20

Endoscopic Lung Volume Reduction for Emphysema

Paulo F. Guerreiro Cardoso
Department of Cardio-Pneumology, Division of Thoracic Surgery,
Heart Institute (InCor)-Hospital das Clínicas,
Faculdade de Medicina, Universidade de São Paulo,
Brazil

1. Introduction

In advanced stages of emphysema there is a sequence of events that start with hyperinflation, followed by a reduction in diaphragmatic mobility, an increase in resting pleural pressures that intensifies expiratory muscle recruitment and reduces elastic recoil of the lungs.

During exercise, the limitation to expiratory flow prolongs the expiratory phase causing dynamic hyperinflation and ultimately reducing exercise tolerance. Such factors altogether will predispose to respiratory infections, will cause body mass consumption, muscular deconditioning and weight loss. This ominous cycle of events in the emphysema patient impacts negatively and progressively on the quality of life. The patient experiences breathlessness during ordinary activities and even at rest. At this stage of the disease process, palliation becomes a more relevant goal than increased longevity (Berger, Decamp et al. 2010).

The medical treatment of this condition includes bronchodilators, costicosteroids, oxygen and the management of exacerbations and infections. The pulmonary rehabilitation programs, when added to the medical management has been shown to reduce dyspnea, improve quality of life, reduce the frequency of hospital admitions but it does not impact on survival (ATS 1999).

The current options for the surgical treatment are surgical ablation of bulous disease (bullectomy), lung volume reduction surgery (LVRS) and lung transplantation. Despite its unequivocal benefits in selected patients, all such procedures carry a considerable morbidity and mortality.

The LVRS was initially proposed by Brantigan in the 1950's, but mortality was a major issue in the early years (Brantigan, Mueller et al. 1959). In the 1990's, Cooper et al published the first successful, series of pacientes submitted to LVRS (Cooper, Patterson et al. 1996). This was followed by randomized studies that demonstrated functional benefits and acceptable mortality in patients with low exercise capacity and upper lobe predominant heterogeneous disease (Ciccone, Meyers et al. 2003). Despite the promising results of LVRS, mortality has remained high and duration of the benefits remained a controversial issue as shown in the National Emphysema Treatment Trial (NETT) (Fishman, Martinez et al. 2003). The application of LVRS for homogeneous emphysema has added to the controversy (Weder,

Tutic et al. 2009). A recent reassessment of the NETT results revealed that only 45% of the LVRS were actually performed in upper lobe predominant heterogeneous emphysema, and more that one half of the patients were lost to follow up at 5 years, both in the medical and the surgical arms of the trial (Sanchez 2009).

The loss of enthusiasm in LVRS was followed by the development of several endoscopic methods and devices for lung volume reduction. There have been several experimental and clinical studies on such devices based on the asumption that a bronchoscopic procedure is less invasive and a safer alternative for achieving LVR. Furthermore, a non-surgical procedure will probably extend the current indications for LVR, resulting in a broader access to a larger number of patients with emphysema (Herth, Gompelmann et al. 2010).

This chapter focuses on the description of the current methods and devices for bronchoscopic lung volume reduction for emphysema and the results of the clinical trials.

2. Principles of bronchoscopic lung volume reduction (BLVR)

Some procedures have shared the same principle of LVRS in which, by reducing the hyperinflated lung size, there is an improvement in elastic recoil of the emphysematous lungs and consequently in the breathing mechanics (Ingenito, Wood et al. 2008).

The one-way valves promote size reduction as a result of selective atelectasis mostly when the devices are applied in the upper lobes. However, this relies upon poor collateral ventilation in order to function properly and to provide sizeable volume reduction (Gompelmann, Eberhardt et al. 2010). A complete fissure is a feature that ensures that there is little or no connection with the ajacent lobe, and therefore less collateral ventilation.

Biologic lung volume reduction (BioLVR) uses polymers administered endobronchially to produce a similar effect. It causes selective occlusion of segmental areas where it is instilled, and blocks collateral ventilation because of the inflammatory reaction it causes across the area treated and permeates deeply into the alveoli. Such properties makes BioLVR amenable to be used for either homogeneous or heterogeneous emphysema.

The production of local fibrosis has also been attempted using endobronchial thermal vapor ablation. The principle here is a definitive volume reduction, only achieved at the cost of an inflammatory response and subsequent local scarring that is not reversible (Snell, Hopkins et al. 2009).

The emphysema with predominantly homogeneous destruction calls for different measures. The principle is opposed to what is found in heterogeneous emphysema. Collateral ventilation is usually abundant in homogeneous emphysema, and the procedure must take advantage of it. The production of extra-anatomic passages communicating the distal bronchi with the lung parenchyma is known as airway bypass. This was originally proposed as communications or "spiracles" between the lung and the chest wall (Macklem 1978; Moore, Cetti et al. 2010). Recently, this procedure was then modified to accomodate such passages within the bronchi, thus enabling it to be performed bronchoscopically (Choong, Macklem et al. 2008). This procedure will reduce hyperinflation and provide a diaphragmatic remodelling that will ultimately improve ventilatory mechanics.

3. Devices and results

The devices developed for endoscopic treatment of heterogeneous emphysema can be divided into 3 categories: Blocking devices (e.g. one-way valves); Reversible non-blocking or

removable (e.g. *coils*); Non-reversible or non-blocking definitive (e.g. vapor thermoablation, endobronchial polymers, airway bypass).

3.1 Blocking devices

3.1.1 One-way valves

These devices have been validated for clinical use in some countries. The Zephyr® (Pulmonx, Redwood City-CA, EUA) (FIGURE 1) is a model that can be placed bronchoscopically.

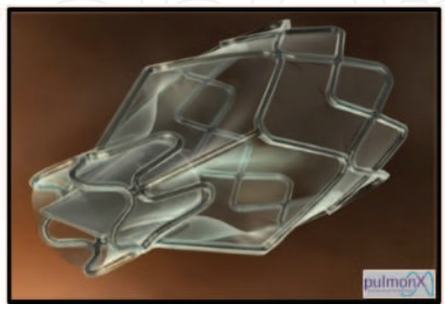


Fig. 1. The Zephyr® one-way valve (Pulmonx, Redwood City-CA, USA)

The success of the procedure is related to presence of complete fissures, high heterogeneity and the presence of atelectasis of the treated lobe. The manufaturer has recently introduced a device for measuring collateral flow which is composed of a catheter with a baloon tip and a flow transducer Chartis™, Pulmonx, Redwood City-CA, EUA) (Figure 2).

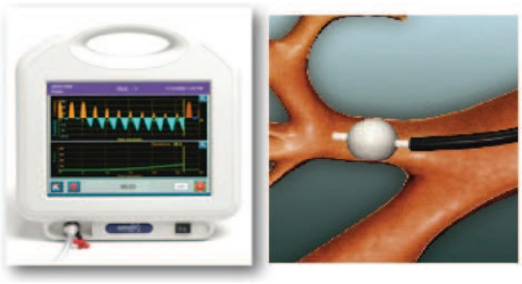
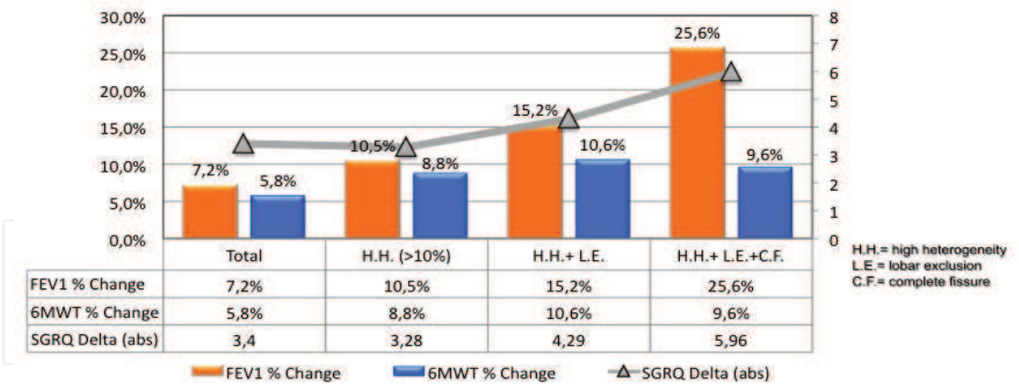


Fig. 2. The console and catheter for the measurement of collateral ventilation (Chartis® system; Pulmonx, Redwood City-CA, USA).

Once the target area is identified radiologically, the catheter is passed through the working channel of the bronchoscope, advanced into the lobar bronchus, the baloon tip is inflated in place occluding the bronchus. The collateral ventilation is then measured on site by the flow transducer connected to the tip of the catheter (Aljuri and Freitag 2009). This allows the examiner to choose the area with the least collateral ventilation for installing the valves. A study with 25 patients using this method of measuring collateral flow showed that in 90% of the cases the resistance measurements correlated with the post-implantation atelectasis visualized on a chest X-ray (Gompelmann, Eberhardt et al. 2010).

The clinical studies carried out so far have been done in a heterogeneous population of emphysema patients and this has impacted the results negatively. A safety and efficacy non-randomized study showed that 90 days post-implant of one-way valves has revealed a 4,9% decrease in residual volume (RV) and a 10% increase in FEV1. There were 8% serious adverse events and 1% mortality (Wan, Toma et al. 2006).

To date, the largest randomized study with one-way valves was the **VENT** study (**V**alve for **E**mphysema Palliatio**N** **T**rial). There were 321 patients included accross 31 centers in the United States and 23 centers in Europe. Major inclusion criteria were: FEV1 between 15-45%; RV ≥ 150% and total lung capacity (TLC) ≥ 100% predicted. All patients underwent a full pulmonary rehabilitation program before and after the procedure. A 2:1 randomization (treatment with valves : control with best medical care) resulted in 214 patients receiving valves and the results have been published recently (Sciurba, Ernst et al.). At 6 months there was a small but significant improvement in FEV1 of 4,3% with a mean difference between treatment versus control group of 6,8% (*p<0.005*). There was a 2,5% increase in exercise tolerance on the 6-minute walk test (6MWT) in the treatment group, versus a decrease of -3,4% in the control group (mean difference of 5,8% *p=0.04*). There were small improvements in dyspnea, a reduction in suplemmental O_2 requirements (-12L/day), and better quality of life (-3,4 points in the St. George Respiratory Questionnaire).
The high heterogeneity (> 15% between lobes by CT) subset analysis at 6 months post-procedure showed that enhanced effects on FEV1 improvements of 10,7% (*p=0,004*) and of 12,4% in the 6MWT (*p=0,002*).
The presence of complete fissure also yielded improvements in FEV1 difference between treatment and control at 6 months (16,2%; *p<0,001*) and at 12 months (17,9%; *p<0,001*). The results at 6 months are summarized in (Figure 3). Major adverse events occurring within 90 days after placement of the one-way valves were mostly COPD exacerbations requiring hospitalization (7,9% in the treated group versus 1,1% in controls;*p=0,03*). Pneumothorax occurred in 4.2% of patients in the treated group early post-procedure follow-up and it was similar between groups in the late follow-up (valves=1%; control=2,4%). All but one resolved spontaneously (Hopkinson, Toma et al. 2005) (de Oliveira, Macedo-Neto et al. 2006).



	Total	H.H. (>10%)	H.H.+ L.E.	H.H.+ L.E.+C.F.
FEV1 % Change	7,2%	10,5%	15,2%	25,6%
6MWT % Change	5,8%	8,8%	10,6%	9,6%
SGRQ Delta (abs)	3,4	3,28	4,29	5,96

Compiled from Sciurba et al. New Engl J Med 2010;363:1233

Fig. 3. Overall % changes (left axis) in FEV1 (orange), 6 MWT (purple) and the delta in the points (right axis) of the Saint George Respiratory Questionnaire (SGRQ) triangle (gray) are shown. The subset of high heterogeneity above 10% increased in about 30% the differences from baseline. When high heterogeneity was added to lobar exclusion, the functional parameters have doubled the differences and, in the subset that congregates high heterogeneity with lobar exclusion and low collateral flow, FEV1 jumped to 25%, 6 MWT to 10% and the delta in SGRQ went up to 6 points.

Hopkinson et al (Hopkinson, Toma et al. 2005) demonstrated that in a series of 19 patients patients treated with one-way valves who developed persisting lobar atelectasis at 1 month after the procedure, showed an improved survival at 6 years of follow-up.
One-way valves have been employed for BLVR as a bridge to lung transplantation in severe COPD patients. There is one report on 4 patients undergoing Zephyr® valve placement (average on 3,5 valves/patient), that showed no procedure related morbidity or mortality. BLVR was able to reduce RV and improve the 6MWT mMRC score. Three out of the four patients were transplanted successfully between 6-7 months, and one patient died 13 months after valve placement still on the transplant waiting list. The authors concluded that in a selected group of COPD patients awaiting lung transplantation, BLVR with one-valves can improve functional status and help patients awaiting lung transplantation for severe emphysema (Venuta, Diso et al. 2011).
Another valve device with a different design has been developed and tested (IBV®, Olympus Co., Spiration, Redmond-WA, EUA) (FIGURE 4). It has the ability of obstructing the airflow selectively in the segments where it is placed and, by the same token, allows secretions to exit the segment. One study with 30 patients showed improvements in quality of life, however without significant differences in pulmonary function (Wood, McKenna et al. 2007). This study has used outcome measures similar to LVRS. An expansion of this study has been published recently and included 91 patients with severe obstruction, hyperinflation and upper lobe predominant emphysema (Sterman, Mehta et al. 2010). A total of 609 bronchial valves placed bilaterally into the upper lobes. There were no procedure-related deaths. Thirty-day morbidity and mortality were 5.5 and 1.1%, respectively and pneumothorax was the most frequent serious device-related complication. There were no significant differences at 1,3,6 and 12 months in pulmonary function, exercise tolerance and gas exchange. There was a significant health-related quality of life improvement (-8.2+/-16.2) change at 6 months and it was associated with a decreased volume in the treated lobes without visible atelectasis.
In another recent study, the IBV® valves were tested and validated for clinical use in persistent air leaks (Wood, Cerfolio et al. 2010).

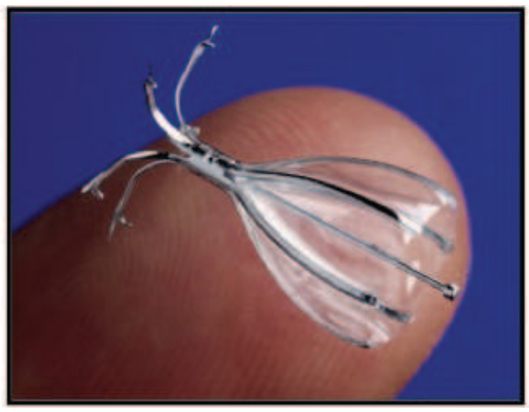


Fig. 4. The IBV® one-way valve (Spiration-Olympus, Redmond-WA, USA)

The studies using one-way valves concluded that this procedures have a good safety profile with low mortality and can be effective in selected subgroups of patients.

3.2 Removable non-blocking devices

3.2.1 Coils

This device is made out of a single nitinol wire with a memory (RePneu® Lung Volume Reduction Coil, PneumRx Inc., Mountain View, CA-EUA) (FIGURE 5). It is placed in a straight position within an introducer sheath that fits in the working channel of the flexible bronchoscope. Once the target segmental bronchus is reached, the device is deployed and its memory causes it to curve around its own axis, forcing the bronchus along with the adjacent lung parenchyma. Volume reduction is achieved when several of such devices are placed within the same lobe.

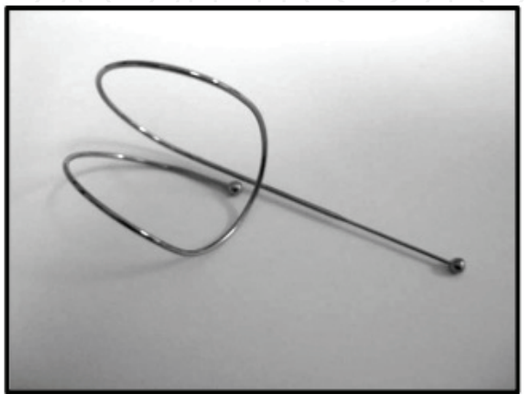


Fig. 5. Endobronchial nitinol coil utilized for BLVR (RePneu® Lung Volume Reduction Coil, PneumRx Inc, Mountain View, CA-USA)

The device a used in a preliminary safety trial on 11 patients, in whom 21 procedures were required to place the coils (average of 4.9 ± 0.6 coils per procedure), lasting 45 minutes each in average. After a follow-up of 7-11 months, efficacy was superior in patients with heterogeneous emphysema (Herth, Eberhardt et al. 2009; Herth, Eberhard et al. 2010).

3.3 Definitive (non-removeable) non-blocking devices

3.3.1 Bronchial thermal vapor ablation (BTVA)

This is a new technology that uses hot water vapor administered via a flexible bronchoscope by means of a baloon occlusion catheter (BTVA-*bronchial thermal vapor ablation*; Uptake Medical Corporation, Seattle-WA, EUA) (FIGURE 6). The system was designed to deliver a precise amount of vapor per gram of lung tissue. The early experimental studies carried out in animal models concluded that an amount of 5cal/gram of lung tissue was sufficient to cause a thermal lesion with subsequent fibrotic scarring and lung volume reduction. A preliminary clinical study on 11 patients with severe heterogeneous emphysema showed no significant improvements in FEV1 or RV at 6 months. However, gas transfer improved, the Medical Research Council Dyspnea Score (mMRC) improved 0,5 points from baseline, and the St. George Respiratory Questionnaire Score improved from 64,4 at baseline to 49,1 (Snell, Hopkins et al. 2009). The complication most frequently found with this procedure was bacterial pneumonia and COPD exacerbation. This technology is still under clinical testing, and new studies with higher amounts of vapor are under way.

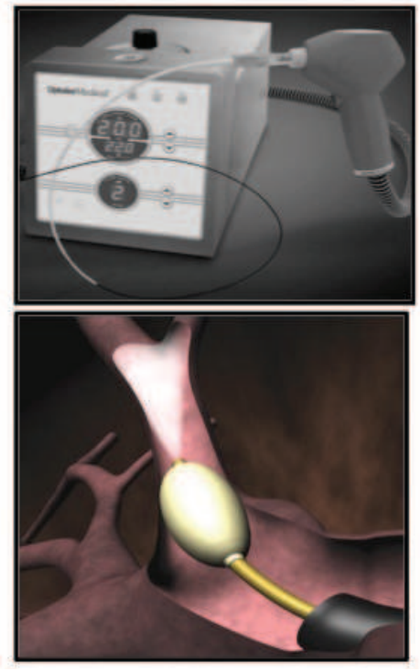


Fig. 6. Vapor generator (top) and catheter (bottom) used for bronchial thermal vapor ablation (BTVA-Uptake Medical Corporation, Seattle-WA, EUA).

3.3.2 Biological lung volume reduction (BioLVR) with polymers

This procedure consists of achieving lung volume reduction after obstruction with biodegradeable polymers instilled endobronchially under flexible bronchoscopy. This substance is a polymer mixed with fibrin and thrombin (*Aeriseal®*, Aeris Therapeutics Woburn-MA, EUA). Once it is delivered via a catheter into the segmental bronchi, its components polymerize resulting in a gel that blocks the bronchi. This substance progresses into the alveoli causing a local inflammatory reaction that causes scarring formation which will ultimately perpetuate the lung volume reduction (Ingenito and Tsai 2007).

The BioLVR has been applied to upper lobe predominant emphysema, both homogeneous and heterogeneous. Experimental data has shown that, by reaching deep into the alveoli, the polymer promotes blockage of the collateral ventilation. A clinical study on patients with homogeneous emphysema has been concluded recently (Reilly, Washko et al. 2007; Refaely, Dransfield et al. 2010). Among the 25 patients that underwent BioLVR, 17 received a dose of 10ml per treated site and 8 received 20ml. The higher dose group had the best results at 6 months. FEV1 reduced 8%, the mMRC dyspnea score reduced by 0,4 points and the St.George's Respiratory Questionnaire reduced by 4.9%. The authors concluded that in homogeneous emphysema the higher dose and the number of segmental bronchi treated were related to a better functional result (Murgu and Colt 2010).

The largest series published on BioLVR included 50 patients with upper lobe predominant emphysema. The FEV1 increased 15.6% at 6 months relative to pre-treatment values ($p=0.002$). On the other hand, subjects receiving higher doses of the polymer experienced more serious adverse events (8%), including pneumonia, pulmonary thromboembolism ad aspiration (Criner, Pinto-Plata et al. 2009).

3.3.3 Airway bypass

As mentioned earlier in this chapter, this procedure was designed to take advantage of the collateral ventilation that occurs naturally and is greatly enhanced in homogeneous emphysema.

This procedure evolved from the earlier concept of extra-anatomical communications between the lung parenchyma and the skin created by Macklem (Macklem 1978), to the production of fenestrations between the segmental bronchi and the adjacent lung proposed by Macklem and Cooper (Macklem, Cardoso et al. 2006).

The procedure consists of the production of orifices in the wall of the distal segmental and subsegmental bronchi (fenestrations), which are kept open with small self-expandable metal stents covered with a thin layer of medical silicone (Choong, Haddad et al. 2005).

The airway bypass procedure uses a proprietary system (Exhale Emphysema Treatment System™, Broncus Technologies Inc., Mountain View, CA-EUA) that includes: a doppler probe, catheter and a processor used for the location of extraluminal vessels through the bronchial wall; a needle-baloon dilator and a baloon catheter that expands the stents and the drug eluting stents loaded with paclitaxel. All devices described above were designed to pass through the 2mm or larger working channel of a flexible bronchoscope (FIGURE 7).

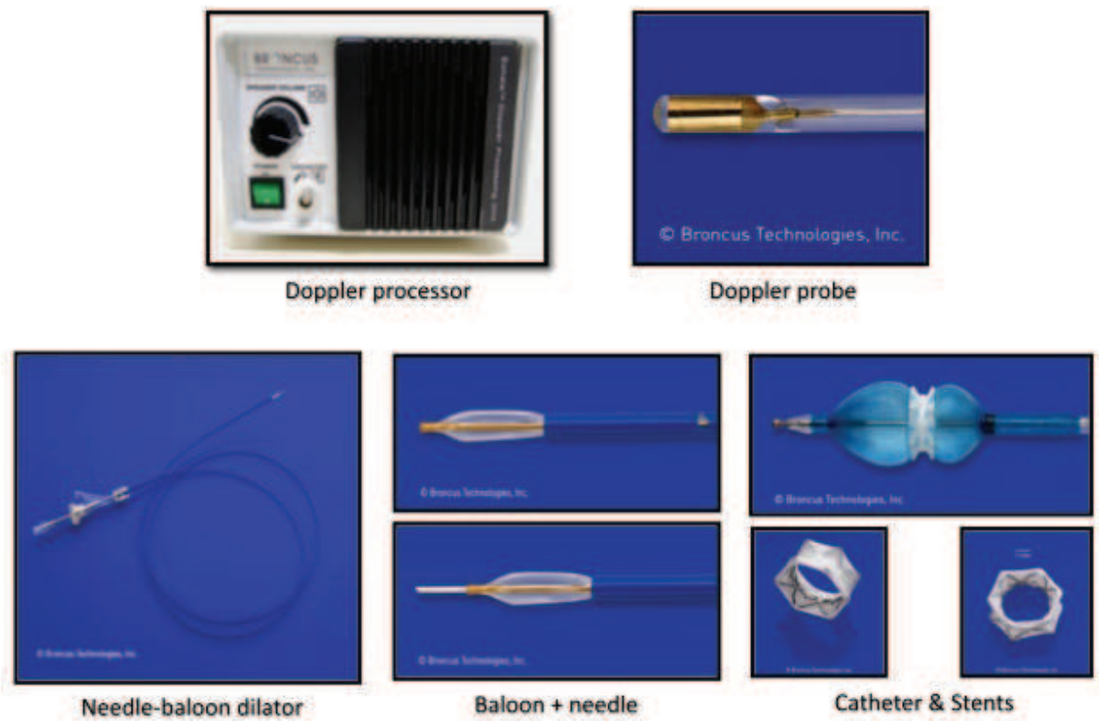


Fig. 7. The Exhale Emphysema Treatment System™, Broncus technologies Inc., Mountain View, CA-USA) used for the airway bypass procedure: doppler processor and probe (top row); needle-baloon dilator and a baloon catheter that expands the stents and the drug eluting stents loaded with paclitaxel (bottom row).

The proof of concept was achieved in a preliminary study on 12 explanted emphysematous lungs extracted from recipients of lung transplants. The lungs were placed in an airtight negative pressure ventilation chamber and connected to a pneumotachometer. Passages

were created in the distal bronchi using a radiofrequency probe and stents were placed to hold the passage open. The creation of the passages resulted in an increase in the cumulative expiratory volumes in a direct proportion to the number of passages created (Lausberg, Chino et al. 2003). Further studies in the same model concluded that airway bypass was able to improve mechanics of breathing in severely emphysematous lungs, therefore supporting that it can improve ventilatory function in patients by reducing gas trapping and flow resistance (Choong, Macklem et al. 2008).

This was followed by a feasibility and safety study in humans prior to lobectomy and lung transplantation using radiofrequency generators to create the passages communicating the distal bronchi with the emphysematous lung parenchyma (Rendina, De Giacomo et al. 2003). The next step was to prolong the patency of the stents. This was achieved experimentally with the use of mitomycin-C in the stents (Choong, Haddad et al. 2005) and later by the development of drug eluting stents loaded with paclitaxel (Choong, Phan et al. 2006).

Prior to the procedure itself, the preferred sites for stent placement were identified on the chest CT scans based on the areas of most emphysematous destruction within the lung parenchyma (FIGURE 8). Efforts were made to place a minimum of three stents in each lung bilaterally. The middle lobe was not treated.

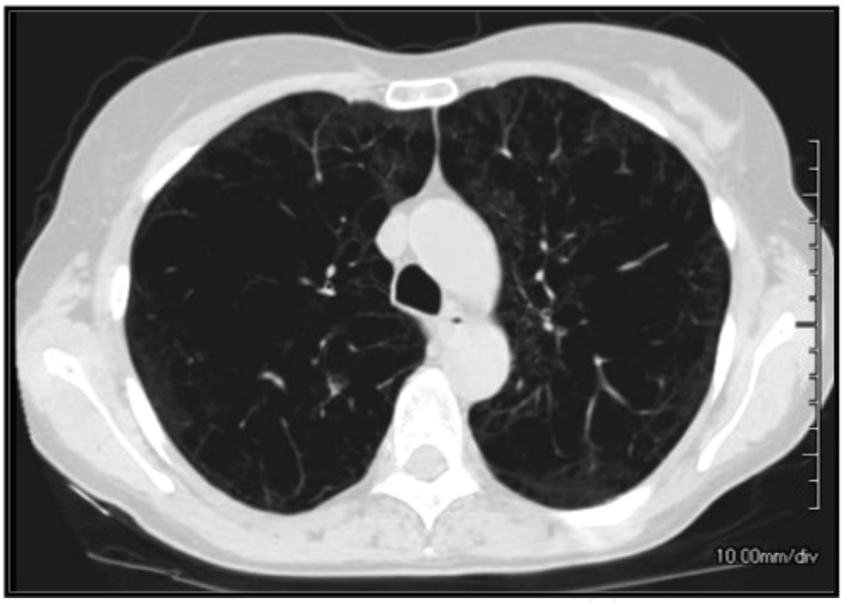


Fig. 8. CT scan showing homogeneous destruction by emphysema in a potentially suitable candidate for the airway bypass procedure.

The creation of each stented passage requires the following steps: 1) identification of a blood vessel-free location with a Doppler probe at the level of segmental bronchi; 2) fenestration of the bronchial wall by means of the needle-baloon dilator; 3) re-scanning the fenestration and its adjacent area with the the doppler probe to ascertain that no vessels were in the vicinity of the puncture site; 4) passage of the stent loaded catheter and deployment of the paclitaxel-eluting stent into the hole by expanding the hidrostatic baloon with a comercially available inflation syringe (FIGURES 9, 10).

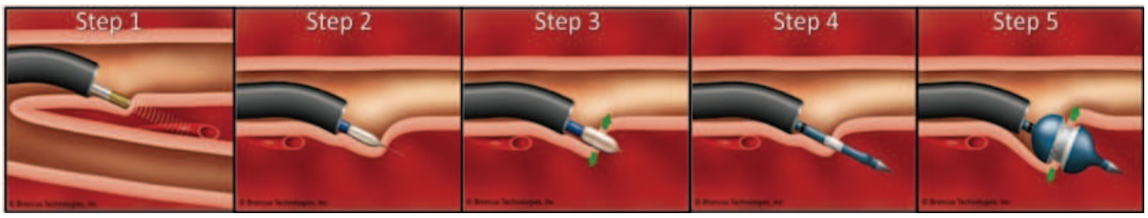


Fig. 9. Steps of the airway bypass procedure: 1- flexible bronchoscope is advanced into the distal airway, the area is scanned by the doppler probe; 2- the needle is passed, the airway pierced; 3- the passage is dilated with the baloon, and scanned again with the doppler probe to ascertain the absence of blood vessels in the vicinity of the passage; 4- the stent is then positioned into the passage; 5- the stent is deployed using a special baloon coupled to the catheter.

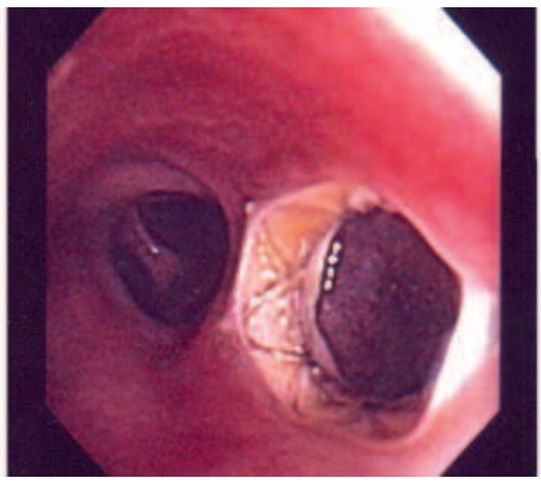


Fig. 10. Paclitaxel eluting stent (right) placed adjacent to a segmental bronchus (left).

The initial feasibility studies were followed by the first clinical studies to evaluate efficacy and safety (Macklem, Cardoso et al. 2006; Cardoso, Snell et al. 2007). A multicentric study included 35 patients with a RV ≥ 220%, FEV1 ≤ 40% and mMRC ≥ 2. Two hundred and sixty four stents were implanted, with an average of 8 stents per patient. There was 1 death secondary to bleeding in this series (mortality of 2,6%). This event triggered an extensive safety revision that resulted in several recommendations made, including re-scanning puncture sites, and the placement of a stand-by bronchial blocker into the airway during the procedure. At 1 month after the procedure there were significant differences in all functional parameters, however such changes got smaller and were restricted to rv (*p=0,04*) and mmrc (*p=0.02*) at 6 months. The subset of patients with RV/TLC ≥ 0.67 sustained the best benefits with significant changes in RV (-14,1% ; *p=0,02*) and mMRC (-0,5% ; *p=0,03*). The most frequent serious adverse events were COPD exacerbation (32%) and respiratory infection (27%), most of them have occurred in the first monthy after procedure. One additional death occurred due to bowel obstruction in the late follow up, which was considered as unrelated to the procedure.

These results led to the design of the *E*xhale *A*irway *S*tents for *E*mphysema (*EASE* Trial) (Shah, Slebos et al. 2011). This was a multicenter phase III trial of airway bypass with paclitaxel-eluting stents. The EASE trial was the first double-blind, randomised, sham-

controlled study on bronchoscopic lung volume reduction in severe homogeneous emphysema.

The EASE Trial used a 2:1 (treatment:sham) randomization. Double-blinding was maintained by dividing the investigators into two teams (blinded Team A with access to pre and post-procedure assessments ; and blinded Team B that performed only the bronchoscopic procedures without further patient contact). All patients underwent a full 6-10 week program of pulmonary rehabilitation prior to the procedure and 8 weeks after the procedure. Follow-up visits were scheduled for 1, 3, 6 and 12 months emphysema (Shah, Slebos et al. 2011).

The 6-month efficacy endpoints required both an improvement greater than 12% in FVC, and a more than 1 point decrease in mMRC over baseline. This trial enrolled 315 patients at 38 centers with homogeneous emphysema and severe hyperinflation (RV ≥ 180% predicted; RV/TLC ≥ 0.65). There were 208 patients randomised for airway bypass and 107 for sham bronchoscopy.

The results of the EASE trial were submitted for publication recently (Shah, Slebos et al. 2011). The airway bypass group received a mean of 4.7±1.4 stents per patient. The 6-month co-primary endpoint was 14.4%for AB vs 11.2% for SC. On day 1, RV decreased significantly in the airway bypass group (change of 379mL from baseline ; *p=0,006*), and this was associated with increases in FEV_1 and FVC. At months 1, 3, 6 and 12 the changes were no longer significant between the groups on FVC, FEV1, mMRC. The functional assessment by Saint George Respiratory Questionnaire was better in the airway bypass group at 1 month, but this coincided with the post-procedural rehabilitation program. The 6MWT showed no significant differences after the first month of follow-up between the groups.

Composite safety endpoints at 6 months were 14,4% in the airway bypass group and 11,2% in the sham controls (*p=1,0*). There was one death after the airway bypass procedure due to a ruptured abdominal aortic aneurysm. Overall mortality at 12 months was similar between airway bypass and sham controls (6,7% and 6,5% respectively).

Further CT analysis showed that there were lobar volume decreases after stent placement at day 1. However, at month 6 the RV increased coincidently with stent loss by expectoration or stent occlusion. Such findings have suggested that the loss of stents or its occlusion were the limiting factors for achieving long term benefit. Further studies must be redesigned with special attention to the functional endpoints and focus on new imaging methods.

Targeting trapped air regions with more accurate mapping in COPD patients is another issue that has to be addressed. Better monitoring for loss of effect and sequential interventions to prolong effect durability with the current technology are therefore required.

In summary, despite the early promising results in the first clinical trial with the airway bypass procedure, the paclitaxel eluting stents used in the EASE trial showed only short term good results. The trial exposed both the need for technical improvements in the stents and for preventing its early occlusion. This will then prolong effect durability if this technology is to be pursued in the future.

The common denominator in all procedures and the few trials on BLVR is the lack of common endpoints and the need for new assessment methods that are both non-invasive and accurate.

4. New methods for the assessment in BLVR

The assessment methods used in BLVR today are essentially the same used a decade ago for LVRS and during the NETT trial.

As BLVR has evolved, this has led the centers to enroll patients with worse pulmonary function and poor performance requiring a more thorough evaluation. On the other hand, all major trials on BLVR did not share the same endpoints, making interpretation of results not only difficult, but sometimes confusing.
All procedures proposed for BLVR so far are based on lung deflation. Surprisingly, none of the methods currently employed have the ability to provide dynamic information as the procedure is being carried out along with the pattern of lung deflation.
Based on the facts abovementioned, new methods for patient selection and post-treatment evaluation must be studied to correct this idiosyncrasy. Such new methods shall be ideally less invasive, able to provide meaningful information and add on to the current evaluation strategy (PFTs, performance testing, Chest CT scan, etc).

4.1 Chest CT scan imaging analysis

Advanced helical scanners have enabled much better imaging management. This has been particularly useful for the detection of target areas in emphysema and airway navigation for bronchoscopy planning. The ability to quantify emphysema based on the CT scan is also a powerful tool for post-treatment assessment.
There are commercially available softwares able to provide an accurate volumetry of each lobe. This is accomplished by mapping the emphysematous areas using the -910 and -950 Hounsfield unit cut-offs and applying the information to complex algorithms. The software will calculate many parameters such as air and tissue volumes. It will generate histograms with the less dense (and more emphysematous) areas, comparing them between the lobes and giving numerical information about heterogeneity. This has become a key for the success of certain procedures such as BLVR with one-way valves (Coxson, Nasute Fauerbach et al. 2008). The software can generate multiplannar images of the airway and its relation to the emphysematous areas, in addition to schematic depictions of the target emphysematous areas with accurate volume calculations (Figure 11). This is particularly useful for obtaining post-procedure static volumetry and to determine heterogeneity between lobes.

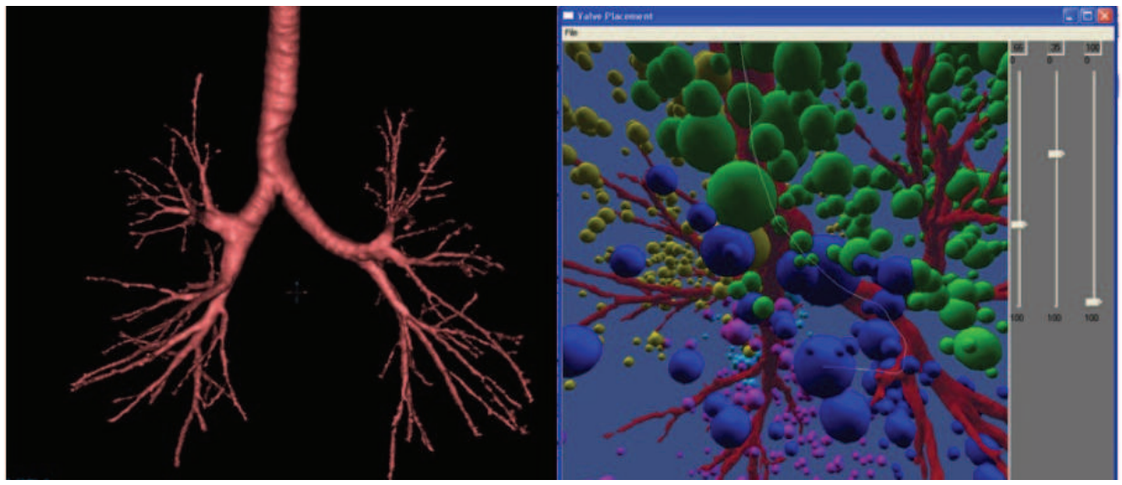


Fig. 11. Images of the airway (left) and a schematic depiction of the emphysematous lobes and its distribution (right) to facilitate navigation and device placement (Apollo®-Vida Diagnostics, Iowa-USA).

The problem limiting repeat CT scans for post-treatment assessment is the cumulative radiation dose. Standard-dose CT for follow-up of BLVR is limited by the risk of administration of a radiation dose of 8-12 mSv for each CT examination. Low-dose CT, in which the radiation dose is six to ten fold less than in conventional CT, has been used for the evaluation of emphysema patients (Gierada, Pilgram et al. 2007). This technique was recently used for the evaluation of the feasibility of thin-section low-dose CT in the radiologic monitoring of patients after placement of bronchial stents for airway bypass (Grgic, Wilkens et al. 2008).

4.2 Electrical impedance tomography (EIT)

EIT uses the injection of high frequency and low amplitude electrical currents through 16 or 32 electrodes placed around the chest to obtain images of a cross section of the lungs. These currents travel through the thorax following pathways that vary according to chest wall shape and thoracic distribution of impeditivities. The resulting electric potentials on the surface of the chest wall are measured and used to obtain the electric impedance distribution within the thorax using a reconstruction algorithm (Figure 12). The output image of such algorithms is usually a 32 by 32 or a 64 by 64 array from which each element corresponds to a pixel on the image and contains the change in impedance in relation to a reference frame, expressed as a percentage (Costa, Lima et al. 2009). This method has been extensively investigated in the intensive care setting for patients undergoing mechanical ventilation.

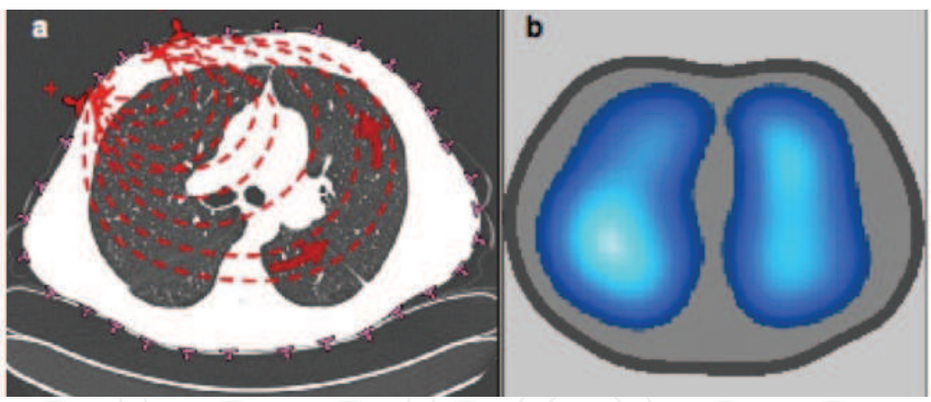


Fig. 12. Electrical impedance tomography (EIT): a) the 32 electrode belt around the chest and the electrical current between 2 electrodes; b) image generated by the software representing the average variation of impedance.

EIT combines two interesting features: it is not invasive and can be performed at the bedside. It has been proven useful for PEEP titration, to optimize ventilation strategies by detecting the imbalances in regional lung ventilation, as well as to detect pneumothorax and small pleural effusions (Victorino, Borges et al. 2004; Costa, Lima et al. 2009). More recently there have been studies showing that EIT can assess lung perfusion through intravenous injection of hypertonic saline, which is a contrast agent for EIT images because of its extremely low impeditivity (Tanaka, Ortega et al. 2008).

The characteristics of EIT makes it a potentially useful tool for the assessment of BLVR. It combines the ability of quantifying lung deflation, to show the redistribution of ventilation during and after the procedure and, by the same token, to detect pneumothorax..

Furthermore, this is the only procedure that can be done at the bedside. We have recently embarked on an experimental study of the patterns on lung deflation after BLVR to detect its feasibility prior to its clinical application.

4.3 Diaphragmatic mobility by ultrasound (US)

One of the hallmarks of advanced COPD is diaphragmatic flattening and dysfunction, both caused by chronic hyperinflation. This causes muscular deconditioning of the diaphragm, that contributes to dyspnea and low exercise tolerance. It is therefore expected that the improvements in diaphragmatic mobility should follow the improvements in breathing mechanics after BLVR in severe COPD patients. Surprisingly, insofar this has not been studied in BLVR protocols.

The US measurement of craniocaudal displacement of the left intrahepatic branches of the portal vein was described as an indirect assessment of right hemidiaphragmatic mobility (Toledo, Kodaira et al. 2003). Paulin et al (Paulin, Yamaguti et al. 2007) created a classification of diaphragmatic dysfunction based on the degree of its mobility. They showed that COPD patients with less than 33.9mm of diaphragm mobility as measured by US had greater dyspnea upon exertion and covered shorter 6MWT distances if compared to patients with more than 34mm of diaphragmatic mobility. Based on this assumption, Yamaguti et al (Yamaguti, Paulin et al. 2009) published an interesting study on the risk of death on COPD individuals with and without diaphragmatic dysfunction based on US evaluation of mobility. They concluded that COPD patients with lower diaphragm mobility had a higher risk of death than COPD patients without diaphragmatic dysfunction and that quality of life was unrelated to the decline in diaphragmatic function in their studies COPD subjects. This has yielded to another major study currently under way at the University of Sao Paulo, Brazil to specifically assess the "Evaluation of ins and expiratory muscles in respiratory diseases".

The US for the measurement of diaphragmatic mobility is also non-invasive and its reproducibility and reliability in COPD patients has been demonstrated. Its use for the assessment of BLVR shall be contemplated in future studies.

4.4 Opto-electronic plethismography (OEP) method

OEP is a new noninvasive technique that is highly accurate method for measuring the total chest wall volume variations, allowing partitioning of the complex shape of the chest wall into basically three different functional compartments (upper chest, thoraco-abdominal and abdominal). It measures breathing patterns and, if combined with pressure measurements, can be used to study statics, dynamics and energetics of the respiratory system (Aliverti, Dellaca et al. 2001). It uses non-invasive video imaging capturing the movement of skin markers while the patient breathes spontaneously. Studies on severe COPD patients using OPE have shown that dynamic hyperinflation is not the only mechanism limiting exercise performance. The measurement of chest wall volumes by OPE can identify the different patterns of respiratory muscle activation during exercise (Aliverti, Stevenson et al. 2004). Another important feature of OPE is its ability to evaluate coordination. One of the semiologic features of COPD is the paradoxical ventilation. This is also known as the Hoover's sign, in which the flattened diaphragm contracts inwards instead of downwards, thereby pulling the inferior ribs inwards with its movement. In normal subjects the expansion of both rib cage and abdomen happen synchronously and in phase. In COPD a

less effective diaphragm alters this mechanism. Lower ribcage paradox at rest is associated with early-onset hyperinflation of the chest wall and predominant dyspnea at exercise. When paradox is absent, the sense of leg effort has been shown to be a more important symptom limiting exercise. On the other hand, COPD patients with an asynchronous abdominal rib cage breathing pattern showed more dynamic hyperinflation and dyspnea as the exercise limiting factor (Aliverti, Quaranta et al. 2009).

Given this is a non-invasive method of measuring both breathing, coordination and chest wall volumes, it makes OPE an excellent tool for screening and evaluating patients for BLVR. We are currently using OPE to measure coordination and lung volume integration in the assessment of COPD patients in our bronchoscopic lung volume reduction program.

5. Conclusion

Bronchoscopic lung volume reduction is an emerging non-surgical alternative for palliation in severe emphysema patients. Despite all the efforts and resources spent into trials and device development, BLVR remains mostly investigational. With the exception of the one-way valves that have been approved for use in Europe and Latin America, all other devices are still under scrutiny. A number of new devices have been proposed and only a few have shown modest benefits if compared to surgical lung volume reduction. Nevertheless, most of the devices have shown a good safety profile and their effectiveness depends greatly on the technology used and on subject selection. The need for development of new methods for evaluation and follow-up following BLVR is another issue that must be addressed in conjunction to the creation of a more uniform data aquisition and interpretation accross the clinical trials.

6. References

Aliverti, A., R. Dellaca, et al. (2001). "Optoelectronic plethysmography: a new tool in respiratory medicine." Recenti Prog Med 92(11): 644-647.

Aliverti, A., M. Quaranta, et al. (2009). "Paradoxical movement of the lower ribcage at rest and during exercise in COPD patients." Eur Respir J 33(1): 49-60.

Aliverti, A., N. Stevenson, et al. (2004). "Regional chest wall volumes during exercise in chronic obstructive pulmonary disease." Thorax 59(3): 210-216.

Aljuri, N. and L. Freitag (2009). "Validation and pilot clinical study of a new bronchoscopic method to measure collateral ventilation before endobronchial lung volume reduction." J Appl Physiol 106(3): 774-783.

ATS (1999). "Pulmonary rehabilitation-1999. American Thoracic Society." Am J Respir Crit Care Med 159(5 Pt 1): 1666-1682.

Berger, R. L., M. M. Decamp, et al. (2010). "Lung volume reduction therapies for advanced emphysema: an update." Chest 138(2): 407-417.

Brantigan, O. C., E. Mueller, et al. (1959). "A surgical approach to pulmonary emphysema." Am Rev Respir Dis 80(1, Part 2): 194-206.

Cardoso, P. F., G. I. Snell, et al. (2007). "Clinical application of airway bypass with paclitaxel-eluting stents: early results." J Thorac Cardiovasc Surg 134(4): 974-981.

Choong, C. K., F. J. Haddad, et al. (2005). "Feasibility and safety of airway bypass stent placement and influence of topical mitomycin C on stent patency." J Thorac Cardiovasc Surg 129(3): 632-638.

Choong, C. K., P. T. Macklem, et al. (2008). "Airway bypass improves the mechanical properties of explanted emphysematous lungs." Am J Respir Crit Care Med 178(9): 902-905.

Choong, C. K., L. Phan, et al. (2006). "Prolongation of patency of airway bypass stents with use of drug-eluting stents." J Thorac Cardiovasc Surg 131(1): 60-64.

Ciccone, A. M., B. F. Meyers, et al. (2003). "Long-term outcome of bilateral lung volume reduction in 250 consecutive patients with emphysema." J Thorac Cardiovasc Surg 125(3): 513-525.

Cooper, J. D., G. A. Patterson, et al. (1996). "Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema." J Thorac Cardiovasc Surg 112(5): 1319-1329; discussion 1329-1330.

Costa, E. L., R. G. Lima, et al. (2009). "Electrical impedance tomography." Curr Opin Crit Care 15(1): 18-24.

Coxson, H. O., P. V. Nasute Fauerbach, et al. (2008). "Computed tomography assessment of lung volume changes after bronchial valve treatment." Eur Respir J 32(6): 1443-1450.

Criner, G. J., V. Pinto-Plata, et al. (2009). "Biologic lung volume reduction in advanced upper lobe emphysema: phase 2 results." Am J Respir Crit Care Med 179(9): 791-798.

de Oliveira, H. G., A. V. Macedo-Neto, et al. (2006). "Transbronchoscopic pulmonary emphysema treatment: 1-month to 24-month endoscopic follow-up." Chest 130(1): 190-199.

Fishman, A., F. Martinez, et al. (2003). "A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema." N Engl J Med 348(21): 2059-2073.

Gierada, D. S., T. K. Pilgram, et al. (2007). "Comparison of standard- and low-radiation-dose CT for quantification of emphysema." AJR. American journal of roentgenology 188(1): 42-47.

Gompelmann, D., R. Eberhardt, et al. (2010). "Predicting atelectasis by assessment of collateral ventilation prior to endobronchial lung volume reduction: a feasibility study." Respiration 80(5): 419-425.

Grgic, A., H. Wilkens, et al. (2008). "Low-dose MDCT for surveillance of patients with severe homogeneous emphysema after bronchoscopic airway bypass." AJR. American journal of roentgenology 191(3): W112-119.

Herth, F., R. Eberhardt, et al. (2009). "Pilot Study of an Improved Lung Volume Reduction Coil for the Treatment of Emphysema." Am J Respir Crit Care Med 179: A6160.

Herth, F. J., R. Eberhard, et al. (2010). "Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study." Ther Adv Respir Dis 4(4): 225-231.

Herth, F. J., D. Gompelmann, et al. (2010). "Endoscopic lung volume reduction." Respiration 79(1): 5-13.

Hopkinson, N. S., T. P. Toma, et al. (2005). "Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema." Am J Respir Crit Care Med 171(5): 453-460.

Ingenito, E. P. and L. W. Tsai (2007). "Evolving endoscopic approaches for treatment of emphysema." Semin Thorac Cardiovasc Surg 19(2): 181-189.

Ingenito, E. P., D. E. Wood, et al. (2008). "Bronchoscopic lung volume reduction in severe emphysema." Proc Am Thorac Soc 5(4): 454-460.

Lausberg, H. F., K. Chino, et al. (2003). "Bronchial fenestration improves expiratory flow in emphysematous human lungs." Ann Thorac Surg 75(2): 393-397; discussion 398.

Macklem, P., Cardoso P., et al. (2006). Airway Bypass: A New Treatment for Emphysema. Annual Meeting of the American Thoracic Society, San Diego-CA.

Macklem, P. T. (1978). "Collateral ventilation." N Engl J Med 298(1): 49-50.

Moore, A. J., E. Cetti, et al. (2010). "Unilateral extrapulmonary airway bypass in advanced emphysema." Ann Thorac Surg 89(3): 899-906.

Murgu, S. D. and H. G. Colt (2010). "Interventional bronchoscopy from bench to bedside: new techniques for central and peripheral airway obstruction." Clin Chest Med 31(1): 101-115, Table of Contents.

Paulin, E., W. P. Yamaguti, et al. (2007). "Influence of diaphragmatic mobility on exercise tolerance and dyspnea in patients with COPD." Respir Med 101(10): 2113-2118.

Refaely, Y., M. Dransfield, et al. (2010). "Biologic lung volume reduction therapy for advanced homogeneous emphysema." Eur Respir J 36(1): 20-27.

Reilly, J., G. Washko, et al. (2007). "Biological lung volume reduction: a new bronchoscopic therapy for advanced emphysema." Chest 131(4): 1108-1113.

Rendina, E. A., T. De Giacomo, et al. (2003). "Feasibility and safety of the airway bypass procedure for patients with emphysema." J Thorac Cardiovasc Surg 125(6): 1294-1299.

Sanchez, P. (2009). "NETT trial: a reassessment." AATS meeting-Abstracts.

Sciurba, F. C., A. Ernst, et al. (2010). "A randomized study of endobronchial valves for advanced emphysema." N Engl J Med 363(13): 1233-1244.

Shah, P., D. Slebos, et al. (2011). "Bronchoscopic lung volume reduction with Exhale Airway Stents for Emphysema (EASE): A Randomised, Sham Controlled Multicenter Trial." Lancet 378: 997-1005.

Shah, P. L., D. J. Slebos, et al. (2011). "Design of the exhale airway Stents for emphysema (EASE) trial: an endoscopic procedure for reducing hyperinflation." BMC Pulm Med 11(1): 1.

Snell, G. I., P. Hopkins, et al. (2009). "A feasibility and safety study of bronchoscopic thermal vapor ablation: a novel emphysema therapy." Ann Thorac Surg 88(6): 1993-1998.

Sterman, D. H., A. C. Mehta, et al. (2010). "A multicenter pilot study of a bronchial valve for the treatment of severe emphysema." Respiration 79(3): 222-233.

Tanaka, H., N. R. Ortega, et al. (2008). "Fuzzy modeling of electrical impedance tomography images of the lungs." Clinics 63(3): 363-370.

Toledo, N. S., S. K. Kodaira, et al. (2003). "Right hemidiaphragmatic mobility: assessment with US measurement of craniocaudal displacement of left branches of portal vein." Radiology 228(2): 389-394.

Venuta, F., D. Diso, et al. (2011). "Bronchoscopic lung volume reduction as a bridge to lung transplantation in patients with chronic obstructive pulmonary disease." Eur J Cardio-Thorac Surg 39(3): 364-367.

Victorino, J. A., J. B. Borges, et al. (2004). "Imbalances in regional lung ventilation: a validation study on electrical impedance tomography." Am J Respir Crit Care Med 169(7): 791-800.

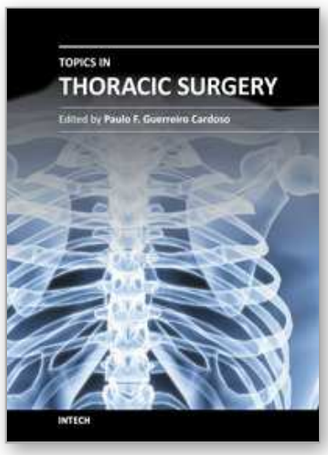
Wan, I. Y., T. P. Toma, et al. (2006). "Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients." Chest 129(3): 518-526.

Weder, W., M. Tutic, et al. (2009). "Persistent benefit from lung volume reduction surgery in patients with homogeneous emphysema." Ann Thorac Surg 87(1): 229-236; discussion 236-227.

Wood, D. E., R. J. Cerfolio, et al. (2010). "Bronchoscopic management of prolonged air leak." Clin Chest Med 31(1): 127-133, Table of Contents.

Wood, D. E., R. J. McKenna, Jr., et al. (2007). "A multicenter trial of an intrabronchial valve for treatment of severe emphysema." J Thorac Cardiovasc Surg 133(1): 65-73.

Yamaguti, W. P., E. Paulin, et al. (2009). "Diaphragmatic dysfunction and mortality in patients with COPD." J Bras Pneumol 35(12): 1174-1181.



Topics in Thoracic Surgery

Edited by Prof. Paulo Cardoso

ISBN 978-953-51-0010-2
Hard cover, 486 pages
Publisher InTech
Published online 15, February, 2012
Published in print edition February, 2012

Thoracic Surgery congregates topics and articles from many renowned authors around the world covering several different topics. Unlike the usual textbooks, Thoracic Surgery is a conglomerate of different topics from Pre-operative Assessment, to Pulmonary Resection for Lung Cancer, chest wall procedures, lung cancer topics featuring aspects of VATS major pulmonary resections along with traditional topics such as Pancoast tumors and recurrence patterns of stage I lung disease, hyperhidrosis, bronchiectasis, lung transplantation and much more. This Open Access format is a novel method of sharing thoracic surgical information provided by authors worldwide and it is made accessible to everyone in an expedite way and with an excellent publishing quality.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen