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Original Article

Functional benefit of smoking cessation in severe COPD patients undergoing bronchial valve implantation

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ABSTRACT

Introduction: Tobacco smoke is the leading cause of chronic obstructive pulmonary disease. The aim of this study is to highlight the effectiveness of smoking cessation along with bronchial valve implantation in subjects with severe COPD.

Methods: A sample of 25 patients, current smokers, affected by severe COPD and heterogeneous emphysema who quit smoking were compared with a group of 15 patients who did not quit smoking.

Measurements and main results: Patients performed plethysmography, 6 minute walking test (WT), haemogasanalysis, exhaled CO test (eCO), COPD assessment test (CAT) together with the mMRC test. A clearer improvement of examined parameters was registered in the group of patients who quit smoking by varenicline and counselling. In particular, we observed a significant increase of FEV1 by 350 ml in the abstainers group compared with 100 ml increase in the non-abstainers($p < .05$) group. We noticed that the RV% decreased by 30% compared with the 10% in the non-abstainers($p < .001$).

The CAT value decreased by 20 compared with 10 in current smokers($p < .001$) as well as the mMRC score ($p < .001$) was more improved in abstainers.

The total resistances were reduced by 30% versus 10% ($p < .01$)and notably there was a higher improvement of walking test (30 m versus 5) ($p < .001$). The eCO was clearly reduced in abstainers, 14 versus 8 ($p < .002$),. PaO2 increased by 4 mmHg versus 1($p < .0001$).

Conclusions: Smoking cessation treatment by varenicline strengthens the effects of bronchial valve implantation and shows up its crucial therapeutic role in severe COPD.

1. Introduction

Selected patients affected by severe COPD and emphysema are potential candidates for valves positioning [1].

Valve positioning is an endoscopic procedure focused on lung volume reduction in heterogeneous emphysema.

The implantable device is inserted occluding bronchi in particular regions of the lung featured by a dilation of airspaces downstream the terminal bronchioles.

The final effect is a reduction of hyperinflation which is a hallmark of emphysema leading to a benefit in terms of symptoms relief [2].

Analyzing the causes of severe COPD, tobacco smoke account for about 70% of COPD and emphysema development. The latter is the leading avoidable cause of mortality worldwide, causing 5 million deaths annually [3]. Nearly 3000 people around the world die every day due to tobacco smoke-related illnesses [4]. It is known that 40% of deaths from cardiovascular disease are related to smoking habit. Of the 40% of smoking-related deaths due to respiratory diseases, lung cancer accounts for 20% and chronic obstructive pulmonary disease (COPD) accounts for another 20% [5,6]. Concerning COPD, it is the fourth cause of death worldwide and it is going to.

become the third cause of death (6). COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. It is often associated with some extra-pulmonary signs. The airflow limitation, a hallmark of the disease, is usually progressive and associated with an abnormal inflammatory response to noxious particles [7].

Symptoms of pulmonary disease which are smoke-related include sputum, cough, exertional dyspnea and exercise intolerance. The most important therapy for chronic bronchial obstruction is smoking cessation treatment according to the GOLD guidelines, and quitting smoking has been shown to slow down the progression of COPD by changing its

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natural history [7]. Accordingly, smoking cessation is strongly recommended for all COPD patients and it can be achieved by both non-pharmacological and pharmacological treatments. The benefits of smoking cessation are evident within a short time [8,9]. Quitting smoking will result in significant improvements in blood pressure and heart rate, and exhaled carbon monoxide can be normalized over a few hours. Quitting will also result, in the short term, in symptomatic relief of chronic cough, sputum and attenuation of other symptoms such as shortness of breath and wheezing [10].

The benefits of smoking cessation are measurable within the first year of abstinence and the rate of decline in lung function becomes similar to the one of non-smokers [11].

The first-line therapies for this dependence include nicotine replacement (NRT), bupropion, varenicline. The effectiveness of the treatment with varenicline versus placebo on smoking cessation has already been demonstrated. Varenicline, an α4-β2 nicotinic-acetylcholine receptor partial agonist, induces a complete abstinence rate up to 42% of all patients and triplicate the rate compared with NRT and bupropion [12,13]. The aim of the current study was to highlight the effectiveness of smoking cessation treatment in patients affected by severe COPD undergoing bronchial valve implantation in the short time. For this purpose we compared two groups of patients, quitter and not quitter, undergoing the same treatment.

The study was approved by Sandrea Ethic Committee including informed consent.

2. Materials and methods

2.1. Study design

We enrolled 25 outpatient smokers (> 10 cigarettes per day) suffering from severe COPD who quit smoking by smoking cessation treatment.

We compared them with a group of 15 patients current smokers affected by severe COPD who did not quit. All patients underwent valve positioning.

The inclusion criteria considered were: smokers > 10 cigarettes per day (moderate smoker), with a pack-year value > 20, and symptomatic for exertional dyspnea. Patients with major depression, cardiovascular conditions, were also included.

All patients were treated with long-acting beta-agonist (LABA) plus long-acting muscarinic- antagonist (LAMA).

Patients were washed out from bronchodilators 24 h before evaluations. A consent written form, approved by the Institution, was provided for sensitive data processing.

The patients smokers underwent clinical and functional tests before and after treatment.

All patients performed a low dose high resolution CT scan HRCT demonstrating a prevalent heterogeneous emphysema which consists of a destruction of alveoli in only some sites of the lobe.

The patients underwent bronchial one-way valve placement in the target lobe. A smoker was defined as a subject who smoked > 100 cigarettes in his lifetime and who currently smokes daily. The pack-year is an index of risk for smoke-related diseases [14]. The medical records of these patients were retrospectively examined (Table 1) and all patients had a ratio forced expiratory volume 1(FEV1)/forced vital capacity (FVC) < 70% and FEV1 < 50% of the predicted value according to the ERS-ATS task force guidelines [15]. The time to detection was at baseline and three months after the end of treatment for smoking cessation. The residual volume was at least 130% of the predicted value.

The schedule dosage for varenicline was 0.5 mg per day for three days, then 0.5 mg twice a day for 4 days, increasing the dosage up to 1 mg twice per day. An abstainer was defined as a subject who reported an exhaled CO level equal or lower than 5 ppm. Information regarding the patients were also recorded, including age, gender, present and past diseases, body mass index (BMI). Demographic baseline data were reported for smoking habits, educational level, employment status, parental history of smoking. The Fagestrom's test for nicotine dependence (FTND) was also administered (range 0–2 no dependence, 3–4 low,5–7 moderate, 8–10 high dependence).The values are displayed in Table 1.

Table 1
Baseline demographic data.

	Absatiners	Non abstainers
Age, yr	65.5 ± 4.0	69.9 ± 4.0
BMI, kg/m^2	26.7 ± 3.5	24.7 ± 3.5
Pack-year	25.0 ± 2.5	26.7 ± 2.5
Exhaled CO ppm	14.7 ± 2.5	15.2 ± 2.5
Systolic blood pressure, mmHg	125 ± 9.0	132 ± 9.0
PaO_2	69.5 ± 4.5	65.7 ± 6.5
FEV1 liters	0.85 ± 2.0	0.88 ± 2.0
Residual volume%	158.6 ± 2.0%	161.6 ± 2.0%
Lung nodule detection percentage	35.0 ± 2.0	32.5 ± 2.0
FTND	4.0 ± 2.1	6.0 ± 2.1°

Definition of abbreviations: BMI = body mass index; ODI = oxygen desaturation index, FTND = fagestrom test nicotine dependence.
Mann Whitney test or Fisher's exact test as appropriate. Data expressed as mean and standard deviation.
° $p < .05$.

BMI was calculated by dividing weight in kg by the square of height in meters.

2.1.1. Endpoint

functional and clinical benefit of smoking cessation treatment in the short time in patients undergoing bronchial valve implantation.

2.1.2. Outcomes

the main outcomes were the smoking abstinence rate obtained by exhaled CO detection and clinical-functional values changes at third-month check.

2.2. Measurements

Patients underwent a dyspnea test mMRC and functional evaluation before and 3 month after valve implantation.

A 6 minutes walking test (WT) was also performed, during which the oxygen saturation and the distance covered were recorded (Nonin pulsoxymeter, USA). An arterial blood gas-analysis sampling was performed to detect the PaO2 by GEM system (Instrumentation CA, USA). The spirometry was performed by body pletismography (Jaeger system masterscreen, Germany) as follows: briefly, flow dynamic volumes were measured with the pneumotacographic method and volumes and resistances with the plethysmographic method. Data considered were post-bronchodilator Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV1), total resistances (tRaw) residual volume(RV). Patients were instructed to stop bronchodilator 24 h before performing the test. Bronchial resistances (tRaw) are expressed in cmH20 /l/s, mMRC dyspnea score test ranging score from 0 to 4 (from exertional dyspnea to dyspnea at rest), FEV1 and FVC are expressed in liters and FEF 25/75 (Forced expiratory flow at 25/75% of forced vital capacity) in l/s. The CAT score range is 0–40, whereas PaO2 is expressed as mmHg. Residual volume was expressed as percentage of predicted.

Exhaled CO examined by Smokerlyzer (Bedfont), normal values up to 7 ppm.

2.3. Statistical analysis

All values are expressed as mean ± standard deviation or median and CI as appropriate. Data were reported in a database and transferred to the SAS system (version 9.2, SAS Institut, Cary, NC) for statistical evaluation. The Kruskal-Wallis test was applied to compare the

variation of parameters between groups at the beginning and at the third month check. To detect the differences between groups at different time point a p value < .05 was considered statistically significant. The Fisher's exact test was used to detect differences regarding sociodemographic and behavioral data. A logistic regression analysis was eventually performed to determine the relationship between the main clinical and functional parameters and smoking cessation outcome.

3. Results

The sample was subdivided in 25 abstainers and 15 current smokers, the average age was 65.5 vs 69.9.

The baseline differences are displayed in Table 1.

At baseline, FEV1 liters was 0.85 in abstainers versus 0.88 l ($p < .31$), whereas the RV was 158.6% of the predicted versus 161.6%($p < .25$).

The FTND was 4 in abstainers versus 6 in non abstainers and it was the only significant difference ($p < .05$), PaO2 was 69.1 versus 65.7 without significant difference ($p < .45$).

No significant differences were found for systolic pressure as well as for pack year that was 25 versus 26.7 ($p < .28$). The BMI was 26.7 in the first group vs 24.7 in the second. Exhaled CO at baseline was almost similar: 14.7 versus 15.2 ($p < .31$).

No significant differences were detected regarding lung nodule percentage detection, too.

Table 2 displays the variation of parameters in group of abstainers compared with non abstainers before and after treatment.

A significant improvement was found of RV by 30% compared with only 10% variation in non abstainers ($p < .001$), the CAT score improved by 20 versus 10 points ($p < .01$)and FEV1 liters by 350 ml compared with 100 ml ($p < .05$), the WT improved by 30 m compared with 5 in non-abstainers ($p < .001$), the exhaled CO dropped down significantly by 14 ppm vs 8 ($p < .002$).

The inspiratory capacity (IC) percentage improved by 6% compared with 4% in the non abstainers ($p < .052$).

The total resistances were also reduced by 30% compared with 10% ($p < .01$).

PaO2 was also improved by 4 mmHg in abstainers compared with 1 (p < .001).

PaCO2 was reduced of about 3 mmHg in both groups ($p < .29$). The mMRC improved by 1 point in both groups ($p < .10$).

The FEV1 percentage of predicted changed more deeply in abstainers ($p < .002$).

A logistic-regression analysis was eventually performed including variables affecting the outcome, smoking cessation (Table 3). The above displayed a significant influence of eCO value on smoking cessation, displaying 10% lower level in abstainers related to positive outcome ($p < .05$).

Table 3
Multivariate logistic regression analysis.

	OR	95%CI	*P* value
BMI, kg/m^2	1.14	0.4–3.0	0.10
Exhaled CO, ppM	0.90	0.64–1.40	0.05
FEV1%	0.2	0.03–2.08	0.25
Pack-year	0.99	0.83–1.18	0.15

Odds ratio regarding the influence of some significant variables on smoking cessation treatment.

4. Discussion

This is a monocentric open retrospective study, it is not a controlled randomized trial. However, significant results were achieved after a short time followed up over three months. This study has a small sample size and is not generalizable, but as a pilot study, it shows promising data which represent the basis for a new larger multi-centric prospective study.

In our study a greater benefit was achieved in patients COPD abstainers undergoing valve implantation aside from bronchodilators.

The effectiveness of pharmacological therapy in COPD has some limits in reducing lung hyperinflation and a plateau of activity with an increase of about 100 ml of FEV1 and a reduction of exacerbations, as demonstrated in recent trials [16].

Non surgical lung volume reduction has acquired a growing interest, acting on pulmonary mechanics and mainly causing lung desufflation. Endoscopic lung one way valve implantation allows airways to exit air trapped without entering of inspired air, it is deployed unilaterally [17]. Complete fissure and lobar occlusion are two conditions producing better results in terms of increase of FEV1. Some trials on the above cited treatment were carried out considering as inclusion criteria residual volume > 175% of predicted, a forced expiratory volume < 50% of predicted and a walking test of at least 100 m [18]. Accordingly our study focused on patients having a baseline RV of about 150% of predicted and it was indeed dropped down after a brief period of three months more notably in abstainers. All clinical parameters and functional were improved at the same time, notably in abstainers. Therefore symptoms such as dyspnea at rest, exertional dyspnea, cough, tightness, asthenia were all improved as reported in the Cat questionnaire.

Table 2
Functional profile for patients abstainers versus non-abstainers before and after valve implantation.

	Abstainers		Non abstainers		*P* value
	Pre	Post	Pre	Post	
BMI, kg/m^2	26.0(21.5–33)	27.5(23 – 33)	27.0(21 – 31)	28.0(23 – 32)	0.10
e CO ppM	16.0(12–28)	4.0(2–8)	17(14–32)	9(6–14)	0.002
RV%pred	150(140–165)	120(115–130)	155(145–160)	145(135–155)	0.001
FEV1% pred	50.0 (30–60)	58.0(32–65)	48.0 (30–65)	50.0(35–65)	0.002
FEV1 liters	0.82(0.46–1.25)	1.17(0.66–1.5)	0.85(0.54–1.4)	0.95(0.58–1.5)	0.05
IC %	62.2(37.4–86)	68.2(38.5–98)	62.5(50–68)	66.0(53–75)	0.052
mMRC	2.5(2.0–3.0)	1.0(1.0–1.5)	2.0(2.0–2.0)	1.0(1.0–2.0)	0.10
PaO_2 mmHg	69.0(65–75)	73.0(70–80)	65.0(63–68)	66.5(60–70)	0.001
$PaCO_2$ mmHg	45.0(40–50)	42.0(40–45)	44.0(40–48)	40.0(40–46)	0.29
WT meters	130(76–197)	160(109–237)	135(120–150)	140(130–141)	0.001
T-resistances	150(142–175)	120(112–135)	155(145–175)	145(130–145)	0.01
CAT	35(25–40)	15 (10 – 30)	30.0(22–37)	20.0(15–35)	0.001

Definition of abbreviations: FEV1 = one second forced expiratory volume; mMRC = modified medical research council dyspnea scale; RV = residual volume; WT = walking test; IC = inspiratory capacity; eCO = exhaled CO; BMI = body mass index; T-resistances = total.
Data expressed as median and CI.
Kruskal Wallis test.

Consistently with the literature, no severe side effects were reported after valve implantation, neither pneumothorax nor hemoptysis.

Previous multicenter European study showed great benefit using bronchial valve implantation with a short follow up, demonstrating an improvement in treated patients both in terms of lung volume reduction and symptoms relief [19]. Other studies confirmed its functional benefit in a long-term follow up [20].

In this current study we highlight the importance of smoking cessation in addition to valve implantation and the results were over three months.

So far double bronchodilation showed to be the best choice in severe COPD leading to a reduced residual volume and a reduced lung hyperinflation at the same time and as a consequence a reduced work overload of the respiratory muscles [21,22].

The efficacy and safety of bronchodilation beta2-agonist were already demonstrated in COPD [23].

However, the improvement of functional variables by bronchodilators have some limitations and smoking cessation is recognized to be a mandatory treatment leading to an improvement of post-bronchodilator FEV1 by itself [9].

Varenicline, first line therapy, showed to triplicate the cessation rate compared with placebo and it is more effective also compared with NRT and bupropion in various categories of subjects, including patients affected by COPD, cardiovascular or psychiatric disease [24,25].

Other randomized studies reported a benefit of smoking cessation by varenicline of about 44% of abstinence at 12 weeks check versus 27% in bupropion arm(OR 1.5) [26] and a benefit of varenicline was stated using the drug beyond the 12 weeks treatment. It was shown that varenicline could maintain the effect of 44% abstainers over a time up to one year follow up [27].

In the present study the data collected showed that an early therapeutic intervention leads to a fast improvement of lung functional and clinical parameters over three months. The effects deriving from the association of varenicline for smoking cessation and valve implantation are probably due to an indirect anti-inflammatory action.

The rate of smoking cessation by varenicline and counselling was very high, > 50%, probably supported by the high motivation to refrain from smoking resulting by the presence of severe bronchial obstruction. High eCO seems to affect the outcome, after 12 weeks of smoking abstinence. No significant side effects were reported.

The short term benefit of the treatment was obtained in terms of symptoms relief leading to a reduced level of dyspnea and respiratory symptoms as demonstrated by a lower level score of mMRC, a reduction of RV and the faster improvement of walking test distance in abstainers. The results were consistent with the literature [28].

The mMRC evaluation showed to be an important tool in clinical evaluation of COPD patients [29]. In our analysis data regarding smoke consumption, the pack-year index, and FTND have been useful for patients recruitment.

The reduction obtained in CAT value suggests that the patients will have lower risk of developing COPD exacerbations. We can deduce that targeting inflammation by smoking cessation and bronchodilation are essential for the successful of additional treatments.

5. Conclusion

The results show that quit smoking is already effective in the early phases of the smoking cessation in severe COPD especially when combined with other therapeutic methods. The comparison between abstainers and non abstainers highlighted a higher improvement of all examined parameters in the first group.

All therapeutic tools are needed to significantly improve lung function and to stop the relentless functional decline.

Smoking cessation, once again, demonstrates its benefit influencing the natural history of the COPD disease and it is recommended in the most important COPD guidelines.

The findings of our study are very important and significant, though further prospective studies are needed to better strengthen the utility of the combined treatments.

Authorship statement

Aldo Pezzuto: designed and performed this study and wrote the document.

Alberto Ricci: contributed to results and discussion.

Alessio Grieco and Michela D'Ascanio contributed with references and results.

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Declaration of Competing Interest

There was no conflict of interest to declare.

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