The blocking therapy of BLVR for Emphysema Phenotype of COPD

Dr. Michela Bezzi
Interventional Pulmonology
University Hospital – Brescia - Italy
drmichela.bezzi@gmail.com
Hyperinflation In Emphysema

Hyperinflation is a devastating & common complication of COPD, especially the emphysematous phenotype

- Decreased Exercise Performance
- Impaired Respiratory Muscle and Chest Wall Mechanics
- Increased Breathlessness, Decreased Quality of Life
- Impaired Cardiac Function
- Increased Mortality (IC/TLC)
Hyperinflation is Associated With ...

**Higher Mortality**

**Worse Quality of Life**

- Higher baseline dyspnea
- Significant intolerance to exercise
- Low peak oxygen uptake
- Lower daily activity levels
- Low BMI and/or muscle strength
- Reduced cardiac and circulatory function

Casanova AJRCCM 2001;171:591-597

Dubé et al. COPD Research and Practice (2016) 2:1
DOI 10.1186/s40749-015-0017-7
Breaking the Downward Spiral

Hyperinflation

Volume reduction

Increased Dyspnea

Reduced Dyspnea

Mortality

Decreased Activity

Deconditioning

Greater Activity

Increased Dyspnea

Decreased Activity

Deconditioning

Adapted from Reardon JZ et al Am J Med 2006; 119 (10 Suppl 1) 32-72
ZuWallack R COPD 2007:4:293-7
Current treatment options

- Medical Management
  - Stop smoking
  - Mono/ double/ triple therapy
  - Supplemental oxygen

- Pulmonary Rehabilitation

- Lung Transplant
  - Highly invasive, limited survival benefit
  - Often restricted availability

... LVRS without surgery!

- Lung Volume Reduction Surgery

Drsssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
Zephyr Endobronchial Valve Treatment

Tiny valves are placed in the lungs through a bronchoscope to occlude a diseased lobe. These valves reduce hyperinflation, enabling better breathing, improved exercise capacity and improved quality of life.
BLVR: proof of principle

before and after valve placement in the LUL

Drsssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
EBV valves for Emphysema
State of the art ..... 10...100...1000!

- Over 10 years of clinical experience with EBV treatment
- Over 110 publications
- Almost 1,000 patients enrolled in 6 RCTs across multiple patient phenotypes
- Expert consensus statements

A total of 6 RCTs, n = 994

- LIBERATE, n = 190
- TRANSFORM, n = 98
- IMPACT, n = 93
- STELVIO, n = 68
- BeLieVeR-HiFi, n = 50
- Euro VENT + US VENT, n = 171 + 321

Enrollment Complete
Data Published

Dr. Michela Bezzi – Interventional Pulmonology University Hospital, Brescia, Italy
Key predictors of response from the VENT Trial

- **Absence of Collateral Ventilation** between target and adjacent lobes
- **Complete Lobar occlusion**

Change from Baseline to 6 Months

<table>
<thead>
<tr>
<th>Subset</th>
<th>Group</th>
<th>FEV₁ (%)</th>
<th>6MWT (m)</th>
<th>SGRQ (pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Population</td>
<td>Control</td>
<td>-1.1%</td>
<td>-2.1</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>5.9%</td>
<td>10.8</td>
<td>-3.4</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>7.0%</td>
<td>12.9</td>
<td>-3.9</td>
</tr>
<tr>
<td>Complete Fissure</td>
<td>Control</td>
<td>-1.2%</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Complete fissure + Lobar exclusion</td>
<td>Treatment</td>
<td>23.5%</td>
<td>29</td>
<td>-6.7</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>24.7%</td>
<td>27.7</td>
<td>-8.4</td>
</tr>
</tbody>
</table>

Sciurba FC et al. N Eng J Med 2010; 363:1233-1244 (including supplementary appendix), data on file at Pulmonx
Editorial

Respiration 2010;80:369–371
DOI: 10.1159/000320726

Published online: October 6, 2010

It Is Tough to Make Predictions, Especially about the Future

M. Bezzi\textsuperscript{a} M. Noppen\textsuperscript{b}

\textsuperscript{a}Spedali Civili di Brescia, Brescia, Italy; \textsuperscript{b}University Hospital UZ Brussel, Brussels, Belgium
Assessing Collateral Ventilation – Chartis System

The Chartis System allows physiologic measurement of whether collateral ventilation is present in a lobe being targeted for treatment.
Chartis and Stratx for CV Assessment

StratX™ Lung Report

Patient ID: V21963
Scan ID: 414095
CT Scan Date: Feb 23, 2017

SUMMARY

RESULTS

RIGHT LUNG

- 62.0
- 87.2
- 87.5
- 87.2

LEFT LUNG

- 96.7
- 95.7
- 75
- 54

Drssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
Fissure analysis with StratX software and Chartis system for bronchoscopic lung volume reduction (BLVR) with EndoBronchial Valves (EBV)

V. Luzzi, M. Innocenti, F. Leoncini, M. Bezzi
Interventional Pulmonology,
University Hospital Careggi - Florence
Methods

- All emphysema patients referred for BLVR in 2017 in Florence underwent Chartis assessment and StratX analysis to quantify fissure integrity on the basis of a Fissure Completeness Score (FCS).
- CV was assumed to be absent if FCS > 95%.
- FCS < 80% meant extensive CV.
- When 80% < FCS < 95% Chartis assessment was recommended to ascertain presence or absence of CV (CV +/-).

[Koster TD et al Respiration 2016;92:150-157]
Results

91 fissures were considered in 25 consecutive BLVR candidates (14M).

Concordance between Chartis and StratX in the groups with FCS < 80% or FCS > 95% was 100% (p < 0.0001).

When 80% < FCS < 95%, 61% of fissures were CV- at Chartis.

20 FCS < 80%
40 FCS > 95%
31 80% < FCS < 95%

Conclusions

Widespread clinical use of StratX can be recommended for fissure assessment, however, a prospective trial is needed before patients can be excluded from valve treatment on the basis of Stratx analysis only.
Summary of Intended Benefits for Patient

- Improved Health Status (BODE)^
- Improved QOL & Exercise (St. George’s, TDI/BDI, CAT, 6MWD)^
- Reduced Breathlessness (mMRC, BORG)^
- Improved Lung Function (FEV₁, DLCO, FRC)^
- Reduced Gas Trapping (RV, IC/TLC)^
- Successful Lobar Occlusion (TLVR)^

* Zephyr valves statistically superior to control at 1 year
* No comparison to control possible

You *ask me if I have a God complex*. Let me tell you something. I am God.

Dr. Jed Hill (Alec Baldwin) in *Malice* is a 1993 American thriller film
Patient selection

WHO IS THE GOOD CANDIDATE?
Lesson learned: who needs it?

Type of COPD:
Emphysema should be the predominant component of the disease (not bronchitis or asthma)

Severity of the disease:
Severe to very severe based on GOLD classification and/or pulmonary function evaluation (FEV1<50%, RV >180%), however should no be considered for “compassionate use”

Pattern of disease:
heterogeneous>>homogeneous disease based on tissue density (CT scan) and perfusion (if possible) to determine the treatment targets

Procedural risk:
Patients should be able to tolerate an interventional bronchoscopic procedure and anesthesia
Optimal medical management

Courtesy of I. Schmidt, MSc

Drsssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
Lesson learned: best practice

Endobronchial Valves for Endoscopic Lung Volume Reduction: Best Practice Recommendations from Expert Panel on Endoscopic Lung Volume Reduction

Dirk-Jan Slebos\textsuperscript{a}  Pallav L. Shah\textsuperscript{b,c}  Felix J.F. Herth\textsuperscript{d}  Arschang Valipour\textsuperscript{e}

\textsuperscript{a}Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; \textsuperscript{b}The National Institute for Health Research Unit, Royal Brompton & Harefield NHS Foundation Trust, and Imperial College, and \textsuperscript{c}Chelsea and Westminster Hospital NHS Foundation Trust, London, UK; \textsuperscript{d}Department of Pneumology and Critical Care Medicine, Thoraxklinik, Translational Lung Research Center Heidelberg (TLRCH), Member of the German Lung Research Foundation (DZL), University of Heidelberg, Heidelberg, Germany; \textsuperscript{e}Department of Respiratory and Critical Care Medicine, Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Otto Wagner Hospital, Vienna, Austria

Drssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
Selection Criteria for EBV Therapy

- Residual volume > 175%
- FEV$_1$ between 15% and 50% of predicted (45% recommended in US)
- Absence of collateral ventilation in the targeted lobe
- Clinically stable prior to the procedure (no AECOPD > 6 weeks)
- No evidence of significant pulmonary pathology other than emphysema on HRCT
- Able to safely undergo sedation/anesthesia and bronchoscopy
- Cessation of smoking (> 8 weeks)
Defining patient stability

- Patients that are **clinically unstable**, with more than 3 severe exacerbations in prior 12 months, should be excluded until stabilized

- Patients with unstable cardiovascular disease should be excluded until stabilized or improved
Exercise capacity

- Patients should have some level of preserved exercise capacity in order to tolerate the procedure and potential complications
  - In patients with a 6MWD below 100 meters, reassessment should be considered after pulmonary rehabilitation
Arterial Blood Gas Analysis

- Patients with **severe hypercapnia** (> 60 mm Hg on room air) and/or **severe hypoxemia** (<45 mm Hg on room air) should be excluded from EBV treatment.

- In patients that display evidence of hypercapnia, reassessment after a trial of at least 3 months of regular non-invasive ventilation may be warranted.
Lesson learned: what do we need?

- LFTs (spirometry & body plethysmography)
- ABG – 6MWD
- Thin slice (0.5 mm)
- Chest X-ray
- Perfusion scan
Perfusion scans - homogeneous

In patients where multiple target lobes are identified with similar destruction, such as homogeneous patients, perfusion scintigraphy may help as a tie breaker.

Physicians should look for the highest perfusion lobe and consider the ipsilateral lobe for treatment.
Exclusion criteria in previous LVR trials

- Alpha-1-AT Deficiency
- Lower lobe predominant emphysema
- Homogeneous emphysema
- FEV1 < 20% DLCO < 20%
- Pulmonary hypertension
Alpha-1 antitrypsin deficiency

Efficacy:
• Improved FEV1 and QOL
• No significant lung function deterioration during 4yr FU

Safety:
• No late complications in 11 patients with > 1 y FU

Conclusion:
• ELVR can be safely performed with encouraging long-lasting results in carefully selected AAT deficiency patients with severe emphysema

Hillerdal et al, Respiration. 2014
In CV-, lobar exclusion EBV patients:

**Efficacy:**
- Both UL and LL cohorts improved clinically
- No difference in mean lung function changes or responder rate between UL and LL

**Safety:**
- No difference in adverse event rate between both cohorts

**Conclusion:**
- Patients with lower or upper lobe predominant emphysema benefit equally from EBV therapy

### Table 2. Clinical outcomes compared to baseline upper versus lower lobe treatments at 180 days

<table>
<thead>
<tr>
<th></th>
<th>Upper lobe treatment</th>
<th>Lower lobe treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁, l</td>
<td>+0.19±0.23</td>
<td>+0.17±0.17</td>
<td>0.71</td>
</tr>
<tr>
<td>ΔFEV₁, %</td>
<td>+23.8±26.4</td>
<td>+22.9±20.7</td>
<td>0.90</td>
</tr>
<tr>
<td>ΔFEV₁, % pred.</td>
<td>+6.6±7.7</td>
<td>+7.2±6.9</td>
<td>0.81</td>
</tr>
<tr>
<td>Δ6MWT, m</td>
<td>+24.06±67.7</td>
<td>+44.00±76.76</td>
<td>0.34</td>
</tr>
<tr>
<td>ΔSGRQ, points</td>
<td>−6.50±11.29</td>
<td>−7.53±17.55</td>
<td>0.82</td>
</tr>
<tr>
<td>ΔTLVR, ml</td>
<td>−1,199±779.7</td>
<td>−1,042±531.5</td>
<td>0.47</td>
</tr>
<tr>
<td>ΔRV, l</td>
<td>−0.40±1.13</td>
<td>−0.95±0.90</td>
<td>0.09</td>
</tr>
<tr>
<td>ΔTLC, l</td>
<td>−0.142±0.785</td>
<td>−0.597±0.652</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data are given as the mean ± SD, unless otherwise specified. TLV = Target lobe volume.
Homogeneous emphysema: IMPACT

FEV1  6MWD  SQRQ  RV

Valipour et al Am J Respir Crit Care Med 2016
EBV in pulmonary hypertension

Pilot study (6 pts)

**Efficacy:**
- @ 3 mo, symptoms, lung function and hemodynamic parameters improved in 5/6 patients

**Safety:**
- ELVR performed without PH-related complications in all patients

**Conclusion:**
- ELVR is feasible in PH patients and results in clinical and hemodynamic improvements. Larger-scale controlled studies needed to confirm.
A low dose thin slice (0.5 to 1.5 mm) volumetric HRCT scan should be used to confirm the degree of emphysema, and rule out other relevant pathologies.
T.C., male, 64a
160cm, 59kg
Mild emphysema
FEV1: 0,59L (25%)
TLC: 5,5L (129%)
RV: 3,0L (221%)

A.G., male, 67a
168cm, 65kg
Severe emphysema
FEV1: 0,53L (22%)
TLC: 6,0L (135%)
RV: 3,5L (250%)
CT assessment of emphysema

- Pleural adhesions
- Fissure
- Diaphragm flattening
- Emphysema distribution
CT assessment of emphysema

- Emphysema
- Emphysema with intralobular heterogeneity
- Fissures
- Diaphragm flattening
CT based exclusion criteria

- Airway disease
- Bronchiectasis
- Paraseptal Emphysema
- Fibrosis
- Suspicious nodule
- Accidental findings
Selection Criteria for EBV Therapy

- Residual volume > 175%
- FEV$_1$ between 15% and 45% of predicted
- Absence of collateral ventilation in the targeted lobe
- Clinically stable prior to the procedure (no AECOPD > 6 weeks)
- No evidence of significant pulmonary pathology other than emphysema on HRCT
- Able to safely undergo sedation/anesthesia and bronchoscopy
- Cessation of smoking (> 16 weeks)
Patient Selection & Treatment Process

Step 1:
• Physical Exam
• Lung function tests
• CT Scan

Step 2:
StratXreport to support lobe selection:
• Lobar volume
• Emphysema destruction score
• Fissure completeness

Step 3:
Chartis procedure
• Confirm target lobe has no collateral ventilation

Step 4:
Zephyr Valves placed to completely occlude the target lobe.

Step 5:
The patient will remain in the hospital for 3 nights following the procedure for observation.

Drsssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
Who should perform the procedures?

Procedures should be done by an experienced bronchoscopist.

Centers doing interventional bronchoscopy will be the best suited to perform procedures and resolve complications.

Training is needed to perform these procedures.
How to treat patients?

Decision should be based on

- Pattern of the disease and treatment goal
- Assessment of patient’s condition and procedure risk/benefit
- Doctor’s experience
- Patient’s attitude

There are several treatment modalities:

- Number of lobes treated: Single or multiple
- Type of device (diameter and length)
- Valve implant - technique
- Procedures per patient: bilateral treatment? (staged)
How we do it...
The day after…

✓ Post operative care

✓ In Hospital for at least 2 (FDA 3) nights

✓ Iv antibiotic prophylaxis before the procedure completed by an equivalent oral regime for a total of 7 days

✓ Post-valve placement and 24 hours (depending on symptoms)

✓ Bed rest and cough suppression has been considered for patient comfort and pneumothorax prevention, BUT THIS ASSUMPTION IS NOT SUPPORTED BY ANY EVIDENCE

✓ Significant volume reduction/atelectasis of the treated lobe may be observed within the first few hours, although some patients may take up to a month

Drssa Michela Bezzi – Interventional Pulmonology
University Hospital, Brescia - Italy
1 month and 6 months

- Chest Xray
- Lung Function
  - Spirometry and plethysmography
  - DLCO
- 6MWD
- BGA

3 months and 12 months

- Chest CT (low dose)
- Lung Function
  - Spirometry and plethysmography
  - DLCO
- 6MWD
- BGA
- Lung perfusion
Patient follow up

What is a responder and when response should be expected?

The treatment may produce different response on the following parameters:

Symptoms
Functional status and activity
Quality of life
Pulmonary function

Some patients experience immediate improvements and in other it may take weeks or months
Patient follow up

What to do with non responders?

In case of worsening of symptoms in the absence of complications, or if there is no visible volume reduction on X-ray at one month, the options are:

- Low dose CT scan to study valve positioning
- Bronchoscopy: consider replacing any valve(s) that do not appear to be correctly positioned
- Remove valves
- Wait longer
Patient Follow Up

If the patient has any of the following, bronchoscopy and possibly valve adjustment or replacement is recommended:

- No volume reduction (at scheduled 30 to 45-day check, or symptom triggering study) on CT scan
- Sudden loss of benefit/loss of volume reduction on CT
- Persistent cough
- Persistent hemoptysis
- Obstruction pneumonia (?)
- Pneumothorax management
Lesson learned: complications

- Pneumonia
- Valve migration
- Pneumothorax
- COPD exacerbation

Translation:
Whatever happened
It’s not my fault!
Is bronchoscopic follow up useful after Bronchoscopic Lung Volume Reduction (BLVR) with EndoBronchial Valves (EBV)?

V. Luzzi, M.Innocenti, S.Romani, F.Leoncini, M.Bezzi
Interventional Pulmonology, Florence
Methods

• We performed a retrospective evaluation of all emphysema patients who underwent BLVR from 2015 to 2017 in our hospital to detect any microbiological airway colonization after BLVR.

• Microbiological samples were always collected during EBV implant.

• Follow up was performed as recommended by best medical practice.

• Only patients who did not present volume reduction of the target lobe though without collateral ventilation at Chartis underwent bronchoscopic examination at 3 months to exclude valve migration or leaking. Microbiological analysis was then repeated.
# Results

<table>
<thead>
<tr>
<th>61 consecutive patients were considered, only 11 patients (18%) needed a follow-up bronchoscopy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial aspirates of 3 patients were positive at baseline bronchoscopy (C. Striatum, M. Stenotrophomonas, S. Pneumoniae).</td>
</tr>
<tr>
<td>When bronchoscopy was repeated at 3 months after BLVR 8 aspirates resulted positive (2 P.Aeruginosa, 1 C.Striatum, 2 S.Aureus, 2 S.Marcescens).</td>
</tr>
</tbody>
</table>

These patients had no radiological or clinical signs of pulmonary infection. None of the patients who were not followed up with bronchoscopy presented any clinically significant pulmonary infection.

# Conclusions

Microbiological contamination can be reported in BLVR patients.

Bronchoscopy is not needed if the patient is asymptomatic unless valve migration/leaking is suspected (bronchoscopy was repeated in **18%** BLVR patients).

It might be useful to re-evaluate patients with microbiological contamination at baseline, but data to support this are poor.

Drsssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
Lesson learnt: complications

- Pneumonia
- Valve migration
- Pneumothorax
- COPD exacerbation

Translation:
Whatever happened
It’s not my fault!
Lesson learnt: complications
Valve migration

Chest xRay 1month-follow up
Lesson learnt: complications
Pneumothorax
Better patient selection → Higher PTX rate

TLVR Pneumothorax v. no pneumothorax

Gompelmann D et al., Respiration 2014

Drssa Michela Bezzi – Interventional Pulmonology University Hospital, Brescia - Italy
Endobronchial valves

Complications - pneumothorax

Interventional Pulmonology,
University Hospital – Brescia, Italy
2007- 2013
Timing of pneumothorax

Gompelmann D, Respiration 2014

Median time to pneumothorax onset following EBV placement was 2 days (0–272 days).

Implications for post-treatment observation!
76% of Pneumothoraces within 3 Days of Procedure

Criner G et al, AJRCCM, 2018, Published on 22-May-2018
Pneumothorax after Bronchoscopic Lung Volume Reduction with Endobronchial Valves (EBV-BLVR):

Is there any correlation with number of valves?

V. Luzzi, M. Novali, M. Bezzi
Interventional Pulmonology, Florence
Methods

- We performed a retrospective evaluation of pneumothorax rate in correlation with number of valves and treated lobe in all EBV-BLVR procedures from 2015 to 2017 in two referral centers, Florence and Brescia.

- We studied the correlation between pneumothorax rate, site of treatment and time of onset.

- We hypothesized an association between pneumothorax rate and the number of valves used.
Conclusions

Our data corroborates those reported by other groups: Overall pneumothorax rate in 99 patients was 24%.

Pneumothorax occurred in 71% of cases within 48 hours after treatment.

There’s no correlation between pneumothorax rate and the treated lung even if it is less common in RLLs.

A number of valves <3 is correlated with a higher rate of pneumothorax (r= 0.97), interestingly using more than 3 valves might reduce the incidence of pnx.

There’s poor knowledge on other possible factors influencing pneumothorax rate. Prospective studies might correlate quantitative features of CT (lobar volume and density) with the likelihood of pneumothorax.

Arschang Valipour\textsuperscript{a}, Dirk-Jan Slebos\textsuperscript{b}, Hugo G. de Oliveira\textsuperscript{c}, Ralf Eberhardt\textsuperscript{d}, Lutz Freitag\textsuperscript{e}, Gerard J. Criner\textsuperscript{f}, Felix J.F. Herth\textsuperscript{d}

- Pneumothorax is an expected „side effect“
- Inform and explain to patient prior to BLVR
- Keep patient in hospital for at least 48 hours
- In case of large PTX use large bore chest tube
- Consider valve removal
- Consider valve replacement
Placebo effect: The joke

Sometimes we think of a placebo effect as something shallow, something that only works for stupid people, or something that is a joke.
Lesson learned: Effect on Survival


Sustained Survival Benefit

Improved survival of emphysema patients with successful EBV treatment

At 5 years post-EBV, patients with atelectasis were 45% more likely to survive than patients without (n=449)

At 10 years post-EBV, patients with atelectasis were more than twice and a half times as likely to survive than patients without (n=19)


Don't be afraid to fail. Be afraid not to try.