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Emerging bronchoscopic treatments for chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by pathophysiological factors including airflow limitation, hyperinflation and reduced gas exchange. Treatment consists of lifestyle changes, lung rehabilitation and pharmacological therapies such as long acting beta-2-agonists (LABA) and long acting muscarinic antagonists (LAMA). More recently bronchoscopic treatments are emerging for COPD. Among them endobronchial valves (EBV) and endobronchial coils (EBC), next to endobronchial stents, sclerosing agents, targeted lung denervation and liquid nitrogen metered cryospray. In this review we aim to summarize the new emerging bronchoscopic treatments and their effect sizes compared with lung rehabilitation and pharmacological therapies.

Contents

1. Introduction - chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gasses (GOLD, 2017). COPD is the third leading cause of death worldwide (Lozano et al., 2012).

COPD is an umbrella term for airflow limitation due to parenchymal destruction (emphysema) and (small) airways disease with inflammation and fibrosis. The relative contribution of airway disease, parenchymal destruction and other changes vary from person to person and even between lung lobes. This results in multiple different phenotypes (Han et al., 2010; Lopez-Campos, Bustamante, Munoz, & Barreiro, 2014; Pinto et al., 2015; Postma, Weiss, van den Berge, Kerstjens, & Koppelman, 2015), most distinctly chronic bronchitis and emphysema. Episodes with worsening of respiratory symptoms and anxiety, exacerbations, further contribute to the decrease in quality of life and survival

Abbreviations: COPD, chronic obstructive pulmonary disease; LABA, long acting beta-2-agonists; LAMA, long acting muscarinic antagonists; EBV, endobronchial valves; EBC, endobronchial coils; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; SGRQ, St George's Respiratory Questionnaire.

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in COPD. These exacerbations are associated with infections and hyperinflation and usually require additional therapy (Lopez-Campos & Agusti, 2015; van Geffen, Douma, Slebos, & Kerstjens, 2016).

2. Pathophysiology

2.1. Bronchus obstruction

COPD is characterized by a chronic airflow obstruction. This can be detected with spirometry. The spirometry then shows a decreased forced expiratory flow in 1 s (FEV_1) and a reduced ratio between the FEV_1 and the forced vital capacity (FVC).

Bronchus obstruction and inflammation were the first factors to be treated in COPD. Bronchus obstruction was treated with bronchodilators and inflammation was treated with first oral corticosteroids and later inhaled corticosteroids. (GOLD, 2017; Hogg et al., 2004).

2.2. Hyperinflation

Hyperinflation is entrapment of air in the lungs during expiration, causing the lungs to hyperinflate. Hyperinflation is caused by bronchus obstruction. This phenomenon is frequently present in COPD, both in stable state, during exercise, and during exacerbations (Mahler & O'Donnell, 2015; O'Donnell & Laveneziana, 2006; van Geffen, Slebos, & Kerstjens, 2015). Hyperinflation causes symptoms such as increased dyspnea and limited exercise capacity due to a decreased inspiratory capacity (IC), increased functional residual capacity (FRC) and increased residual volume (RV). These changes in lung volumes are accompanied by a decrease in FEV_1 in most hyperinflated COPD patients (Fig. 1) (O'Donnell & Laveneziana, 2007). Hyperinflation usually has an important dynamic component, since during exercise, hyperinflation increases further (Cooper, 2006; Guenette, Webb, & O'Donnell, 2012). Hyperinflation is a predictor of mortality in stable state (Moore et al., 2010).

2.3. Gas exchange limitations

The main gasses to be influenced in COPD are oxygen and carbon dioxide. These gasses are important for the metabolism of all living cells of the human body. Abnormalities in their transfer can result in hypercapnia and hypoxia in COPD. Gas transfer is influenced by the entrance of gasses in the alveoli, by the pulmonary vascular system and their ratio (ventilation/perfusion ratio). Additionally, the number of alveoli, the amount of haemoglobin in the blood and the membrane separating air and blood in the alveoli are all influencing gas exchange (Elbehairy et al., 2015; GOLD, 2017; Rodriguez-Roisin et al., 2009).

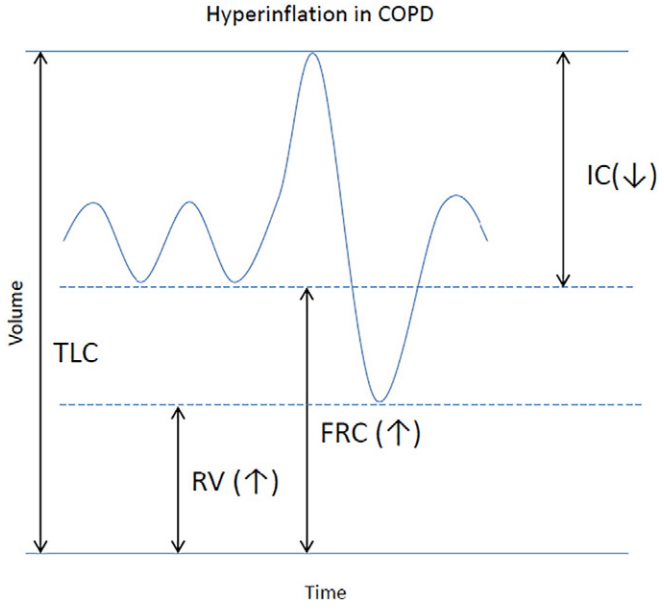

Fig. 1. Schematic volume time curve showing change in lung volumes in hyperinflated COPD patients. Arrows indicate the direction changes. IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity.

Specific treatment mainly aimed to influence the gas exchange is not in common use. Long-term oxygen does not provide symptom or survival benefit ("A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation, 2016"). Thus far it is not possible to recreate destroyed alveoli. Stem cells, originating from the embryonic mesoderm although seem safe to administer. However, thus far they didn't improved gas exchange but where used for their antiinflammatory effects (Weiss, Casaburi, Flannery, LeRoux-Williams, & Tashkin, 2013). Vasodilators do not improve and may even worsen gas exchange (Barbera et al., 1996; Blanco et al., 2013; GOLD, 2017).

3. Pharmacological treatment

Bronchodilators are the cornerstone of therapy for stable COPD. Two major classes of bronchodilators are advocated in guidelines, β2-agonists and muscarinic antagonists. Bronchodilators are mainly administered via inhalers, most commonly by pressurized metered-dose inhalers or dry powder inhalers (Global Initiative for Chronic Obstructive, 2016). The first substances worked for a short period of time and are therefore called short acting bronchodilators. Long acting bronchodilators are especially useful in treating hyperinflation (O'Donnell, Lam, & Webb, 1999). Their benefit however is still limited. Their effects are most commonly measured via changes in FEV_1. The most commonly accepted minimal clinical important difference for FEV_1 is 100 ml. The median increase in trough FEV_1 in COPD patients treated with LABA is 99 ml. For LAMA this is a median change of 104 ml (Kew, Dias, & Cates, 2014). When LAMA are combined with a LABA, the FEV_1 increases further by 60 ml (Farne & Cates, 2015).

Quality of life in COPD is most commonly measured via the St George's Respiratory Questionnaire (SGRQ). The minimal clinical important difference for regular COPD patients difference is considered to be four (Jones et al., 2014). LABA show an improvement in SGRQ of 2.29 points; LAMA with 2.63 points. When LAMA are combined with a LABA the SGQR improves further by 1.34 points (Farne & Cates, 2015). Although lung rehabilitation should not be perceived as pharmacological treatment and does not primarily aim to improve FEV_1, it is a very important treatment for COPD patients. Lung rehabilitation improves quality of life measured by SGRQ with 6.89 points (McCarthy et al., 2015). Inhaled corticosteroids in COPD are aimed to reduce airway inflammation. Treatment with inhaled corticosteroids alone does not conclusively modify long-term decline of FEV_1 or mortality in COPD (GOLD, 2017; Yang, Clarke, Sim, & Fong, 2012).

With the perception that hyperinflation is an important contributor to symptoms and to morbidity, came the idea that targeted treatment of hyperinflation is an important goal and therefore a treatable trait. Hyperinflation can be reduced with long-acting bronchodilators, and the following personalized non-pharmacological strategies have been shown to be able to reduce hyperinflation and improve dyspnea: rehabilitation programs, non-invasive ventilation, cognitive-behavioural strategies, and specific lung volume reduction interventions (Cooper, 2006; Mahler & O'Donnell, 2015).

4. Lung volume reduction surgery

The first lung volume reduction was performed by surgery, and already as early as 1957 (Brantigan & Mueller, 1957). As the name suggests, lung volume reduction surgery (LVRS) reduces lung volume, by removing the most destructed and hyperinflated part of the lung (Criner et al., 1999; Geddes et al., 2000). LVRS can be done unilaterally and bilaterally. Reduction of the volume of hyperinflated COPD patients

reduces exertional breathlessness at a given workload. This is attributed to a combination of reduced thoracic hyperinflation, reduced breathing frequency, and reduced mechanical constraints on lung volume expansion (O'Donnell, Webb, Bertley, Chau, & Conlan, 1996; van Geffen & Slebos, 2015). The largest surgical lung volume reduction trial (The 'NETT trial') assessed 1218 patients with severe emphysema who underwent pulmonary rehabilitation (Fishman et al., 2003). These patients were randomly assigned to undergo lung volume reduction surgery or to receive continued medical treatment only. The trial showed no survival advantage for surgery over medical therapy. The highly invasive surgical technique was associated with increased morbidity and mortality, especially in patients with either a FEV_1 or diffusion capacity below 20% of predicted, and in patients treated in the lower lobes of the lung. A subgroup analysis showed a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity. These results severely limit the applicability of LVRS. These results also led to creative new approaches such as full lobar resections by VATS and so called "non-cutting" techniques, both aiming at reducing postsurgical prolonged air leak complications (Beckers et al., 2016; Pompeo, Tacconi, & Mineo, 2011).

5. Bronchoscopic treatments

Since the NETT trial and its ambiguous results, much less invasive bronchoscopic treatment options for achieving lung volume reduction in patients with the predominantly emphysema disease phenotype have been developed, aimed at improving quality of life and reduction of mortality and morbidity both by deflation itself, whilst evading much of the mortality and morbidity associated with surgery (Fishman et al., 2003; Shah, Herth, van Geffen, Deslee, & Slebos, 2017). Different technologies have been tested, with most of them still being performed in clinical trials only, though some of them have already made it in into clinical practice in some European countries (Shah et al., 2017). Due to the different mechanisms of action of the different bronchoscopic treatments it is important to carefully phenotype patients who might benefit from each bronchoscopic treatment. We will discuss the different technologies separately.

5.1. Endobronchial stents

Airway bypass is a bronchoscopic treatment whereby transbronchial passages through the walls of the more central airways into the lung parenchyma are created to release trapped air. These passages are supported with paclitaxel drug eluting stents to facilitate the mechanics of breathing with an aim of lung volume reduction.

This technology was tested in a multicenter randomized, double-blind, full sham bronchoscopy controlled trial, the EASE trial (Shah et al., 2011). 208 patients were treated and the control group consisted of 107 patients. Patients with severe hyperinflation were included (FEV1 below 50% predicted or 1 l, RV > 180% predicted). All patients had pulmonary rehabilitation before the procedure. Although the patients improved considerably initially after the procedure, the trial failed to show any longer lasting superiority of airway bypass for the primary endpoints (FVC and mMRC) and FEV_1. Also quality of life measured by the SGRQ nor the 6-minute walk test showed a lasting benefit for the patients treated with this technique. It is noteworthy that the sham control patients did not show any placebo effect on SGRQ. The therapy failed because the majority of the airway stents showed no (lasting) patency due to either obstruction by mucus, fibrotic tissue, the next bullae, or simply dislocated.

5.2. Valves

One-way endobronchial and intrabronchial valves are devices designed to prevent air from flowing into the most damaged lobe of the lungs. Whilst prevented to enter the lobe, air is able to exit the lobe thus creating a resorption atelectasis of the target lobe. This atelectasis causes lung volume reduction and thus reduces hyperinflation. The first randomized trial assessing endobronchial valves in 2010 showed only a relatively small benefit in favour of the valves (Sciurba et al., 2010). Included patients all had heterogeneous emphysema, a predicted FEV_1 between 15 and 45% and a residual volume of >150% predicted. Post hoc analysis of this trial, and the results of the European part of the VENT trial showed big differences between responders and non-responders (Herth et al., 2012). A better response was associated with a complete fissure on the chest CT scan, and a complete occlusion of the lobe. Recently, a single center, sham controlled RCT showed that when the completeness of the fissure is deemed present assessed on HRCT before the procedure, the responder rates increase and a significant benefit in symptoms and FEV_1 ensues (Davey et al., 2015). Exacerbations and pneumothoraces were increased in the treated group, and two patients in the treatment arm died during follow-up.

The Stelvio study also included patients which complete fissures on the HRCT (Klooster et al., 2015). The completeness of the fissure in the target lobe was confirmed with an actual measurement of the collateral flow by the Chartis system during bronchoscopy. The use of this system resulted in an even better responder rate in the treated patients than preceding studies. The Stelvio trial included patients with both heterogeneous and homogenous emphysema. The patients showed an increase in FEV_1 of 140 ml compared with placebo on top of maximum bronchus dilatation. Their quality of life measured by the SGRQ improved with 14.7 points compared with placebo.

After post-hoc data using endobronchial valves showed promise in treating homogeneous emphysema patients, a group that has no surgical alternative, the Impact trial was designed to prospectively assess the usefulness of endobronchial valve treatment in patients with homogenous emphysema (Valipour et al., 2016). The results confirmed the earlier found beneficial effect of the endobronchial valves. The most common adverse events in this trial were pneumothoraces (26%) and exacerbations of COPD requiring hospitalization (16%). An advantage of this therapy is that valves can be removed if patients do not benefit from the treatment.

The trials testing intrabronchial valves in patients with occlusion of the whole target lobe in patients with complete fissures are currently awaited. An earlier trial treating patients without complete occlusion did not show results comparable with the endobronchial valves yet (Eberhardt, Gompelmann, Schuhmann, Heussel, & Herth, 2012; Ninane et al., 2012; Wood et al., 2014).

5.3. Endobronchial coils

Endobronchial coils are shape-memory nitinol devices delivered bronchoscopically into the airways. They induce lung volume reduction by contraction of lung parenchyma. Patients are most commonly treated bilaterally with a total of approximately 11 coils per lung. The first pilot studies with this technique were published in 2010 and 2012 (Herth, Eberhard, Gompelmann, Slebos, & Ernst, 2010; Slebos, Klooster, Ernst, Herth, & Kerstjens, 2012). Since then the technique has been tested in several randomized controlled trials and coils are now used commercially in some European countries. Three randomized controlled trials have been published with a total of 231 patients in the treated group and 230 in the standard medical care group (Deslee et al., 2016; Sciurba et al., 2016; Shah et al., 2013). Those treated with coils showed an improvement in 6-min walk distance, FEV_1 and symptoms measured by SGRQ compared with the patients who received standard care. The largest of these trials, the RENEW trial showed an improvement in FEV_1 in patients treated bilaterally of 130 ml from baseline, they did not report a between group difference in millilitres, SGRQ improved with 8,9 points after 6 months compared with placebo (Sciurba et al., 2016). The REVOLENS trial reported a difference of 90 ml between the treatment and placebo group (Deslee et al., 2016) on top of maximum bronchus dilatation. Treatment was associated

with more adverse events, mainly COPD exacerbations (28%), pneumonia (20%) and pneumothorax (10%). Once placed, endobronchial coils cannot be removed (Sciurba et al., 2016).

5.4. Sclerosing agents

Two different techniques aimed at sclerosing the most the diseased part of the lung have been tested. The sclerosis causes a lung volume reduction effect in the treated part of the lung. The results of the techniques are irreversible (Shah et al., 2017).

The first technique is known as bronchoscopic thermal vapour ablation. This technology works by locally applying steam to induce a permanent fibrosis and atelectasis. The Step-up trial randomized patients with upper lobe predominant emphysema only. A total of 46 patients was randomized to vapour therapy and 24 to standard care (Herth et al., 2016). Treated patients improved in FEV_1 (11% at 6 months), quality of life (9.7 points in SGRQ at 6 month) and exercise capacity (31 m in the 6 minute walk test compared with the untreated group). The most common side effects were an increased rate of exacerbations and pneumonitis in the treated patients.

The second technique uses a lung sealant called Aeriseal. This is a solution mixed by air which is delivered by bronchoscope at a diseased part of the lung. The technique was first published in 2009 and was tested with an aim of lung volume reduction in advanced, upper lobe predominant emphysema (Criner et al., 2009; Herth et al., 2011).

The Aspire trial is the only randomized trial assessing this technique, however the sponsor ran out of financial resources and therefore the trial was terminated prematurely. Data from the trial has been published for a follow-up period up to 6 month (Come et al., 2015). The few patients who were treated showed an increased response rate in FEV_1, symptoms and 6 minute walk test. The low numbers in the treated patient group diminished further by 2 deaths and over 40% of the patients had to be admitted at the hospital with serious adverse events due to severe inflammatory responses. Because of its great potential to specifically target interlobar emphysematous areas, its use has been redefined and efforts are underway to more carefully use this device using slowly increasing dosages and repeat bronchoscopies. (NCT 02877459).

5.5. Targeted lung denervation

In 2015 a pilot study performed in South Africa and the Netherlands was performed with a system to elicit targeted lung denervation (Slebos et al., 2015). This system is designed to disrupt parasympathetic pulmonary nerves surrounding the main bronchi using a special RF-energy releasing system, thereby decreasing the release of acetylcholine in the airways, resulting in a permanent anti-cholinergic effect. Twenty-two patients were treated, showing feasibility of the intervention. The trail showed a better outcomes for the highest RF energy dose used. One year changes from baseline in the 20 W dose compared to the 15 W dose were: FEV1 ($+11.6\% \pm 32.3$ vs $+0.02\% \pm 15.1$, $p = 0.324$), submaximal cycle endurance ($+6.8$ min $\pm$ 12.8 vs 2.6 min $\pm$ 8.7, $p = 0.277$), and St George's Respiratory Questionnaire (-11.1 points $\pm$ 9.1 vs -0.9 points $\pm$ 8.6, $p = 0.044$). The adverse event analysis showed that 59% of the patients developed a COPD exacerbation in the first year. The first randomized sham controlled trial assessing this technology is currently underway (ClinicalTrials.gov identifier: NCT02058459).

5.6. Liquid nitrogen metered cryospray

Liquid Nitrogen Metered Cryospray is a method designed to bronchoscopically deliver liquid nitrogen to the central airways in such a way that is leads to a cryoablation depth of 0.1 to 0.5 mm for the treatment of chronic bronchitis. This treatment is intended to induce a regenerative airway tissue healing effect, by initially destroying the hyperplastic goblet cells and excess submucous glands by cryo necrosis. After treatment rapid rejuvenation of normal epithelium occurs, without scarring occurs, a hallmark of cryoablation, and it is thus a potential future treatment for chronic bronchitis (Coad & Bischof, 2003; Godwin & Coad, 2009). The first in human trials testing this system and its hypothesis are currently underway (NCT02106143, NCT02483052, and NCT02483637).

6. Concluding remarks

Different emerging bronchoscopic treatments for COPD have been tested recently, most of them with an aim of lung volume reduction in hyperinflated emphysema patients. Most of the evidence has been collected for the use of endobronchial valves and endobronchial coils. In highly selected patients these therapies do show benefit both in quality of life (Fig. 2), and in lung function (Fig. 3).

Although the bronchoscopic procedures can be regarded as minimally invasive, serious adverse events have been observed. The occurrence of pneumothoraxes, especially with successful valve placement, and increase in infectious and inflammatory events when using coils probably being the most important.

More research is need to better select the patients who will benefit from the different treatments. Also additional research is needed to better predict and treat the procedure related adverse events. More therapies are being developed and the existing are being developed further. The fast development of these bronchoscopic treatments will extend the therapeutic arsenal of the respiratory physician for patients with COPD.

Conflict of interest statement

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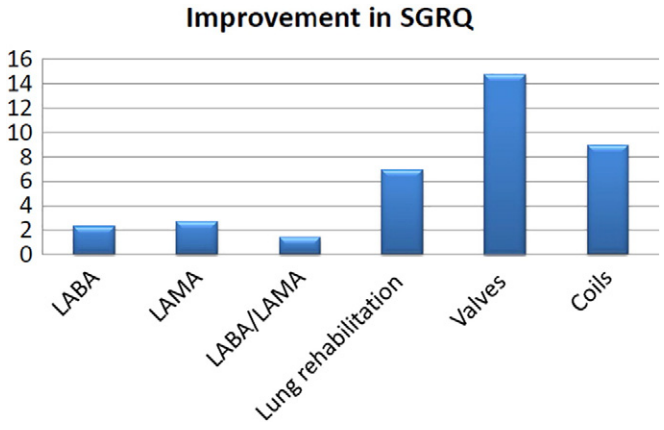

Fig. 2. Effect sizes of different therapeutic options in COPD on quality of life as measured with the SGRQ. Y axis: Improvement in SGRQ in points. X axis Different therapeutic options. LABA: long acting beta-2-agonists, LAMA: long acting muscarinic antagonists. Effect size for LABA/LAMA is the additional effect when a LAMA is combined with a LABA. Effect sizes for rehabilitation, valves and coils are on top of maximum bronchodilation. Compiled from the following references: (Farne & Cates, 2015; Kew et al., 2014; Klooster et al., 2015; McCarthy et al., 2015; Sciurba et al., 2016).

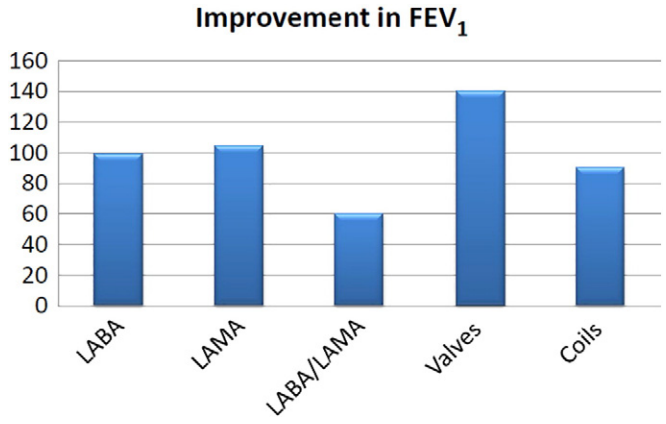

Fig. 3. Effect sizes of different therapeutic options in COPD with FEV_1. Y axis: Improvement in FEV_1 in millilitres. X axis Different therapeutic options. LABA: long acting beta-2-agonists, LAMA: long acting muscarinic antagonists. Effect size for LABA/LAMA is the additional effect when a LAMA is combined with a LABA. Effect sizes for valves and coils are on top of maximum bronchodilation. Compiled from the following references: (Deslee et al., 2016; Farne & Cates, 2015; Kew et al., 2014; Klooster et al., 2015).

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