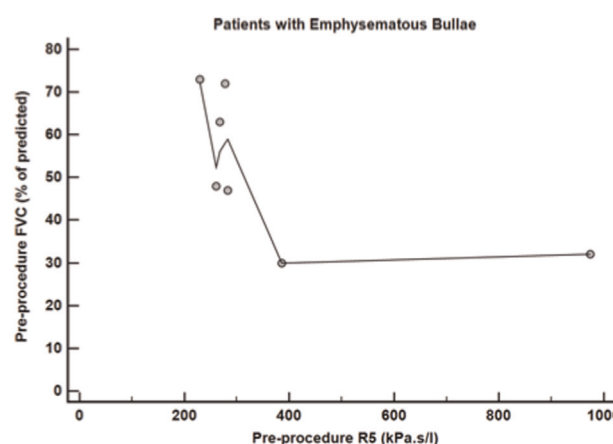
Table 3 highlights the improved parameters with statistical significance after 4 weeks of BBLVR among the studied patients, whereas Table 4 reflects the comparison between each group regarding the percentage of change in the outcome measurements. It is evident that the percentage of change after BLVR in the following four measurements (ΔR20 , ΔX5 , ΔPaO_2 , and Δ6MWT) recorded a statistical significant difference, deducing that the improvement is more among the emphysematous bullae group.

Using Spearman's rank correlation coefficient to assess the relationship between spirometry and IOS, it was found that before procedure there was a strong negative correlation between FVC and R5 in the emphysematous bullae group ($\rho=0.82$ and $P<0.023$; Fig. 1). After BBLVR, there was mild to moderate negative

correlation between FVC and R5 in the heterogenous emphysema group ($\rho=0.47$ and $P<0.025$; Fig. 2); moreover, the FEV1 showed strong positive correlation with X5 in emphysematous bullae group ($\rho=0.82$ and $P<0.023$; Fig. 3).

Regarding the complications, no death was encountered. Overall, two patients developed pleuritic chest pain 24 h after the procedure, and it was self-limiting, and one patient developed pneumonia after 1 week and was hospitalized for 5 days to receive antibiotics and bronchodilators.

Figure 1



Scatter plot showing correlation between FVC and R5 pre-procedure in emphysematous bullae group.

Table 1 Modified Borg scale of dyspnea, 6-min walk test, and arterial blood gas parameters of the patients before and after biological bronchoscopic lung volume reduction

Parameters	Before procedure (mean \pm SD)	After procedure (mean \pm SD)	<i>P</i> value
MBSD	4.13 \pm 1.3	3.88 \pm 1.2	0.494
6MWT (m)	237.13 \pm 40.6	281.70 \pm 35.5	0.001
pH	7.43 \pm 0.068	7.42 \pm 0.062	0.828
PaCO_2 (mmHg)	41.20 \pm 4.9	40.66 \pm 3.88	0.743
PaO_2 (mmHg)	66.70 \pm 6.06	77.13 \pm 5.58	0.0006
HCO_3 (mEq/l)	27.62 \pm 2.66	27.44 \pm 2.45	0.758
SaO_2 (%)	93.34 \pm 1.71	92.66 \pm 1.5	0.709

HCO_3 , bicarbonate; MBSD, Modified Borg scale of dyspnea; 6MWT, 6-min walk test; PaCO_2 , arterial partial pressure of carbon dioxide; PaO_2 , arterial partial pressure of oxygen; pH, potential of hydrogen; SaO_2 , oxygen saturation.

Table 2 Spirometry and impulse oscillometry parameters before and after bronchoscopic lung volume reduction in both groups

Parameters	Heterogenous emphysema (mean \pm SD)		<i>P</i> -value	Emphysematous bullae (mean \pm SD)		<i>P</i> -value
	Before	After		Before	After	
FVC (l)	1.653 \pm 0.65	2.103 \pm 0.85	0.005	2.04 \pm 0.79	2.588 \pm 0.42	0.002
FEV1 (l)	2.106 \pm 0.33	2.511 \pm 0.63	0.405	1.204 \pm 0.36	2.037 \pm 0.57	0.001
FEV1/FVC (%)	70.48 \pm 20.61	71.61 \pm 22.41	0.045	66.511 \pm 24.8	76.25 \pm 20.95	0.050
MMEF 25–75 (l)	41.73 \pm 17.39	51.93 \pm 28.70	0.046	54.571 \pm 20.7	65.85 \pm 13.68	0.049
R5 (kPa.s/l)	307.56 \pm 142.30	227.56 \pm 64.03	0.005	282.71 \pm 61.33	239.28 \pm 58.5	0.025
R20 (kPa.s/l)	161.26 \pm 76.10	128.36 \pm 37.7	0.034	219.85 \pm 82.3	134.28 \pm 38.4	0.001
X5 (kPa.s/l)	3018.16 \pm 1836	2345.83 \pm 1485.6	0.257	1425.14 \pm 725.4	640.10 \pm 187.4	0.248

FEV1, forced expiratory volume at first second; FVC, forced vital capacity; R20, resistance at 20 Hz; R5, resistance at 5 Hz; X5, reactance.

Discussion

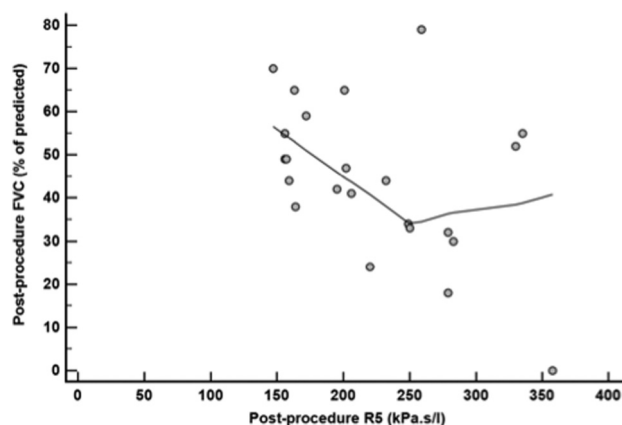
Previous clinical trials [16–18] reported the safety and efficacy of BBLVR. After BBLVR functional improvements are usually assessed by 6MWT and spirometry. The purpose of this study was to use IOS to measure the functional parameters after BBLVR in comparison with the conventional spirometry, which is a novel approach to evaluate an old underrated but easy and applicable procedure.

In this study, BBLVR with histoacryl gel was done for 30 patients who were divided into two groups:

seven (23.3%) patients had single upper lobe emphysematous bullae whereas 23 (76%) patients displayed heterogenous upper lobe emphysema, of which 13 (56%) had unilateral and 10 (43%) had bilateral presentation.

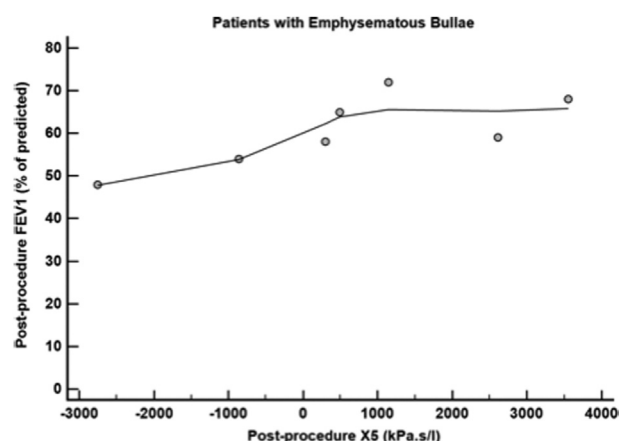
Statistical comparison of the data before and 4 weeks after the procedure revealed that the 6MWT and PaO₂ improved in all the patients; however, the modified Borg scale of dyspnea decreased but had no statistical significance (Table 1). This was in agreement with the

Figure 2



Scatter plot showing correlation between FVC and R5 post procedure in heterogeneous emphysema group.

Figure 3



Scatter plot showing correlation between FEV1 and X5 post procedure in emphysematous bullae group.

Table 3 Outcome measures before and after the biological bronchoscopic lung volume reduction

Variables	Before procedure		After procedure		P-value
	Mean	IR	Mean	IR	
FEV1 (%P)	34	26–41	49	32–59	0.002
R5 (kPa s/l)	273	229–340	213	164–271	0.001
R20 (kPa s/l)	141	123–183	120	99–142	0.004
X5 (kPa s/l)	2413	1854–3508	1750	1146–2613	0.006
PaO ₂ (mmHg)	66	61–72	80	74–86	0.001
6MWT (m)	212	165–288	264	180–348	0.001

%P, percentage of predicted value; 6MWT, 6-min walk test; FEV1, forced expiratory volume at first second; IR, interquartile range; PaO₂, arterial partial pressure of oxygen; R20, resistance at 20 Hz; R5, resistance at 5 Hz; X5, reactance.

Table 4 Change in outcome measures as percentage of preprocedure value in both groups

Percentage change of preprocedure value	Heterogenous emphysema		Emphysematous bullae		P value
	Mean	IR	Mean	IR	
ΔFVC	25.7	–15.4–72.3	35.4	–20.3–57.8	0.677
ΔFEV1	25.0	–7.0–58.1	44.0	32.6–80.6	0.100
ΔMMEF 25–75	13.8	0.7–53.2	67.3	–15.4–75.7	0.540
ΔR5	–22.0	–33.4 to –5.2	–26.4	–38.9 to –15.0	0.418
ΔR20	–12.8	–29.8–1.3	–39.3	–51.4 to –14.0	0.042
ΔX5	–19.3	–37.6 to –1.1	–45.1	–57.0 to –23.6	0.047
ΔPaO ₂	15.3	4.3–23.1	24.6	19.5–29.0	0.042
Δ6MWT	17.1	6.9–27.8	26.9	11.0–45.4	0.001

Data are expressed as percentage of change of preprocedure value, Δ=change, mean, IR, interquartile range and P-value. FEV1, forced expiratory volume at first second; FVC, forced vital capacity; IR, interquartile range; MMEF, maximum mid-expiratory flow; 6MWT, 6-min walk test; PaO₂, arterial partial pressure of oxygen; R20, resistance at 20 Hz; R5, resistance at 5 Hz; X5, reactance.

work of Reilly *et al.* [16] who found that the 6MWT progressed irrespective to whether the patients underwent BLVR of two or four pulmonary segments. Moreover, the modified research council dyspnea scale dropped by 2 points.

The outcome measures of the spirometry were in conformity with many previous studies [6,17,18]. The FVC improved after BBLVR in both groups, whereas FEV1 increased in the emphysematous bullae group only. Meanwhile, the FEV1/FVC means did not change. The principle behind functional restitution in BBLVR is explained by Fessler *et al.* [19], In heterogenous upper lobe emphysema, BBLVR lessens the residual volume, and to a less extent the total lung capacity, as the inspiratory muscles can work better enhancing both the vital capacity and the FVC.

The increase in FEV1 is attributed mainly to the restored vital capacity after reducing the size of the lung with the induced atelectasis of the large bullae allowing the healthy lung to inflate, diminishing lung compliance and improving the airway resistance. The increase in FEV1 in BBLVR is dependent on the increase in FVC, hence the unchanged FEV1/FVC [19].

Regarding the IOS parameters, decrement of both R5 and R20 was registered among both groups with statistical significance after BBLVR, whereas X5 did not differ. Before procedure, the mean values of the R5 and R20 were more than 150% of predicted in all the patients, but the R5 values were higher than the R20, indicating that the elevated resistance is because of increase in small airways resistance. These findings reflect the pathology of emphysema. It is essentially a peripheral airway disease with reduced elastic recoil and early airways collapse owing to compression and/or destruction of the lung parenchyma augmenting the resistance of small airways [20]. It also explains the strong negative correlation ($\rho=0.82$ and $P<0.023$) between R5 and FVC among the emphysematous bullae group before procedure (Fig. 1).

After procedure, as we mentioned earlier, the resistance of small airways decreases, the residual volume decreases, and the FVC increases, thus, the presence of mild to moderate negative correlation between R5 and FVC ($\rho=0.47$ and $P<0.025$) among the heterogenous emphysema group (Fig. 2).

Moreover, there was a strong positive correlation between FEV1 and X5 after procedure among the

emphysematous bullae group (Fig. 3). This was in concordance with the study of Tse *et al.* [21]. They concluded that the degree of air trapping among patients with COPD was correlated with the reactance parameters of IOS. Furthermore, Kolsum *et al.* [22] reported a strong correlation between X5 and FEV1 ($r=0.48$) and that R20 did not show any correlation. This association between FEV1 and X5 could be attributed to both hyperinflation and lack of lung compliance in emphysema.

To compare the outcome measures among both groups, the percentage of change of the preprocedure values was calculated. The following parameters featured statistical significance – $\Delta R20$ ($P<0.042$), $\Delta X5$ ($P<0.047$), ΔPaO_2 ($P<0.042$), $\Delta 6MWT$ ($P<0.0001$) – emphasizing that the emphysematous bullae group benefited more, and this should be taken in consideration amidst the selection criteria of the patients.

Regarding the radiological follow-up, 13 (43%) patients developed radiological atelectasis after BBLVR whereas 17 (57%) did not. This was described by Fessler [23] as failure of the emphysematous segment to collapse owing to the presence of collateral ventilation and higher collateral resistance. This was in agreement with many previous studies [16–18]. Nevertheless, it should be mentioned that the follow-up period of 4 weeks maybe short for the development of atelectasis as highlighted by Criner *et al.* [6] who stated that scarring occurred at 6 week.

Long-term follow-up would enable further understanding of the effect of BBLVR clinically, radiologically, and functionally. In addition, it will unravel future complications; therefore, it is considered one of the limitations of this study. Other limitations include the small sample size, and the lack of adjusted reference values regarding the IOS parameters.

Conclusion

BBLVR with histoacryl gel improves the exercise capacity and pulmonary functions of patients with emphysema, but further larger scale studies are needed to establish standard protocols. IOS outcome measures provided a detailed functional assessment and were in good correlation with the spirometry measurements.

Hereby, the dispute about whether the IOS being an easy, effortless, and reliable test could be used as an alternative to spirometry is validated, and it should be used widely in clinical practice.

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Conflicts of interest

None declared.

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