V/Q Scans for Non-Acute Indications:
—a Clinical Perspective

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UTSW Medical Center, Dallas

Conflict of Interests to Declare: consultant for Bayer
Outline

Lung Transplantation
  - pre-transplantation
  - peri-operative
  - post-transplant

Pulmonary Hypertension

Lung Volume Reduction Surgery
Pre-Transplant
Pre-Transplant (cont.) - ventilation
Pre-Transplant (cont.)- perfusion
Pre-Transplant (cont.)
Pre-Transplantation period

- Evaluation of right to left shunts
- Evaluation for PE or CTEPH
- Identify if there is a perfusion difference between the lungs
32 yo female with history of CF
-underwent bilateral lung transplantation off ECMO.
-bleeding during explantation, but oxygenation and hemodynamics were preserved.

-few days after transplant:
  -right lung has infiltrates.
Peri-operative- case #1 (cont.)
Peri-operative case #1 (cont.)
Peri-operative case #1 (cont.)

TEE: no evidence of right upper lobe pulmonary vein drainage into the LA.

Dx: pulmonary vein stenosis
Peri-operative case #1 (cont.)

Resection of Right Upper Lobe
53 yo male with history of ILD who underwent left single lung transplant.

Portable Perfusion scan shows 80% perfusion to the native lung at 48 hours post transplant.
Stenosis of the left main pulmonary due to a kink at the anastomosis. Lesion required surgical repair.
Peri-operative period

- evidence of poor lung performance with poor perfusion
- evidence of vasculature injury
Post-Transplant
Post-Transplant
Post-Transplant
Post-Transplant- 1 year
Post-Transplant - 1 year
Post-Transplant- 1 year
Post-Transplant- 1 year

Study Date: 12/09/2016

Geometric Mean

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counts</td>
<td>045K</td>
<td>066K</td>
</tr>
<tr>
<td>Upper</td>
<td>045K</td>
<td>066K</td>
</tr>
<tr>
<td>Middle</td>
<td>133K</td>
<td>202K</td>
</tr>
<tr>
<td>Lower</td>
<td>045K</td>
<td>103K</td>
</tr>
<tr>
<td>Total</td>
<td>223K</td>
<td>371K</td>
</tr>
</tbody>
</table>

(% Ratios)

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper</td>
<td>7.66</td>
<td>11.16</td>
</tr>
<tr>
<td>Middle</td>
<td>22.32</td>
<td>34.00</td>
</tr>
<tr>
<td>Lower</td>
<td>7.57</td>
<td>17.29</td>
</tr>
<tr>
<td>Total</td>
<td>37.55</td>
<td>62.45</td>
</tr>
</tbody>
</table>

The future of medicine, today.

UT SOUTHWESTERN
Medical Center
Post-Transplant Period

- looking for CTEPH/PE
- evidence of air trapping
- evidence of reversal of perfusion towards the native lung

Remember:
- 8th largest lung transplant program in the nation
Pulmonary Hypertension
Elevated Pulmonary Artery Pressures Are Seen in Wide Range of Conditions

Group I
PAH

Most Common

Group II
Left heart disease
HFrEF
HFrEF
Valvular Disease

Elevated PAP

Group III
Hypoxia
OSA
Obstructive
Restrictive
Altitude

Group IV
CTEPH

Rare

Rare

Image courtesy of Jean Elwing, MD.
1. Pulmonary Arterial Hypertension
   - Idiopathic/Heritable
   - Drugs/toxins
   - Connective tissue disease
   - HIV
   - Portal hypertension
   - Congenital heart disease
   - Schistosomiasis
   1'
   - Pulmonary veno-occlusive disease
   - Pulmonary capillary haemangiomatosis

2. PH-Left Heart
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease

3. PH-Lung Disease/Hypoxia
   - COPD
   - Interstitial lung disease
   - Sleep disorder
   - Alveolar hypoventilation

4. Chronic Thromboembolic Pulmonary Hypertension
   - Operable
   - Inoperable

5. Multifactorial/unclear
   - Hematological
     - Chronic hemolytic anemia
     - Myeloproliferative disease
     - Splenectomy
   - Systemic Disorders
     - Sarcoidosis
     - Langerhans cell histiocytosis
     - Lymphangioleiomyomatosis
     - Neurofibromatosis
     - Vasculitis
   - Metabolic Disorders
     - Glycogen storage disease
     - Gaucher’s disease
     - Thyroid disorder
   - Others
     - Tumour obstruction
     - Fibrosing mediastinitis
     - Chronic renal failure
Material Removed From Right and Left Pulmonary Arteries by PTE

Case Example: Resulted in normal post-operative hemodynamics

### Potential Scope of the Problem

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 million</td>
<td>Estimated annual cases of acute pulmonary embolism (PE) in the United States</td>
</tr>
<tr>
<td>100,000 – 200,000</td>
<td>Estimated annual deaths from acute PE</td>
</tr>
<tr>
<td>~1%</td>
<td>Estimated rate of development of CTEPH from persistent or unresolved PE</td>
</tr>
<tr>
<td>8,000 – 9,000</td>
<td>Potential CTEPH burden in the United States annually</td>
</tr>
</tbody>
</table>


Risk Factors for CTEPH

N=433. Patients with CTEPH compared with patients with pulmonary arterial hypertension (PAH).

International CTEPH Registry: Patient History of Pulmonary Embolism

- Confirmed previous deep vein thrombosis: 56.1%
- PE diagnosed more than once: 32.8%
- Confirmed previous acute PE: 74.8%

N=679 newly diagnosed (≤6 months) consecutive patients with CTEPH, from February 2007 to January 2009.

Untreated CTEPH is associated with significant mortality

2-year survival <20% in patients with mPAP >50 mm Hg
  Prior to advent of pulmonary endarterectomy (PTE)
3-year survival <10% in patients with mPAP >30 mm Hg
  Treated with anticoagulants only
Mean 6.8-year survival in Japanese case series
Diagnosis of CTEPH
Diagnostic Algorithm for CTEPH

- PH and a history of PE
- Perfusion-scintigraphy (V/Q)
  - Normal perfusion scan
    - CTEPH ruled out
  - Indeterminate or multiple perfusion defects
    - Further imaging including CT, MR, and angiography and pulmonary angiography showing evidence of CTEPH
A: Eccentric thrombotic material within the pulmonary arteries

B: Characteristic mosaic attenuation of the pulmonary parenchyma with the darker areas corresponding to the hypo-perfused lung sections
Ventilation Perfusion (V/Q) Scintigraphy in CTEPH

Case Example: Perfusion is intact primarily to the right upper lobe

Blue Arrows: Hypo-perfused regions representing perfusion defects

**V/Q Scan More Sensitive Than Multidetector CT Pulmonary Angiography (CTPA)**

<table>
<thead>
<tr>
<th></th>
<th>V/Q High-Probability Scans</th>
<th>CTPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.2%</td>
<td>51.3%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.6%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>95.2%</td>
<td>82.8%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>97.9%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>90.3%</td>
<td>97.6%</td>
</tr>
</tbody>
</table>

*N=227 undergoing both V/Q and CTPA at a single center.*

Echocardiogram: Apical Four Chamber

Normal structure and function

Abnormal structure and function

Image courtesy of Vallerie McLaughlin, MD
Echocardiogram:
Tricuspid Regurgitation

Modified Bernoulli Equation:

\[ 4 \times (V)^2 + RAP = RVSP (PASP) \]

V=tricuspid jet velocity (m/s); RAP= right atrial pressure; RVSP=right ventricular systolic pressure; PASP=pulmonary artery systolic pressure.

Image courtesy of Vallerie McLaughlin, MD
Pulmonary Angiogram

Case Example: Bilateral proximal CTE disease

2015 ESC/ERS Guidelines: Work-up Following an Echo Finding of Suspected PH

Symptoms, signs, history suggestive of PH

Echocardiographic probability of PH

High or intermediate

Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLco, chest radiograph and HRCT, arterial blood gases

Yes

No signs of severe PH/RV dysfunction

Treat underlying disease

No

Diagnosis of left heart diseases or lung diseases confirmed?

Yes

V/Q scan

Mismatched perfusion defects?

Refer to PH expert center

No

Refer to PH expert center

Low

Consider other causes and/or follow-up

Yes

Signs of severe PH/RV dysfunction

Refer to PH expert center
Initial Evaluation of Patients With Suspected PH

ECG
Pulmonary function tests
Chest X-ray
Transthoracic echocardiography
ECG Associated With Right Axis Deviation (RAD) and Right Ventricular Hypertrophy (RVH)

Image courtesy of Vallerie McLaughlin, MD.
Pulmonary Function Test Findings Suggestive of CTEPH

Mild-to-moderate restrictive defect
- Due to parenchymal scarring from prior lung infarct
- Seen in ≈20% of patients with CTEPH

Modest reduction in DLco
- Severe reduction in DLco suggests alternate diagnoses

Hypoxemia and elevated dead-space ventilation
- Worsening with exercise
- Marked hypoxemia at rest may indicate severe right heart dysfunction

Case Example: Oligemia to the left lung and right lower lobe

QuERI: V/Q Scan Often Not Performed During PAH Diagnostic Workup

N=786 patients with PAH enrolled in QuERI database.

*P<0.0001 versus academic center.

Treatment for CTEPH
Modified Treatment Algorithm for CTEPH

CTEPH diagnosis
Continue lifelong anticoagulation

Operability assessment by CTEPH team

Operable
- Pulmonary endarterectomy
- Persistent symptomatic pulmonary hypertension

Non-operable
- Recommend 2nd opinion by experienced center
- Targeted medical therapy
- Refer for lung transplantation
- BPA?

Criteria for Operability of CTEPH Lesions

10% to 50% of patients may be deemed ineligible for PTE
- Subjective and dependent on center experience
- High-volume, experienced surgeon may be capable of distal endarterectomy

Screen not just for the presence of proximal disease, but the potential for concomitant microvascular disease
- Compare PVR to angiographic burden

CTEPH Survival: Operated vs Non-operated Patients

N=679 incident patients with CTEPH included in an international prospective registry over a 24-month period.

Survival Following Successful PTE

N=532, single-center experience. Survival probability is 75% >6 years.

Therapeutic Options for Patients With CTEPH Who Are Not Considered Suitable Surgical Candidates or With Persistent PH Following PTE
Riociguat for CTEPH

Recently approved for use in patients with CTEPH
Should not be considered for use in lieu of surgical therapy in patients who have not been fully evaluated for PTE
CHEST-1: Riociguat Monotherapy for Inoperable or Residual CTEPH

Mean Change in 6MWD

N=263. Double-blind placebo-controlled trial. Patients were not allowed to be on other PAH-specific therapy.

Placebo-corrected treatment effect = 46 m (95% CI: 25-67 m), P<0.0001.

Riociguat for CTEPH: Improvement in Hemodynamics

N=261 patients with inoperable CTEPH or residual PH following PTE. Riociguat monotherapy. No other PAH-specific medication allowed.


Mean difference -246 dyn·s·cm⁻⁵

*P<0.0001 versus placebo.

CHEST-2: Change in 6MWD Using Long-term Riociguat for Inoperable CTEPH

N=211 of 261 patients included in CHEST-1. Open-label extension of placebo-controlled trial.

Organized thrombi is forced on one side of the vessel enlarging the lumen

BPA causes local dissection of the media with thinning (arrowheads) of the vascular wall leading to the expansion of the luminal diameter over time

Experience using this technique is largely confined to Japan

Experts suggest that this technique may be appropriate for patients with residual PH following PTE
Efficacy of Balloon Pulmonary Angioplasty in Patients With Inoperable CTEPH

N=72 inoperable CTEPH patients undergoing BPA. Mean follow-up period = 21 months.

The future of medicine, today.
### Complications of BPA in Patients With Inoperable CTEPH

<table>
<thead>
<tr>
<th>Complications</th>
<th>N = 372*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial dissection</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>64 (17)</td>
</tr>
<tr>
<td>Use of NPPV</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Oral intubation</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Death associated with the procedures</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* N=72 inoperable CTEPH patients undergoing BPA.

* Total number of procedures during study period.
Pulmonary Hypertension Program

CTEPH is a rare (~1%) complication of PE. Clinical presentation may be indistinguishable from other forms of PH. V/Q scan is recommended for screening. CT angiography cannot rule out CTEPH. PTE in appropriate candidates can be curative; accordingly, patients should be first considered for surgery. Medical therapy should be reserved for patients with CTEPH deemed inoperable or for those patients with residual symptomatic PH following PTE.
Emphysema
Emphysema

Permanent destruction and enlargement of the air-spaces distal to the terminal bronchiole
Loss of elastic recoil and gas exchange surface
Early closure of the small airways during exhalation
Air-trapping and hyperinflation
Flat diaphragm and respiratory muscle disadvantage
Emphysema: Heterogeneous and Upper Lobe Predominant Vs Homogenous

Subjective and Objective analysis
LVRS

Resizing the hyper-inflated lung to the chest cavity
Improvement in elastic recoil
Less ventilation/ perfusion mismatch:
  - Expansion of compressed atelectatic lung
  - Decreased dead space ventilation
“Un-flattens” the diaphragm and improves efficiency
Reduction in dynamic hyperinflation during exercise
Reduce the work of breathing

LVRS
Before and After
National Emphysema Treatment Trial (NETT)

1218 patients
Pulmonary rehabilitation (6-10 weeks)
Randomized to receive:
- Continued medical treatment (610) or
- Bilateral LVRS
Patients were well matched regarding: age, race, gender, distribution of emphysema, perfusion ratio (to the upper lobes), PFT (FEV1 ~ 27%, DLCO 28% predicted), PaO2, PaCO2 and respiratory symptoms scores.

Primary outcomes:
- mortality
- Improvement in maximal exercise capacity (an increase in the maximal workload of more than 10 W from the post rehabilitation baseline level).

High Risk of Death (NETT)

FEV1 < 20% predicted with evidence of homogeneous emphysema on CT and/or DLCO < 20% predicted

![Graph showing probability of death over months since randomization with surgery and medical therapy groups compared. The graph illustrates a statistically significant difference, marked with P < 0.001.](image)

The future of medicine, today.
NETT
Subgroup analysis (overall mortality was 26% for both groups at 29 months)

19% Vs 34%: RR of 0.47

25% Vs 13%: RR of 2.06
Early mortality and Morbidity

90-day mortality was 5.2% in the surgical group compared to 1.5% for the medical group.

2.4 year mortality was not different (26% for both medical and surgical groups).

Significant early morbidity.
NETT: Long Term Survival

RR of death at 4.3 years 0.57

LVRS: Candidates: Upper lobe predominance (heterogeneous) and low baseline exercise capacity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 75 years</td>
</tr>
<tr>
<td>Severe dyspnea</td>
<td></td>
</tr>
<tr>
<td>6 months of smoking cessation</td>
<td></td>
</tr>
<tr>
<td>FEV1&lt; 45%</td>
<td></td>
</tr>
<tr>
<td>DLCO &gt; 20%</td>
<td></td>
</tr>
<tr>
<td>TLC &gt; 100%</td>
<td></td>
</tr>
<tr>
<td>RV &gt; 150%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity of emphysema</td>
<td>on CT imaging</td>
</tr>
<tr>
<td>Post pulmonary rehabilitation 6MWT</td>
<td>&gt; 140 m</td>
</tr>
<tr>
<td>Low exercise capacity</td>
<td>(&lt; 40 W for men and &lt; 25 W for women)</td>
</tr>
<tr>
<td>PaO2 &gt; 45 mm Hg</td>
<td></td>
</tr>
<tr>
<td>PaCO2 &lt; 60 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Mean PAP &lt; 35 mm Hg (systolic &lt; 45 mm Hg)</td>
<td></td>
</tr>
<tr>
<td>LVEF &gt; 40%</td>
<td></td>
</tr>
</tbody>
</table>
Bronchoscopic Management Approaches for Emphysema

Using minimally invasive bronchoscopic techniques to achieve comparable results to LVRS with less morbidity, mortality and recovery time
Goal is volume reduction and volume redistribution
Similar criteria to LVRS
Intrabronchial unidirectional valves in the airways

Concepts:

- Complete lobar treatment: a goal of complete atelectasis
- Partial segmental treatment: a goal of segmental atelectasis and volume redistribution
Humanitarian Device Exemption by the FDA for Persistent Air-Leaks

Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation

Karin Klooster, Nick H.T. ten Hacken, M.D., Ph.D., Jorine E. Hartman, Ph.D., Huib A.M. Kerstjens, M.D., Ph.D., Eva M. van Rikxoort, Ph.D., and Dirk-Jan Slebos, M.D., Ph.D.

CONCLUSIONS

Endobronchial-valve treatment significantly improved pulmonary function and exercise capacity in patients with severe emphysema characterized by an absence of interlobar collateral ventilation. (Funded by the Netherlands Organization for Health Research and Development and the University Medical Center Groningen; Netherlands Trial Register number, NTR2876.)
### STELVIO Study: EBV

**Table 2. Mean Change from Baseline to 6 Months of Follow-up in Primary Efficacy Outcomes in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>EBV Group (N = 34)</th>
<th>Control Group (N = 34)</th>
<th>Between-Group Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milliliters (95% CI)</td>
<td>161 (80 to 242)</td>
<td>21 (−9 to 52)</td>
<td>140 (55 to 225)</td>
<td>0.002</td>
</tr>
<tr>
<td>Percentage (95% CI)</td>
<td>20.9 (11.1 to 30.7)</td>
<td>3.1 (−0.4 to 6.6)</td>
<td>17.8 (7.6 to 28.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Response rate — %</td>
<td>59</td>
<td>24</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td>Change in FVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milliliters (95% CI)</td>
<td>416 (201 to 631)</td>
<td>69 (−50 to 187)</td>
<td>347 (107 to 588)</td>
<td>0.005</td>
</tr>
<tr>
<td>Percentage (95% CI)</td>
<td>18.3 (9.3 to 27.3)</td>
<td>4.0 (−0.7 to 8.6)</td>
<td>14.4 (4.4 to 24.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Change in distance on 6-min walk test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meters (95% CI)</td>
<td>60 (35 to 85)</td>
<td>−14 (−25 to −3)</td>
<td>74 (47 to 100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage (95% CI)</td>
<td>19.6 (10.4 to 28.9)</td>
<td>−3.6 (−6.9 to −0.4)</td>
<td>23.3 (13.6 to 32.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Response rate — %</td>
<td>59</td>
<td>6</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Statistical and clinical significance**

NEJM, 2015

UT Southwestern Medical Center

The future of medicine, today.
At the expense of more complications (Pneumothorax!)

Table 3. Serious Adverse Events during 6 Months of Follow-up.*

<table>
<thead>
<tr>
<th>Event</th>
<th>EBV Group (N = 34)</th>
<th>Control Group (N = 34)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of serious events</td>
<td>23</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (3)‡</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>COPD exacerbation with hospitalization</td>
<td>4 (12)</td>
<td>2 (6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>6 (18)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Resolved ≤14 days after onset, without drainage</td>
<td>1 (3)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Resolved ≤14 days after onset, with drainage</td>
<td>2 (6)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Required temporary valve removal</td>
<td>1 (3)§</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Required permanent valve removal because of recurrent pneumonia</td>
<td>1 (3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax</td>
<td>1 (3)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
EMPROVE study: IBV

Initial trials with good safety profile and proof of concept
Unilateral lobar bronchoscopic volume reduction for emphysema using IBV system (one way valve, intact interlobar fissure, heterogeneous emphysema)
FEV1 < 45%, TLC > 100%, RV > 150%, PaCO2 < 55 mm Hg
Available protocols
EMPROVE study: IBV

EMPROVE: patient information

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Medical Center
IBV Protocol: Before and After
IBV Protocol: Before and After
Clinical Decision Making and Severe Emphysema Management at UTSW

Patient has severe COPD with FEV1 < 50%
Maximum medical therapy
Does the patient have significant emphysema on CT? what phenotype
Available Surgical options including LVRS and giant bullectomy?
Available clinical trials?
Abnormality on imaging requiring resection? + LVRS
Bridge to lung transplant
Lung transplant candidate? And evaluation
Patient preference and individualized care plans