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

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The future of medicine, today.

Conflict of Intersts to Declare: consultant for Bayer

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Outline

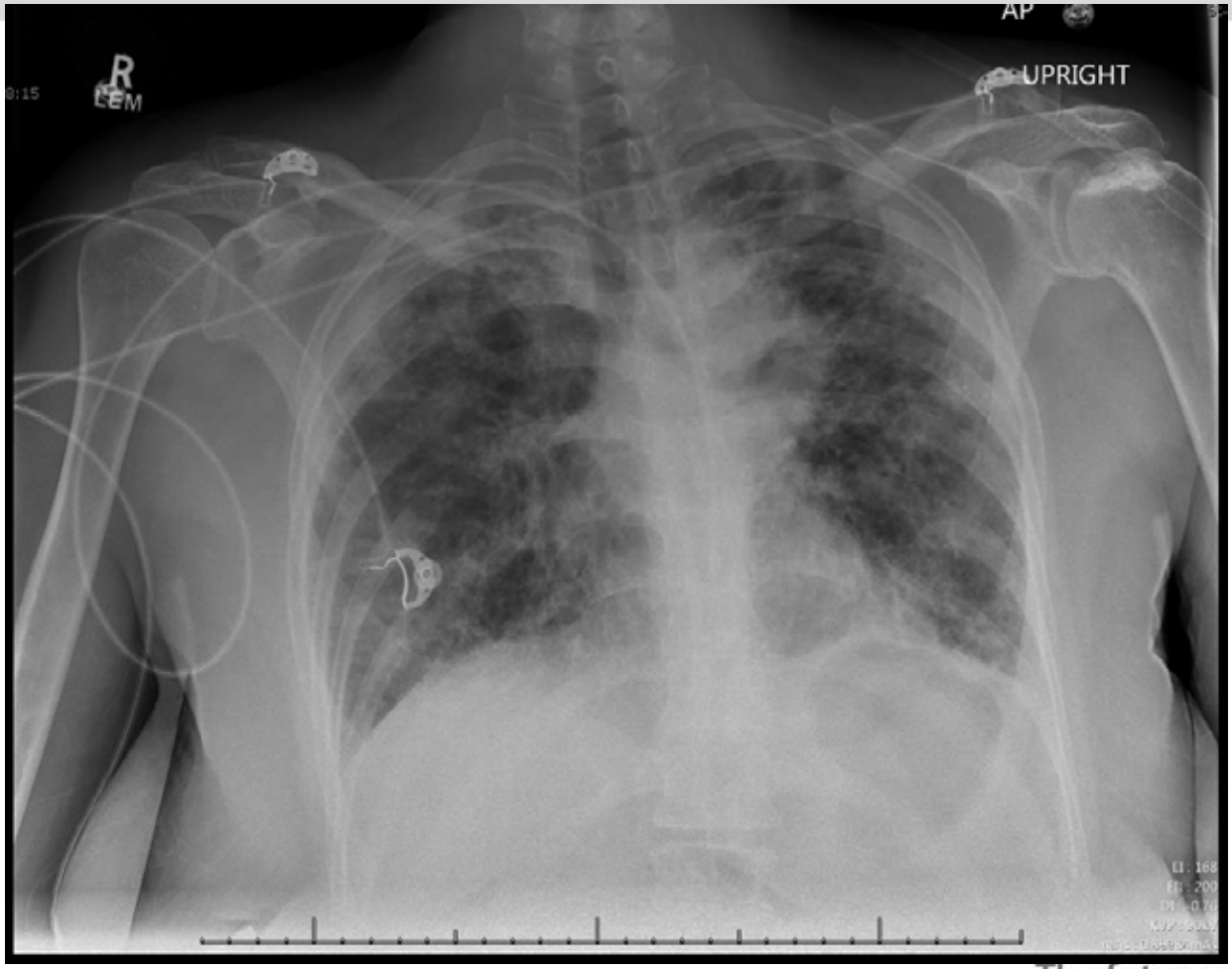
Lung Transplantation

- -pre-transplantation
- -peri-operative
- -post-transplant

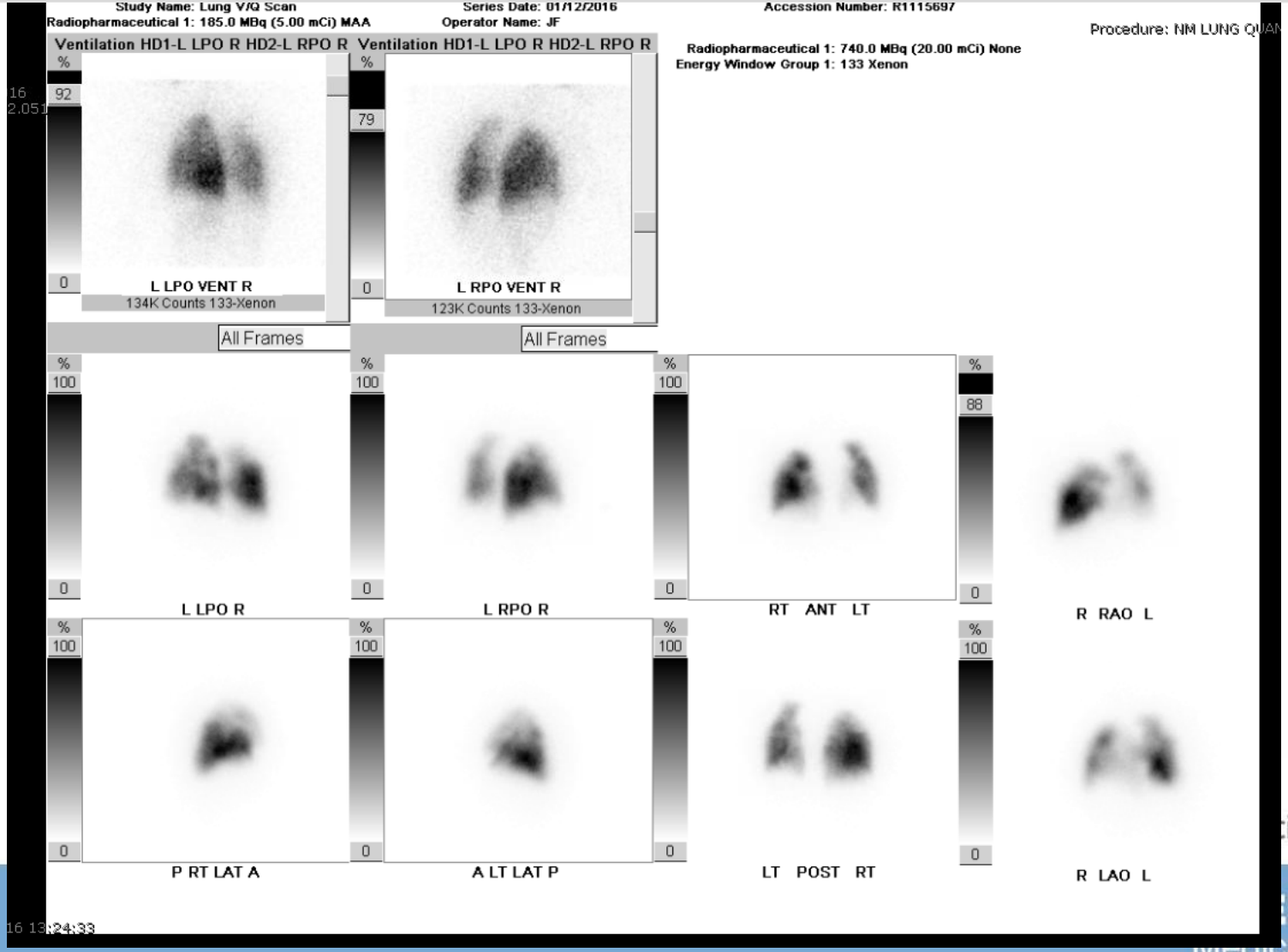
Pulmonary Hypertension

Lung Volume Reduction Surgery

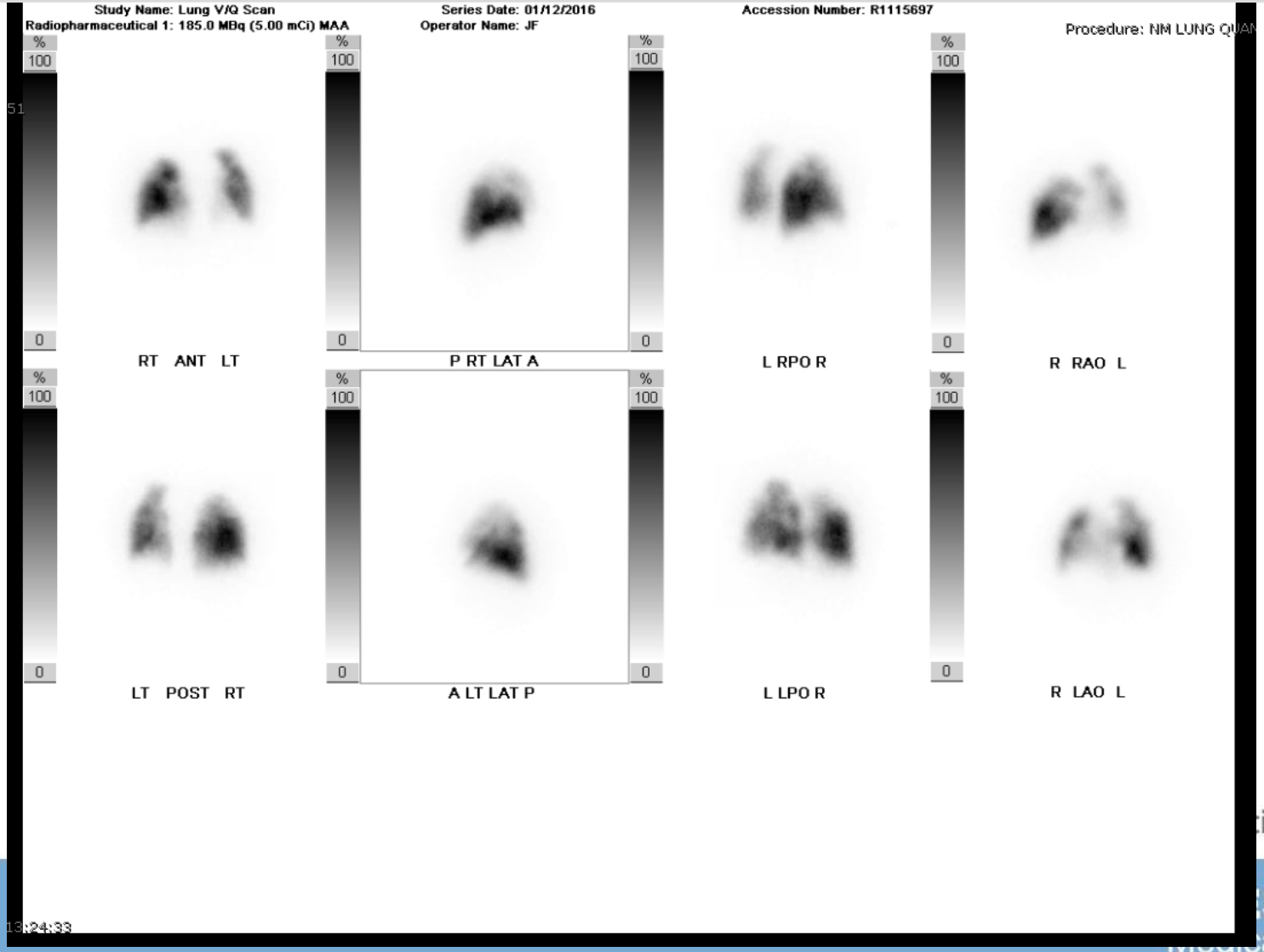
Pre-Transplant



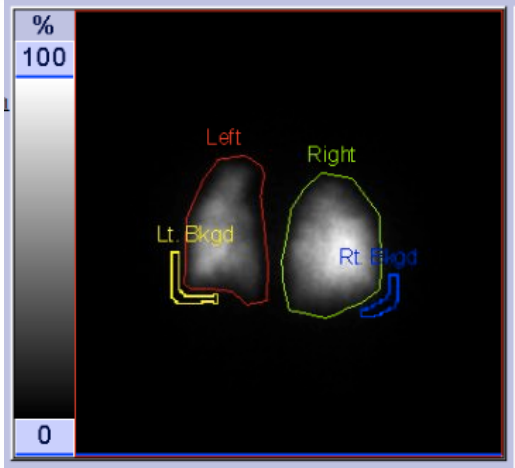
Pre-Transplant (cont.) - ventilation

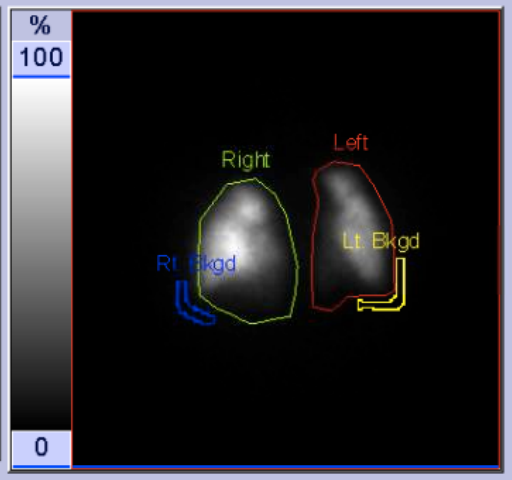


Pre-Transplant (cont.)- perfusion



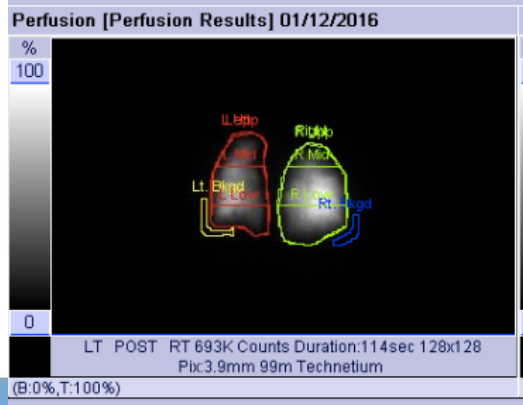
Pre-Transplant (cont.)

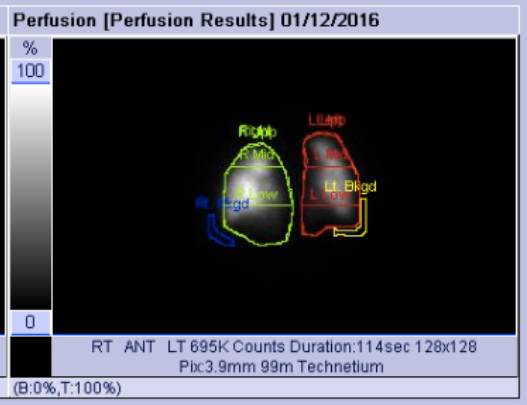




Geometric Mean		
(Counts)	Left	Right
Upper	044K	034K
Middle	127K	230K
Lower	029K	089K
Total	200K	353K

(% Ratios)	Left	Right
Upper	7.88	6.12
Middle	23.06	41.55
Lower	5.27	16.12
Total	36.21	63.79





Pre-Transplantation period

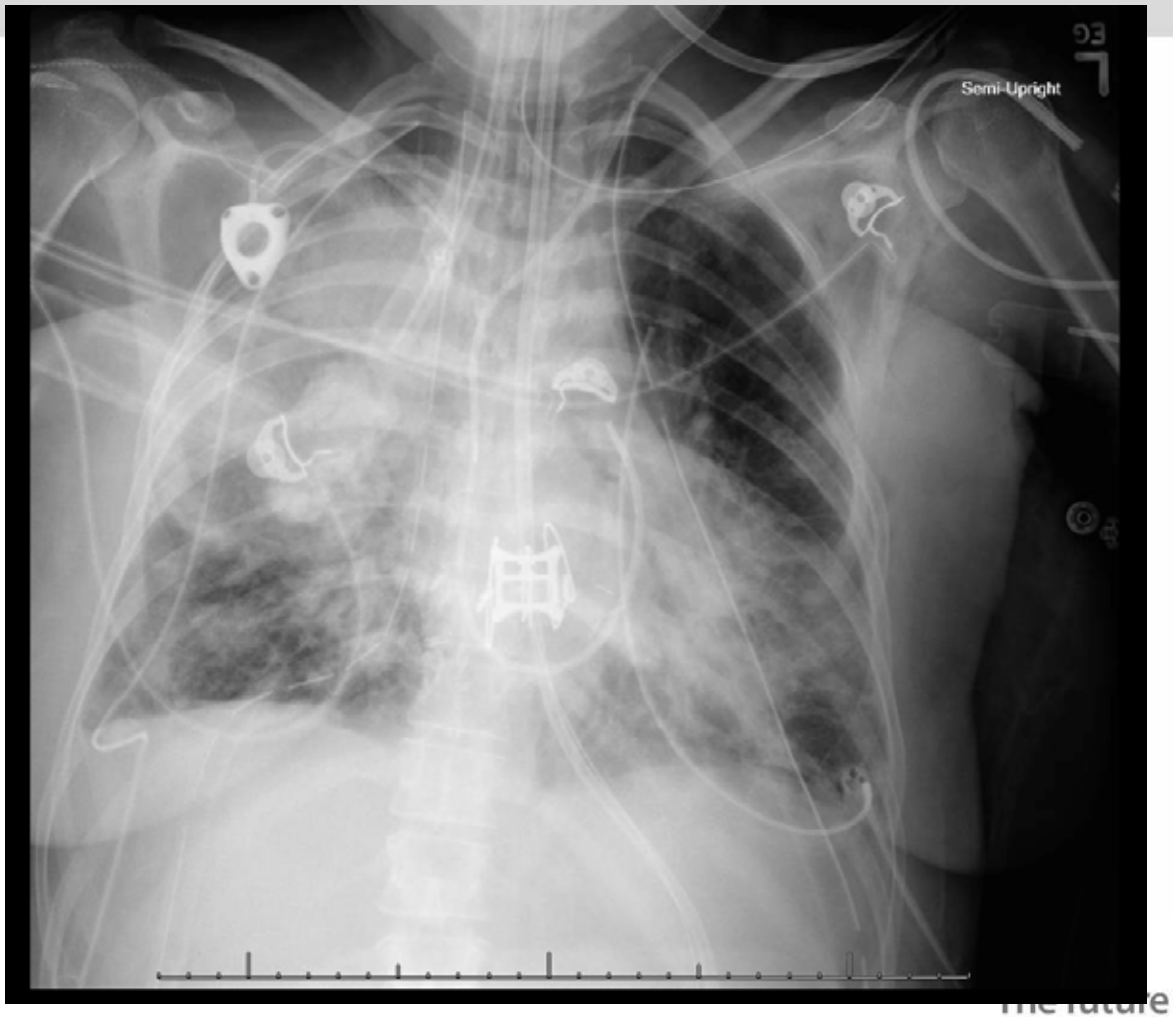
-Evaluation of right to left shunts
-Evaluation for PE or CTEPH
-Identify if there is a perfusion difference between the lungs

Peri-operative case #1

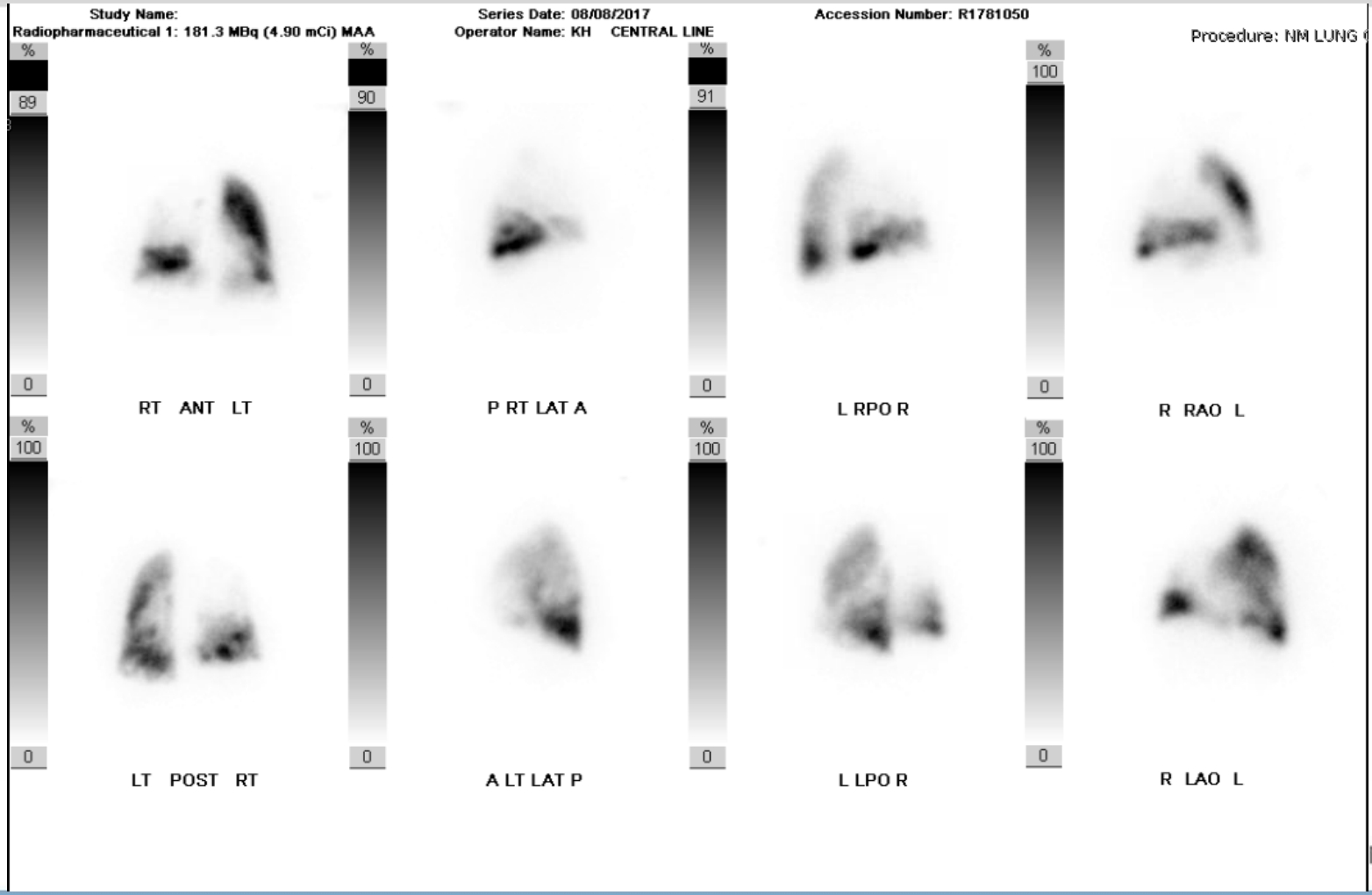
32 yo female with history of CF
-underwent bilateral lung transplantation off ECMO.
-bleeding during explantation, but oxygenation and hemodynamics were preserved.

-few days after transplant:
-right lung has infiltrates.

Peri-operative- case #1 (cont.)



Peri-operative case #1 (cont.)



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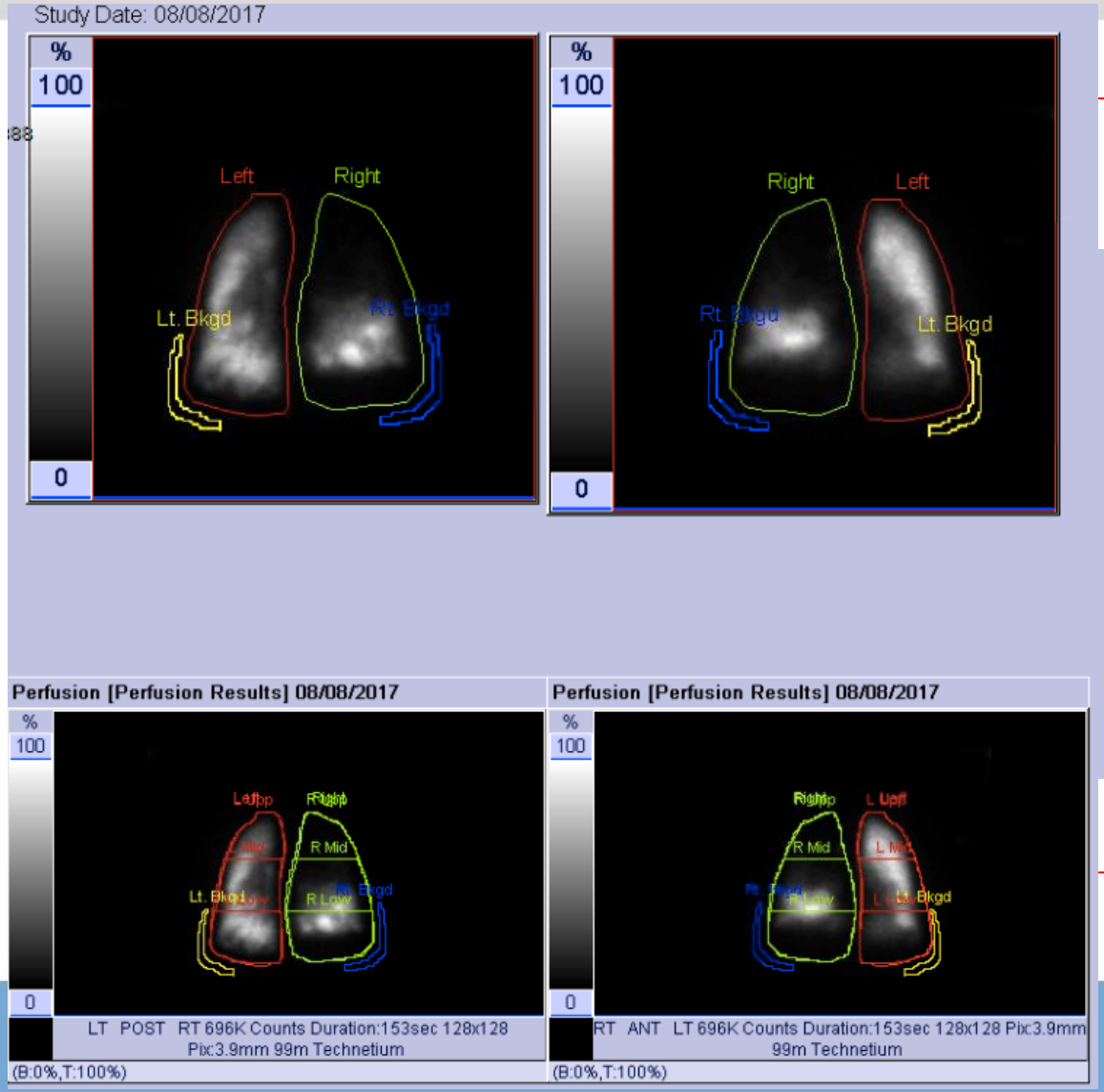
Peri-operative case #1 (cont.)



Geometric Mean (Counts)	Left	Right
Upper	102K	006K
Middle	166K	131K
Lower	110K	083K
Total	378K	220K

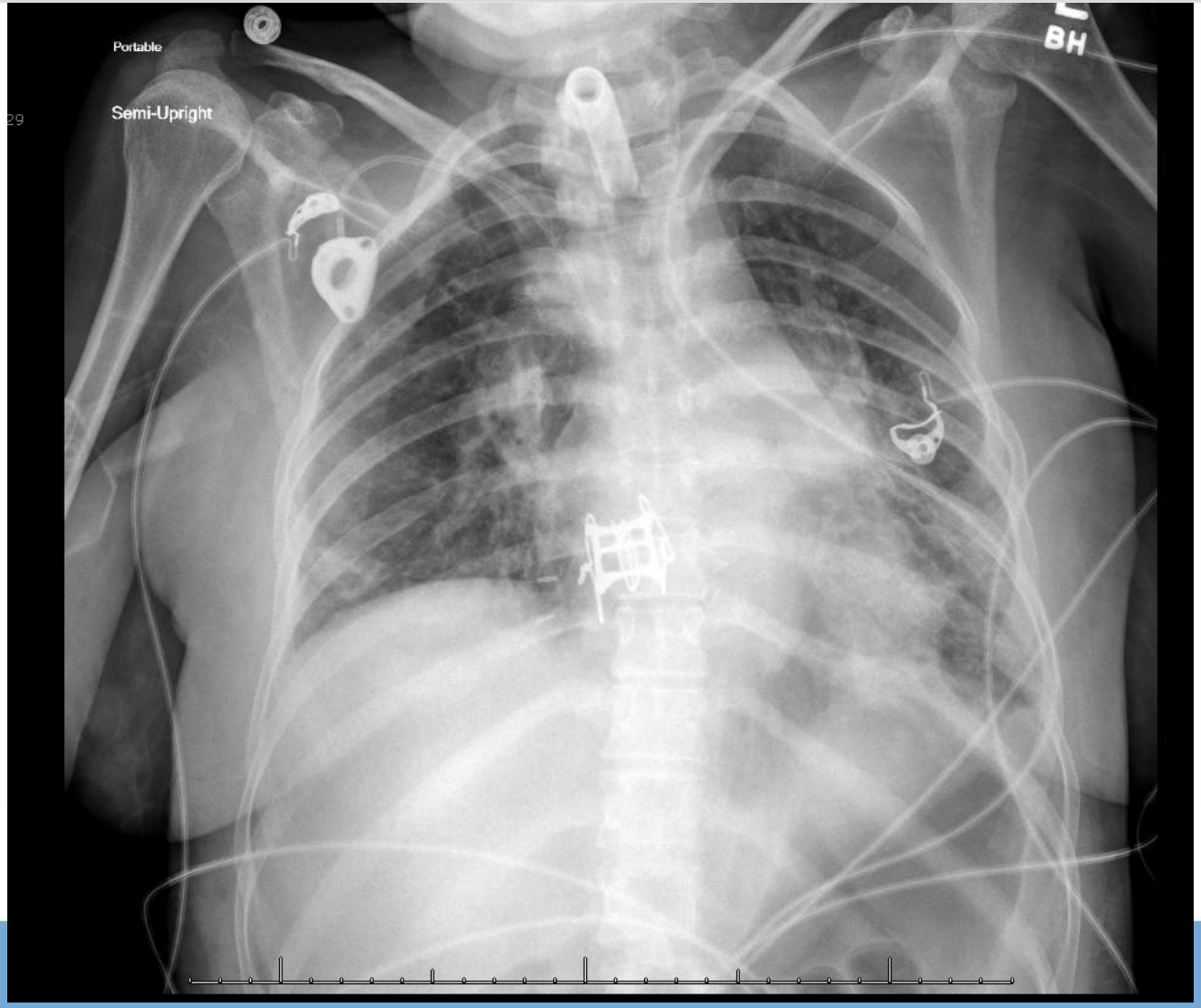
(% Ratios)	Left	Right
Upper	17.00	0.97
Middle	27.84	21.93
Lower	18.34	13.93
Total	63.18	36.82

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

Peri-operative case #2

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.

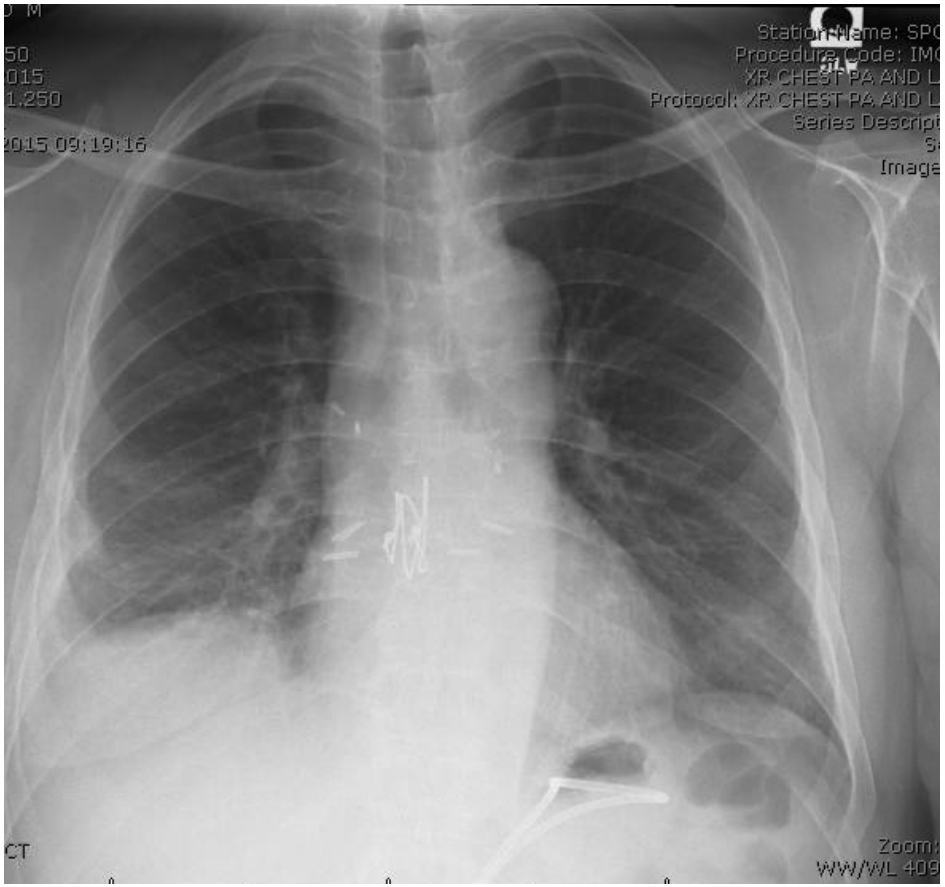
Peri-operative case #2 (cont.)

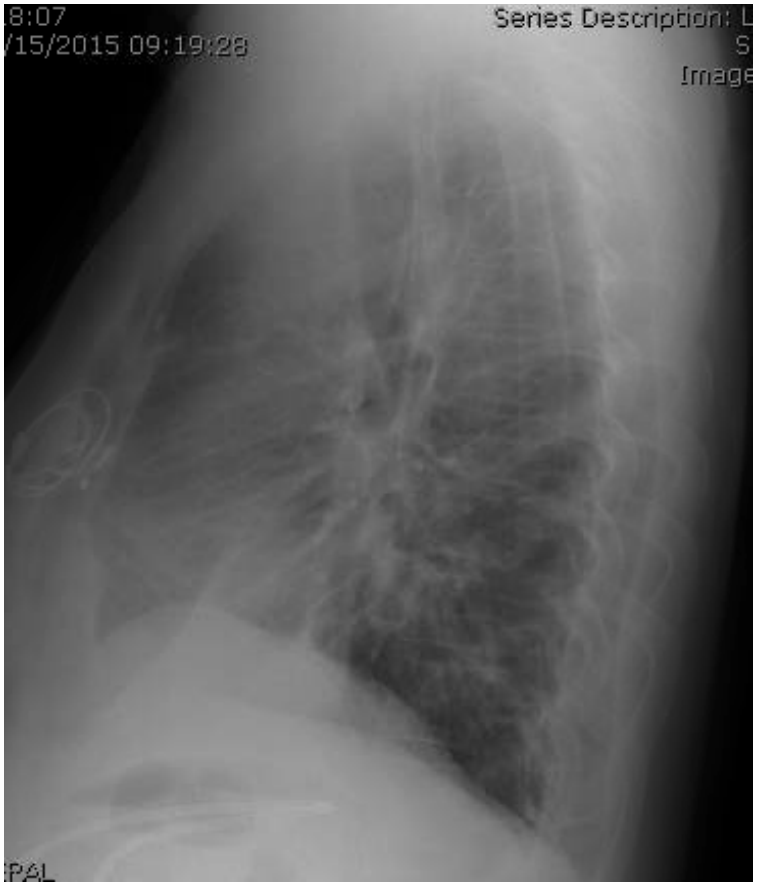
Stenosis of the left main pulmonary due to a kink at the anastomosis. Lesion required surgical repair.

Peri-operative period

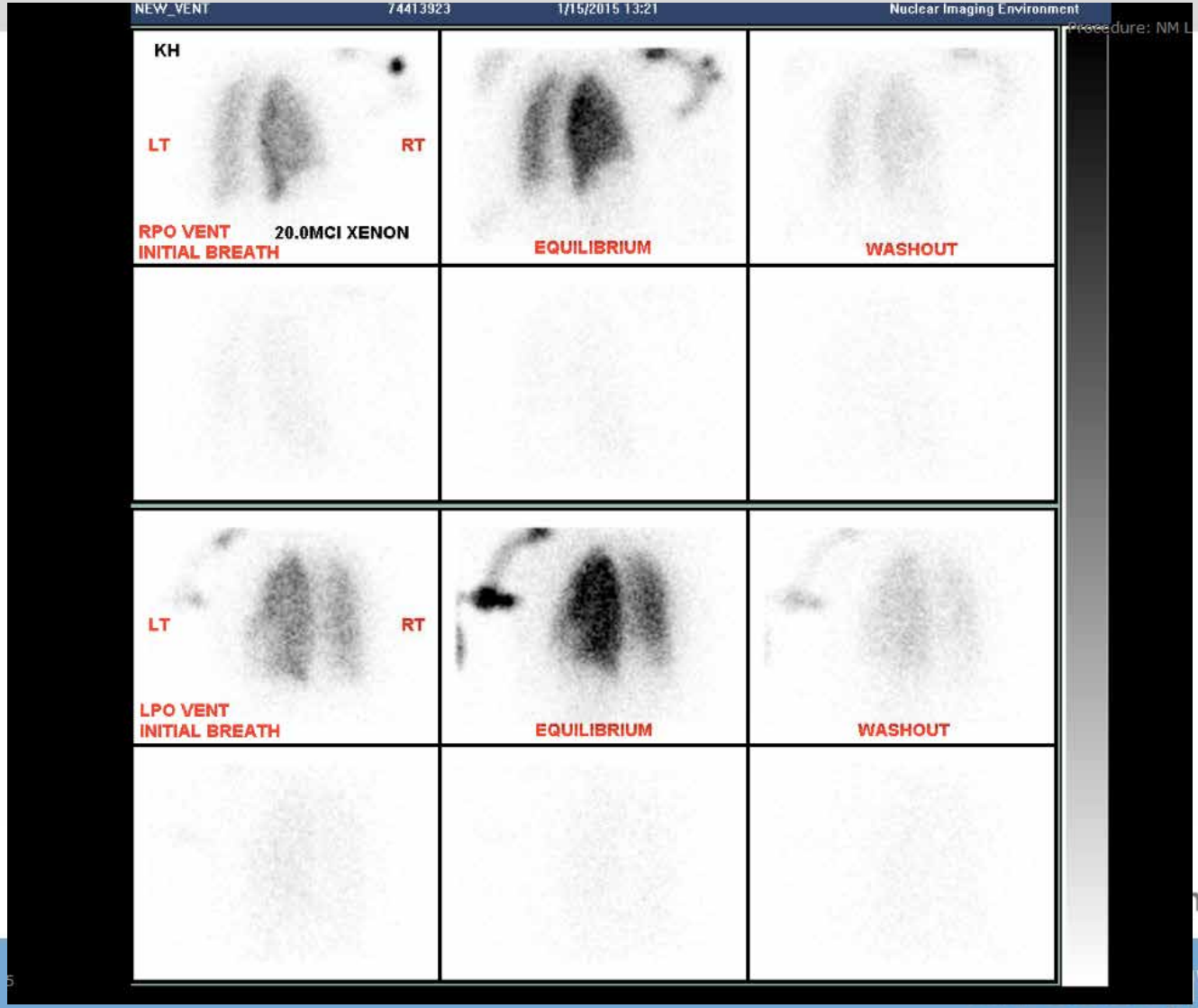
-evidence of poor lung performance with poor perfusion
-evidence of vasculature injury

Post-Transplant

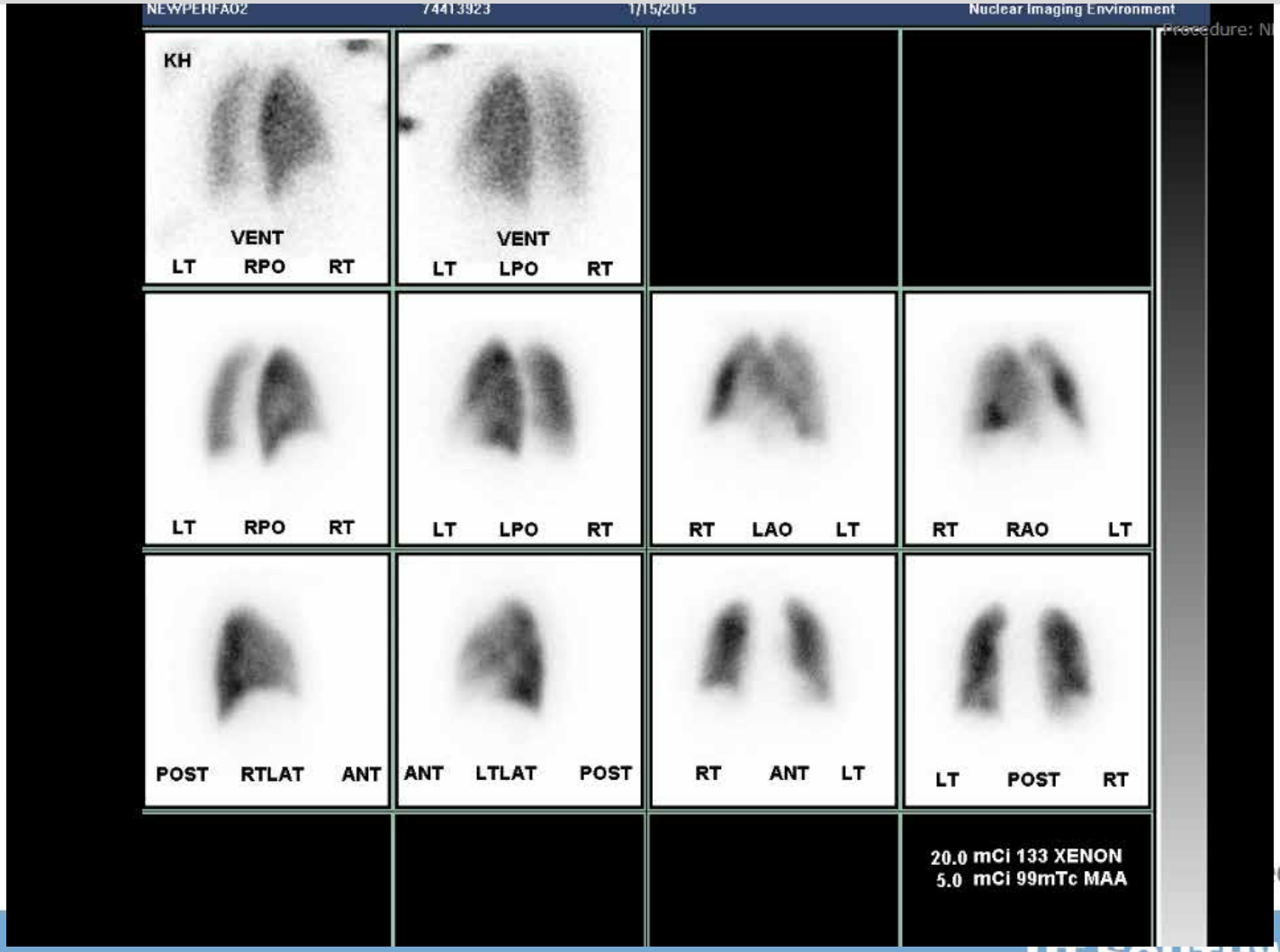




Post-Transplant

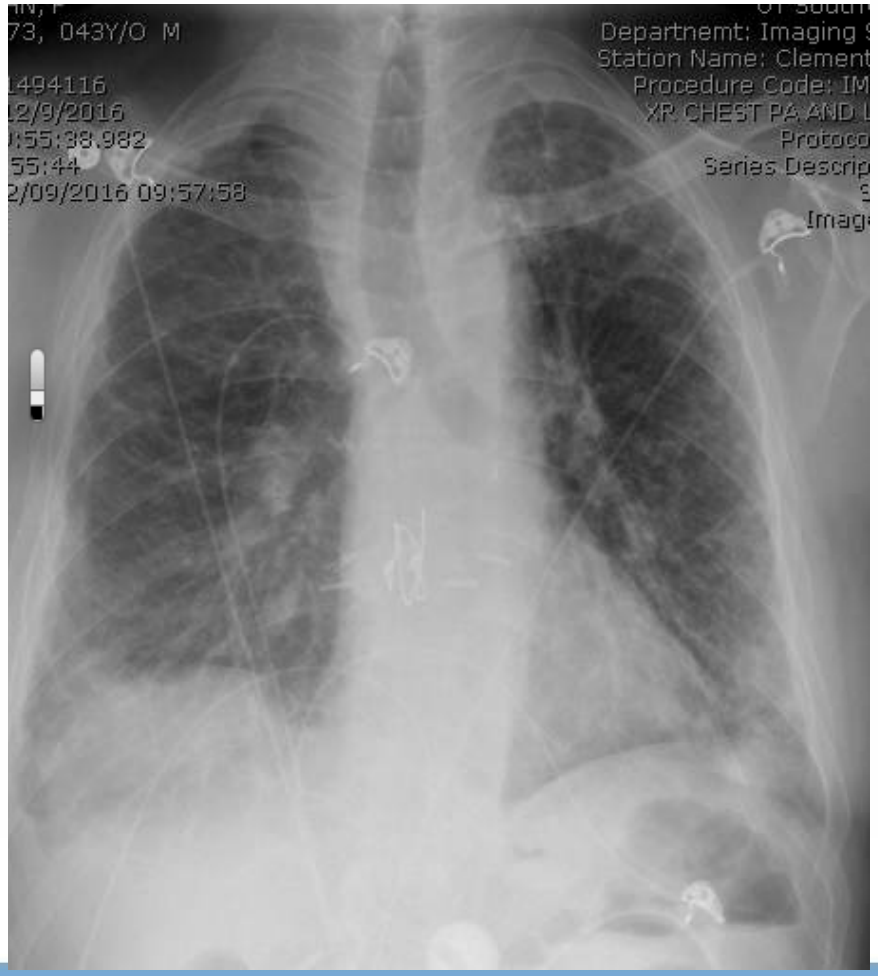


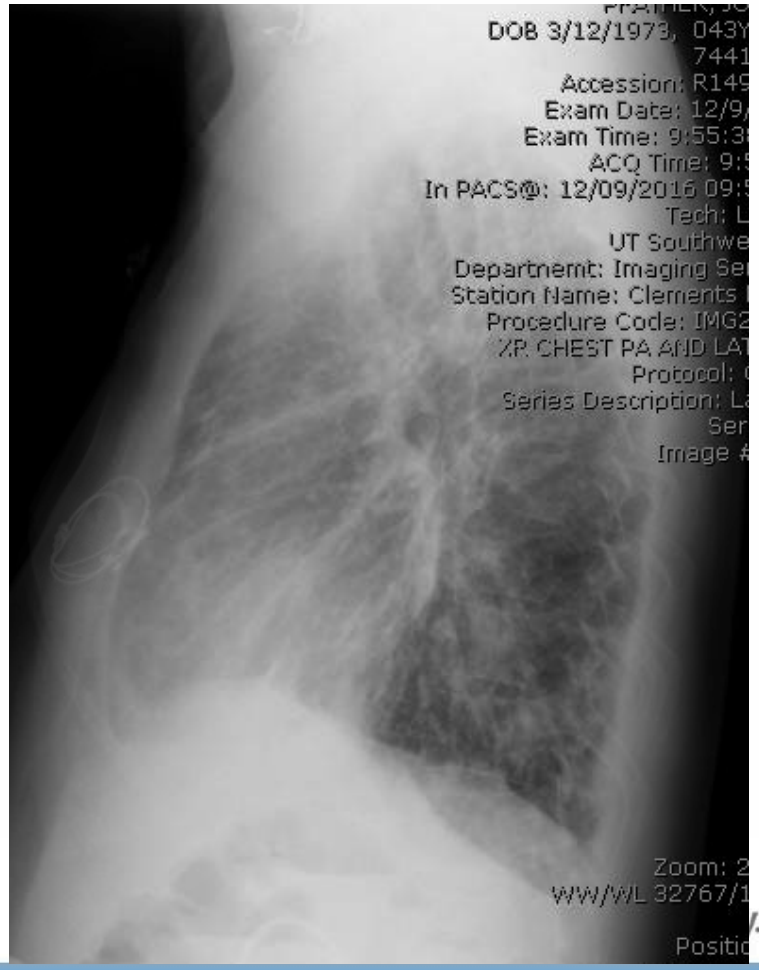
Post-Transplant



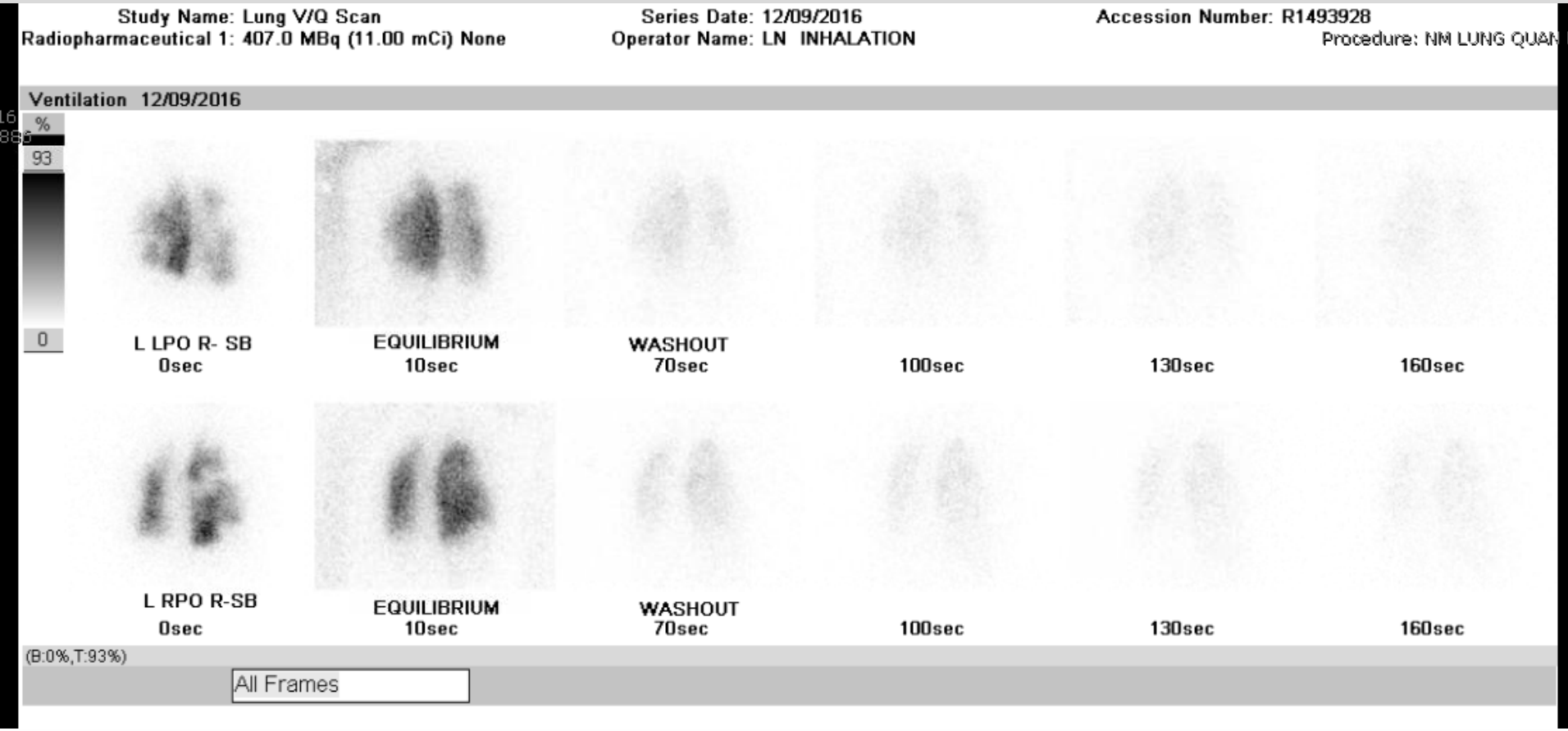
Post-Transplant

Post-Transplant- 1 year

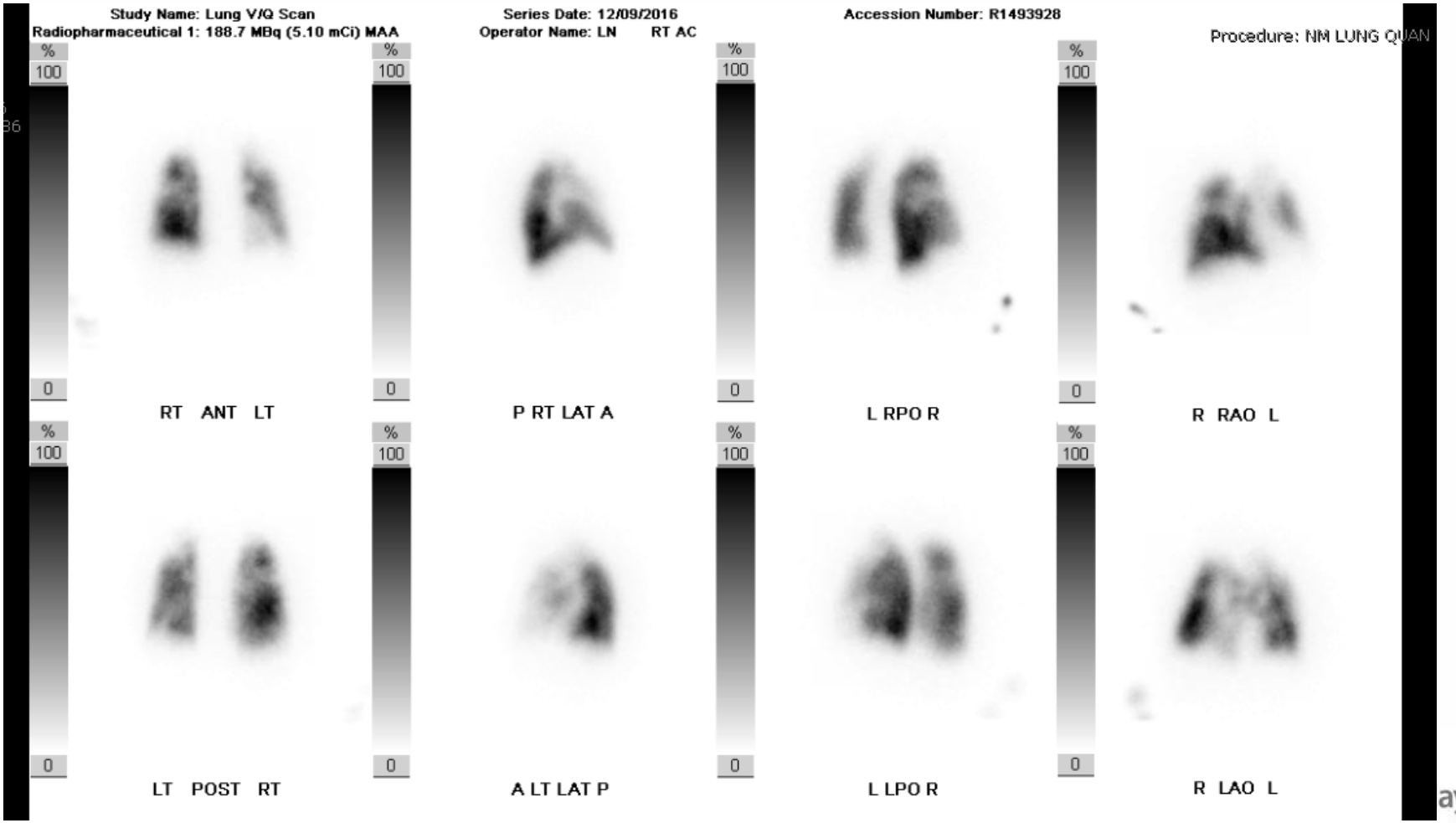




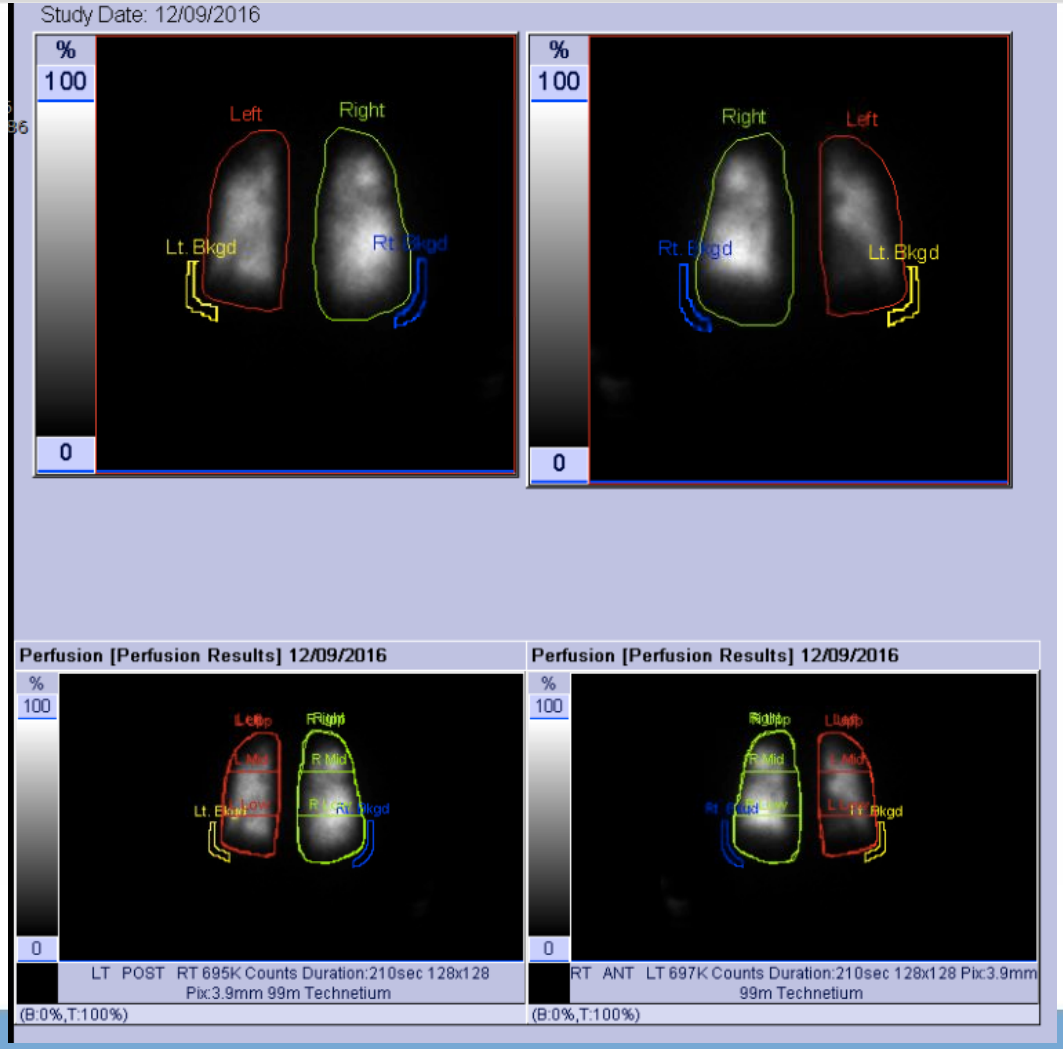
Post-Transplant- 1 year



Post-Transplant- 1 year



Post-Transplant- 1 year



Geometric Mean (Counts)	Left	Right
Upper	045K	066K
Middle	133K	202K
Lower	045K	103K
Total	223K	371K

(% Ratios)	Left	Right
Upper	7.66	11.16
Middle	22.32	34.00
Lower	7.57	17.29
Total	37.55	62.45

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

PHA Center of Comprehensive Care

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Elevated Pulmonary Artery Pressures Are Seen in Wide Range of Conditions

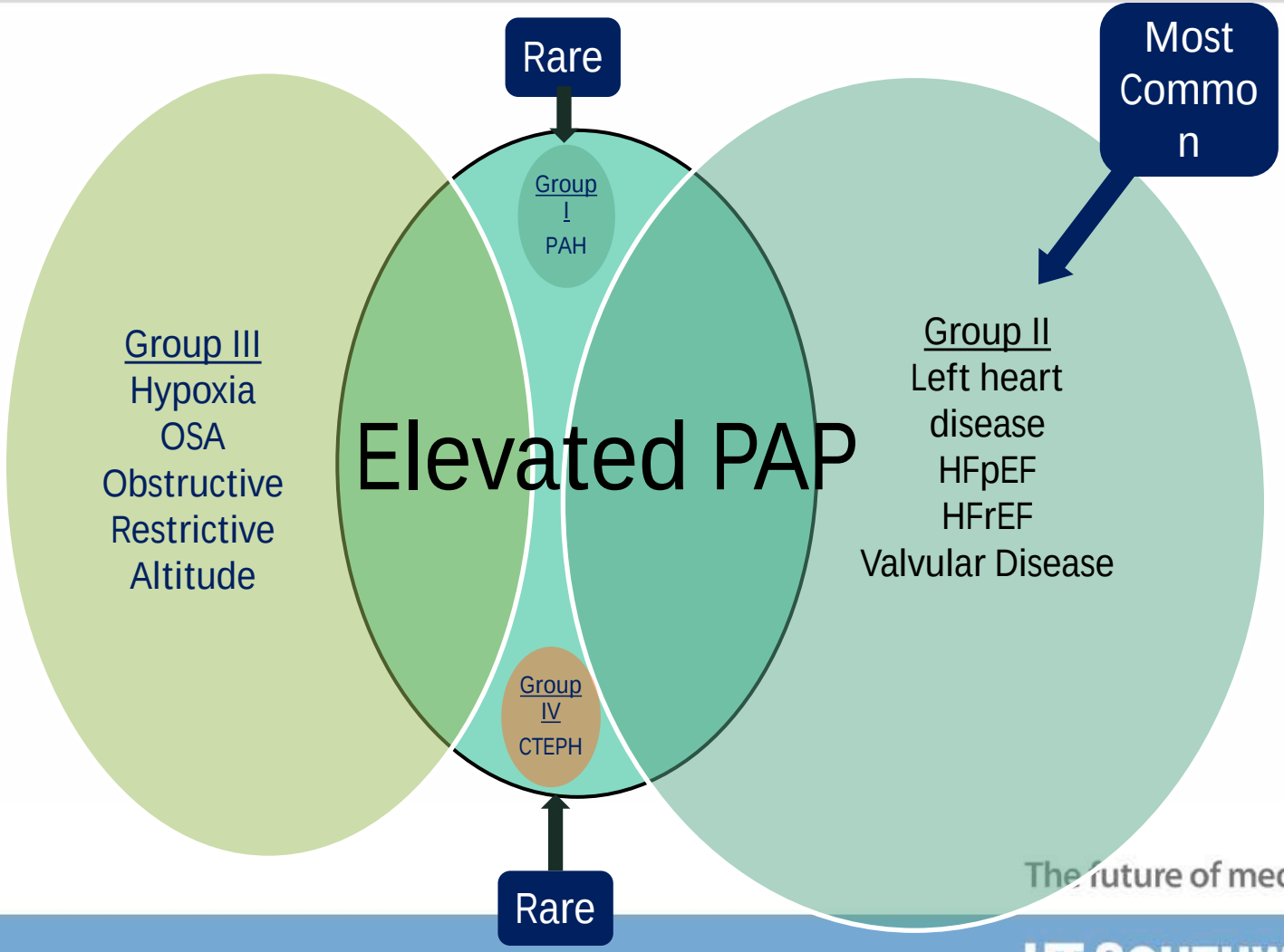


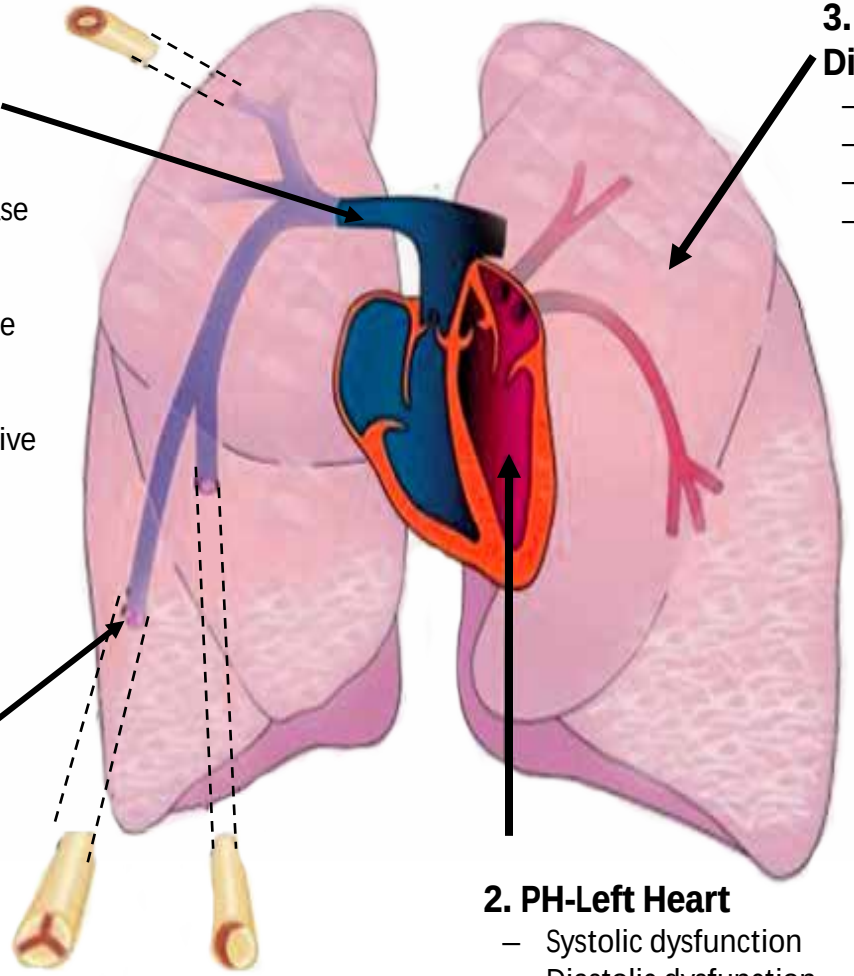
Image courtesy of Jean Elwing, MD.

5th World Symposium on Pulmonary Hypertension Classification Scheme

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 haemagiomatosis

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



4. Chronic Thromboembolic Pulmonary Hypertension
- Operable
- Inoperable

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

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

Adapted from: Condliffe R, et al. *F1000Prime Rep*. 2015;7:06.

Material Removed From Right and Left Pulmonary Arteries by PTE

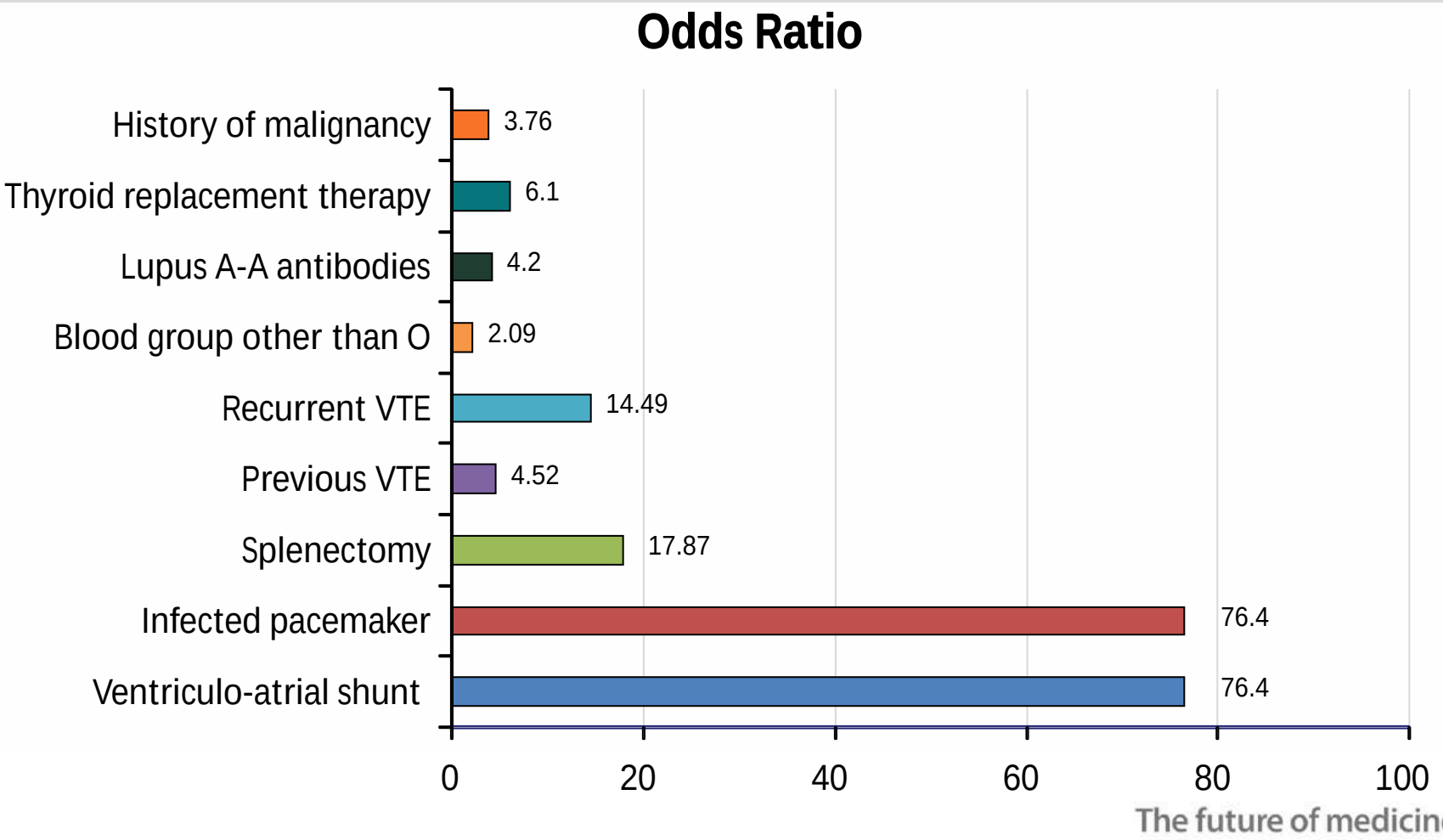
Case Example: Resulted in normal post-operative hemodynamics

Auger WR, et al. *Clin Chest Med.* 2010;31:741-758.

Potential Scope of the Problem

1 million	Estimated annual cases of acute pulmonary embolism (PE) in the United States
100,000 – 200,000	Estimated annual deaths from acute PE
~1%	Estimated rate of development of CTEPH from persistent or unresolved PE
8,000 – 9,000	Potential CTEPH burden in the United States annually

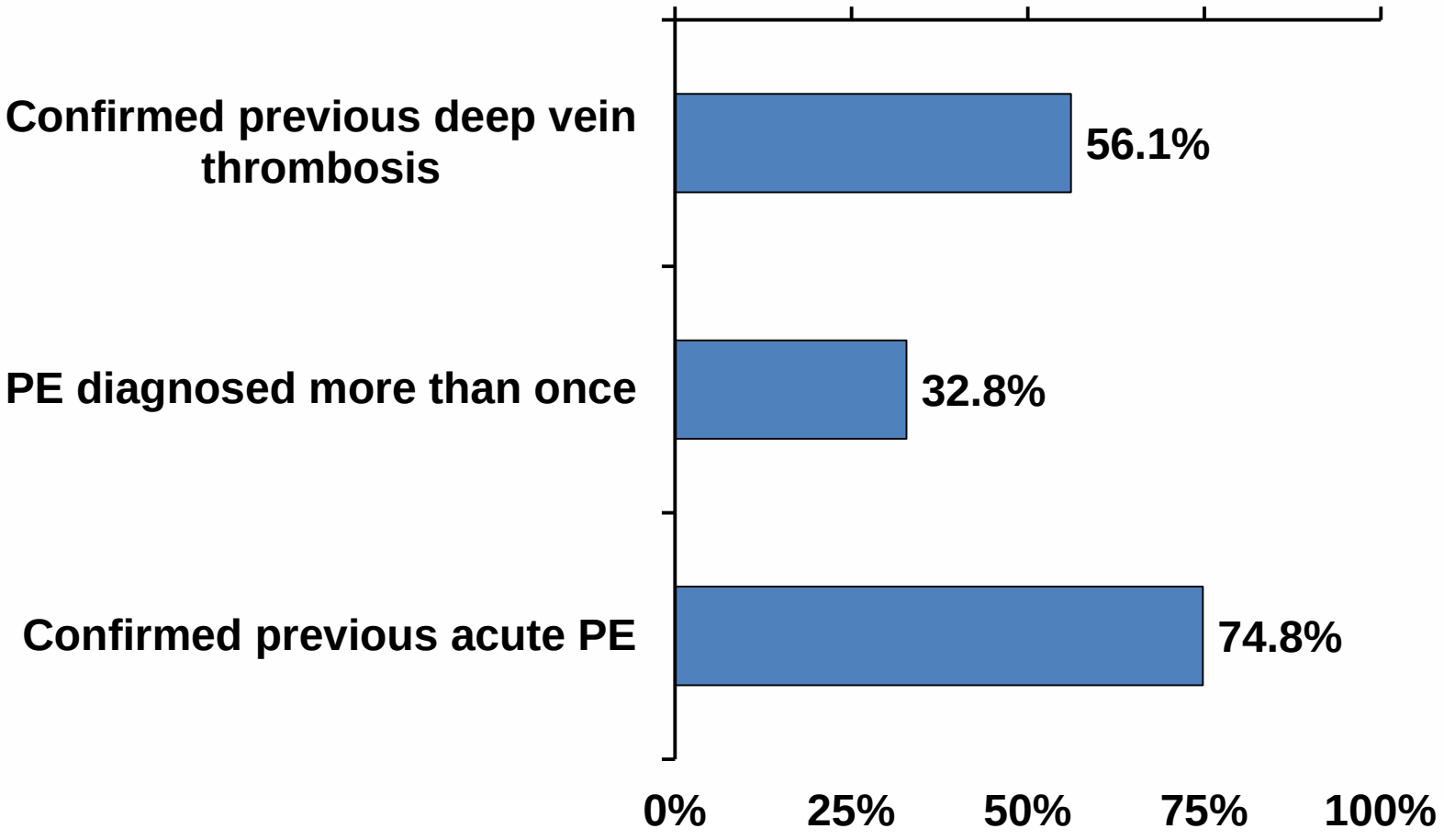
Risk Factors for CTEPH



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

Bonderman D, et al. *Eur Respir J.* 2009;33:325-331.

International CTEPH Registry: Patient History of Pulmonary Embolism



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

Pepke-Zaba J, et al. *Circulation.* 2011;124:1973-1981.

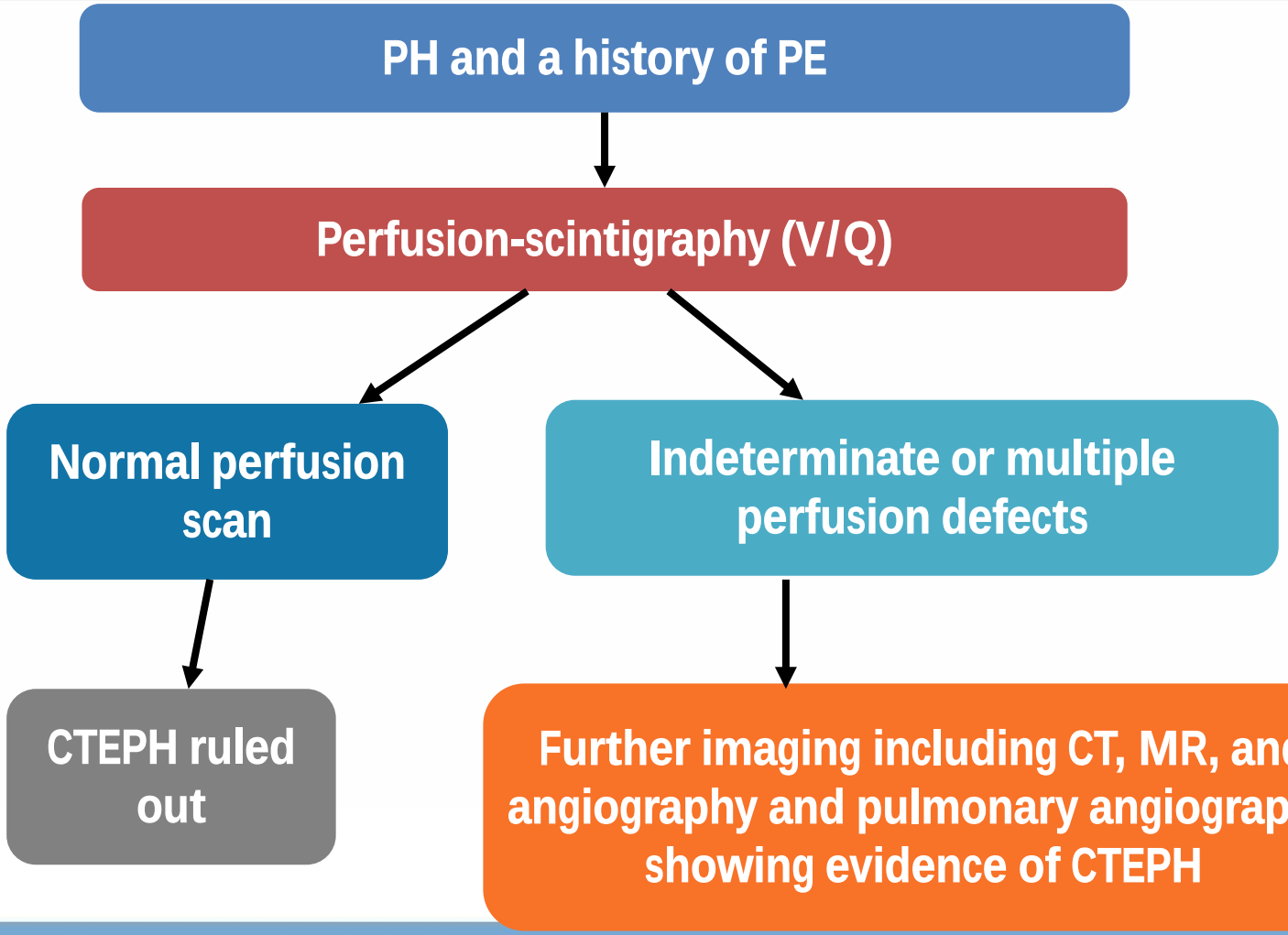
Natural History/Survival

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

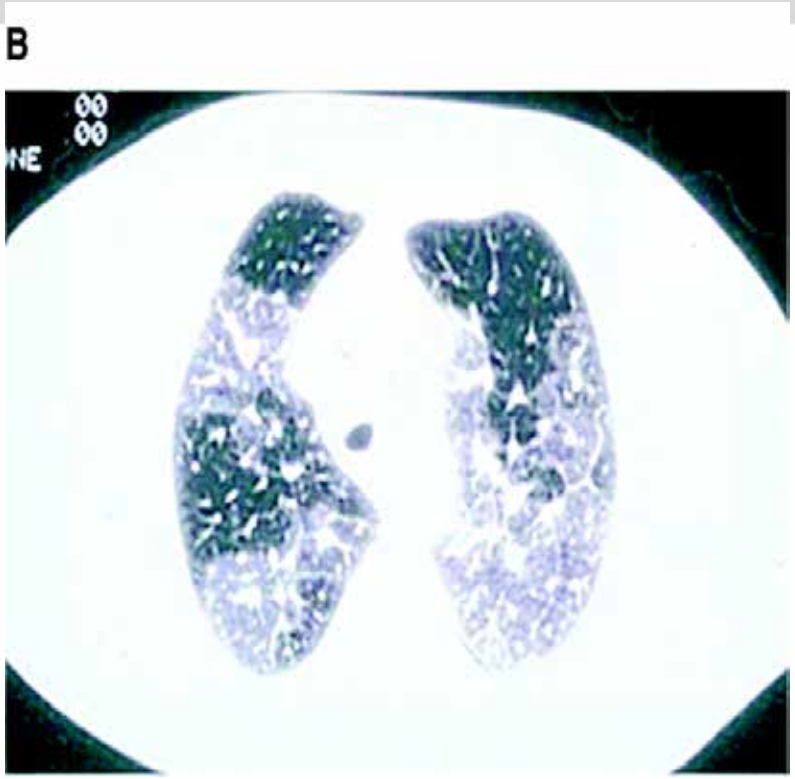
Diagnostic Algorithm for CTEPH



Hoeper MM, et al. *J Am Coll Cardiol.* 2009;54(1 Suppl):S85-S96.

Chest CT Scans in CTEPH

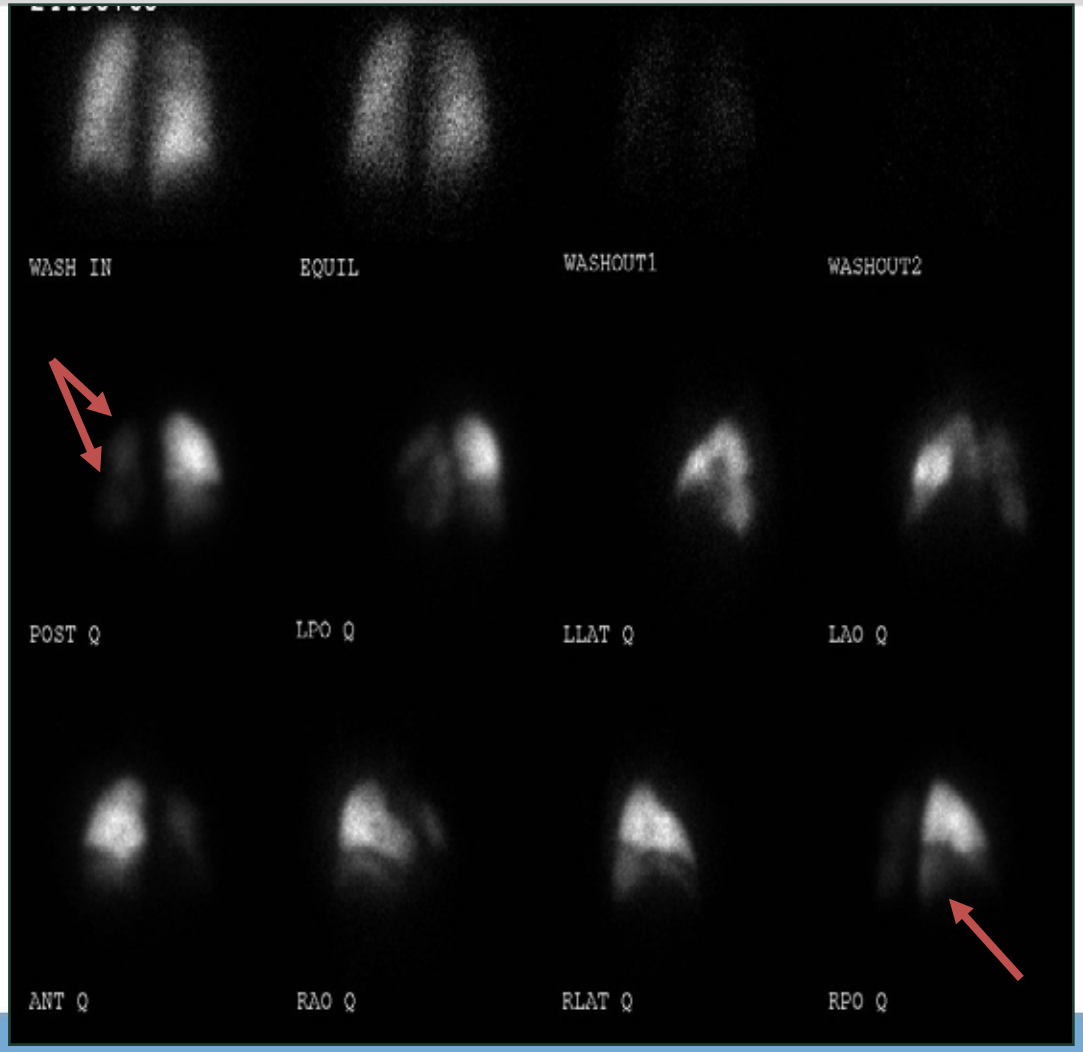
A: Eccentric thrombotic material within the pulmonary arteries



B: Characteristic mosaic attenuation of the pulmonary parenchyma with the darker areas corresponding to the hypo-perfused lung sections

Hoeper MM, et al. *Circulation*. 2006;113:2011-2020.

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

Auger WR, et al. *Clin Chest Med.* 2010;31:741-758.

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

	V/Q High-Probability Scans	CTPA
Sensitivity	96.2%	51.3%
Specificity	94.6%	99.3%
Accuracy	95.2%	82.8%
Negative Predictive Value	97.9%	79.7%
Positive Predictive Value	90.3%	97.6%

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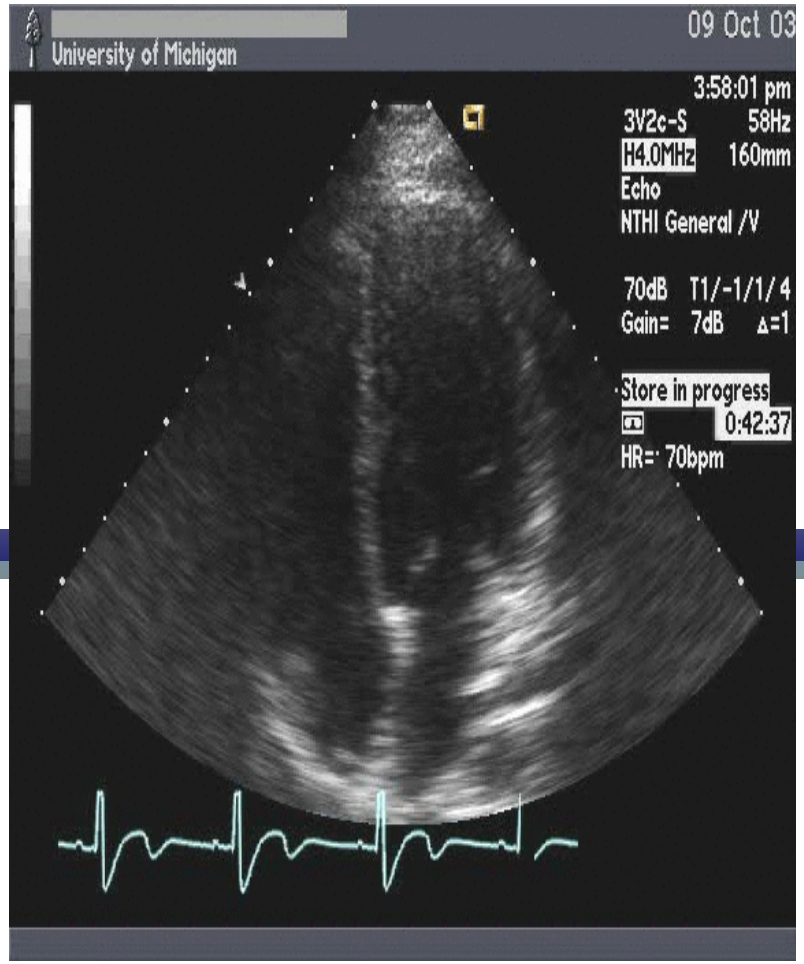
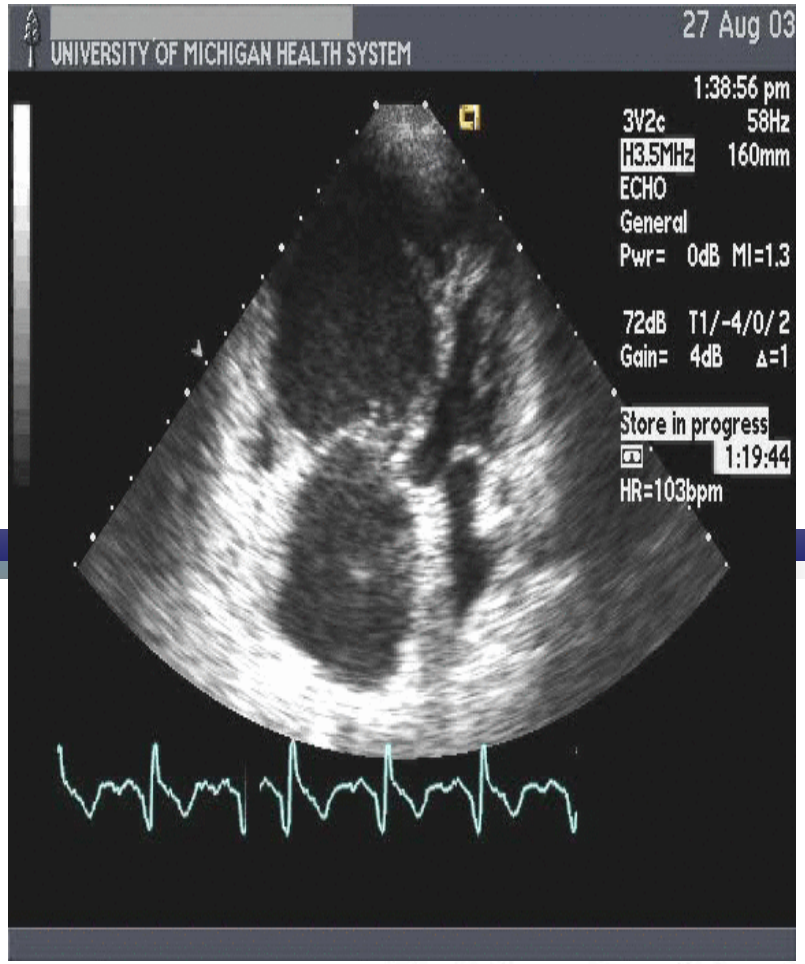
N=227 undergoing both V/Q and CTPA at a single center.

Tunariu N, et al. *J Nucl Med.* 2007;48:680-684.

Echocardiogram: Apical Four Chamber



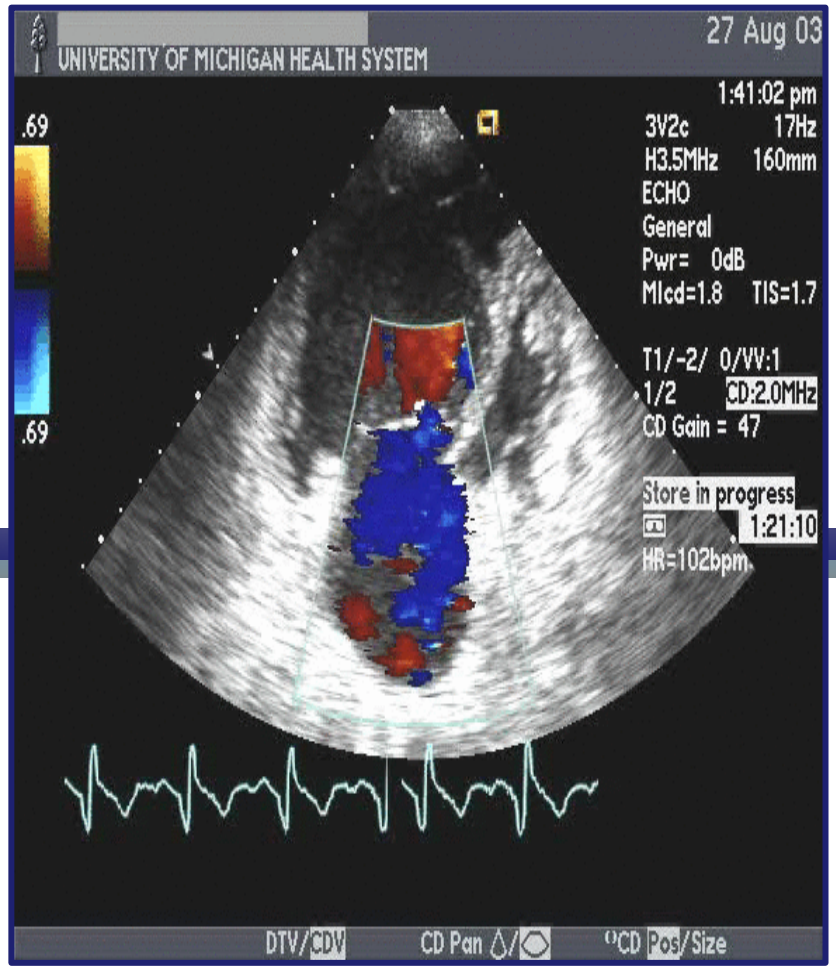
Normal structure and function



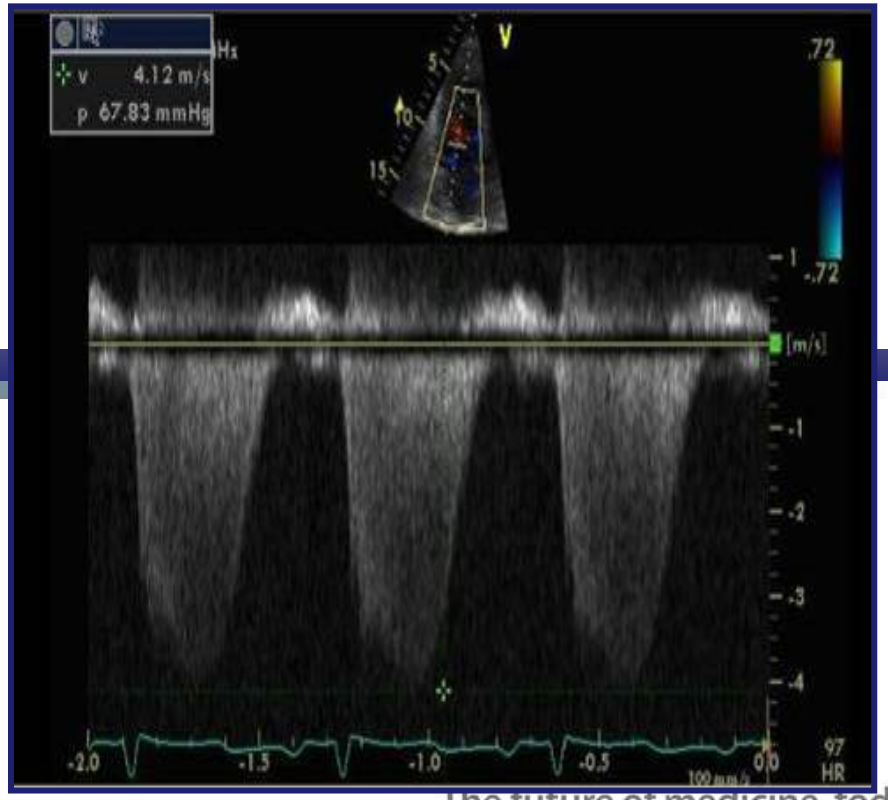
Abnormal structure and function

Image courtesy of Vallerie McLaughlin, MD

Echocardiogram: Tricuspid Regurgitation



Modified Bernoulli Equation:
4 x (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.

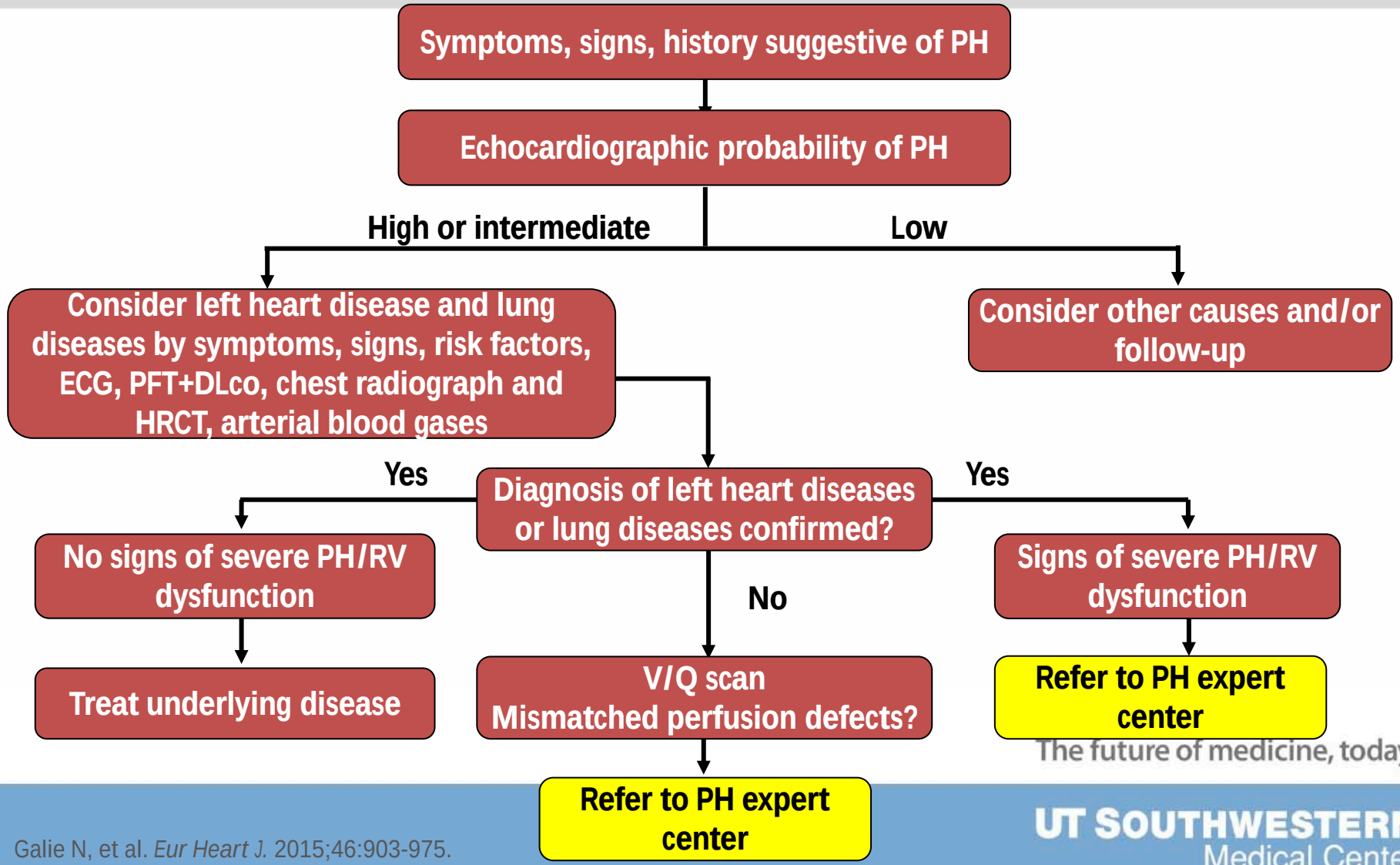
Image courtesy of Vallerie McLaughlin, MD

Pulmonary Angiogram

Case Example: Bilateral proximal CTE disease

Auger WR, et al. *Clin Chest Med.* 2010;31:741-758.

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



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Galie N, et al. *Eur Heart J.* 2015;46:903-975.

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Initial Evaluation of Patients With Suspected PH

ECG
Pulmonary function tests
Chest X-ray
Transthoracic echocardiography

Galie N, et al. *Eur Heart J.* 2009;30:2493-2537.

ECG Associated With Right Axis Deviation (RAD) and Right Ventricular Hypertrophy (RVH)

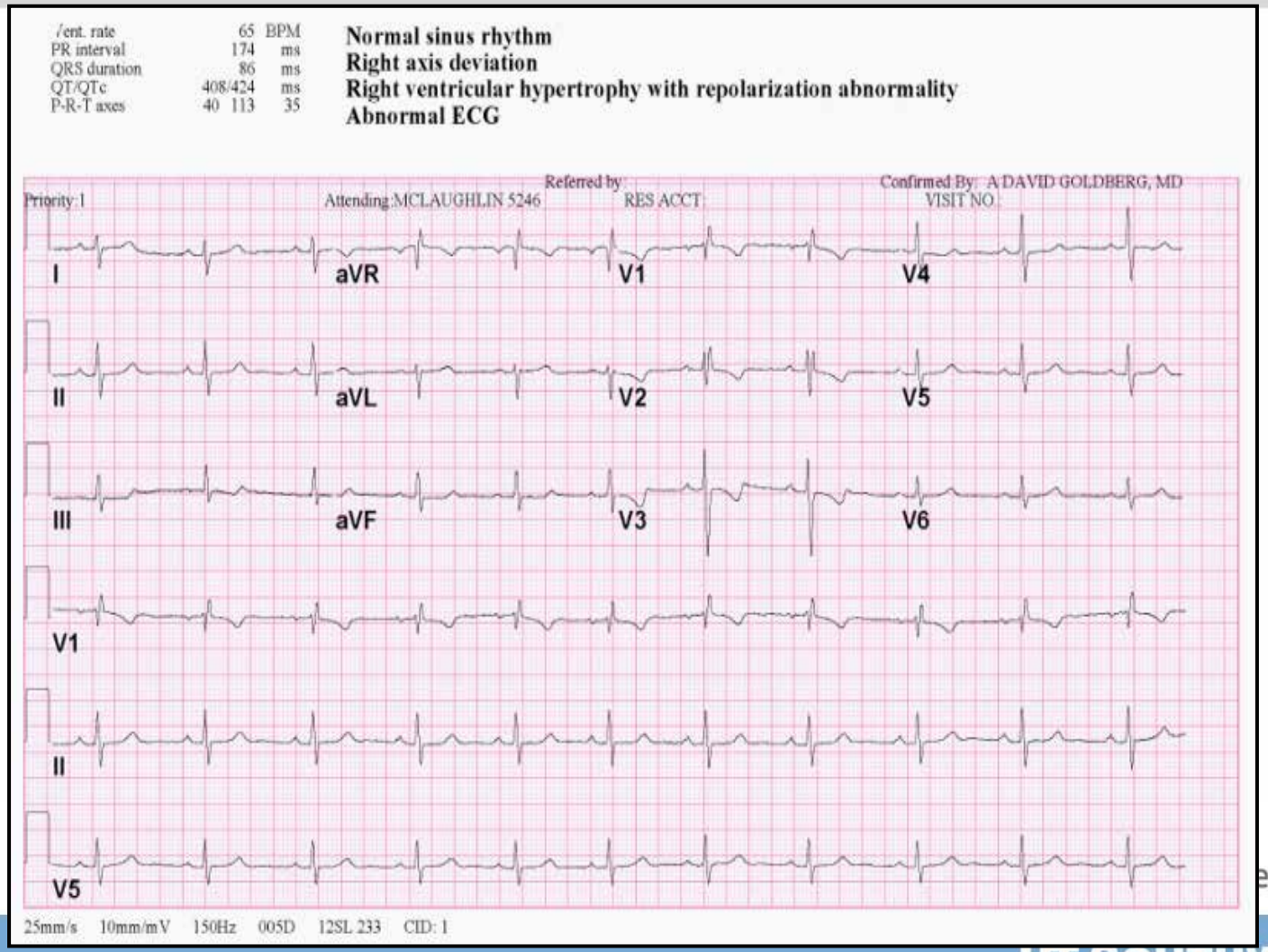
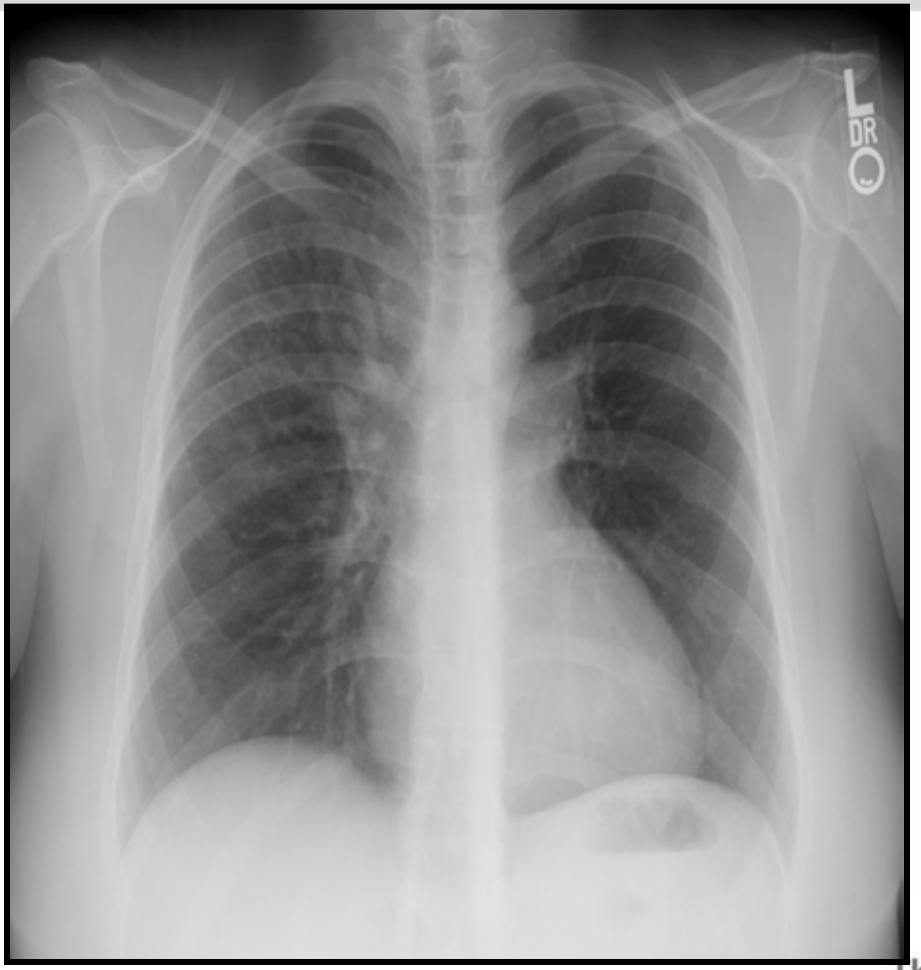


Image courtesy of Vallerie McLaughlin, MD.

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

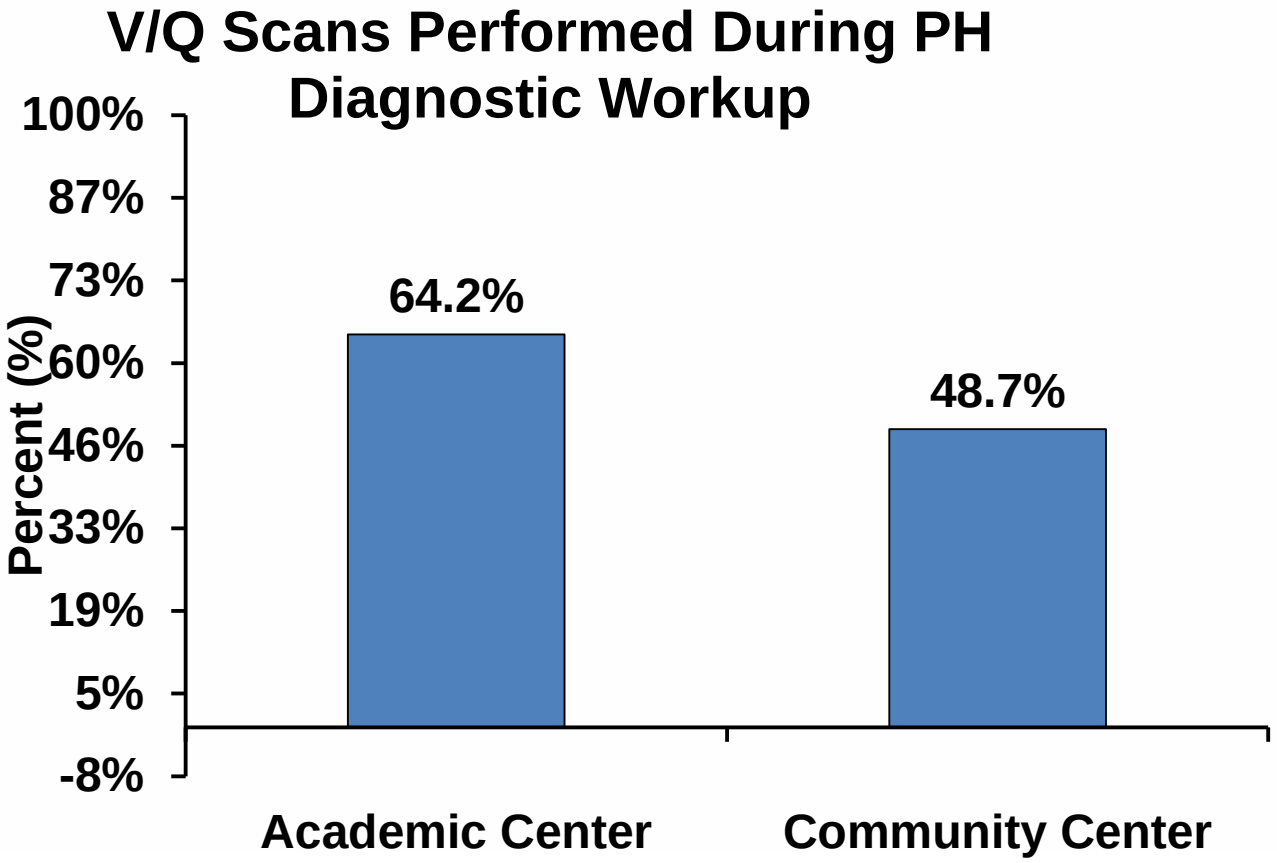
X-ray Findings Suggestive of CTEPH



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

Auger WR, et al. *Clin Chest Med.* 2010;31:741-758.

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



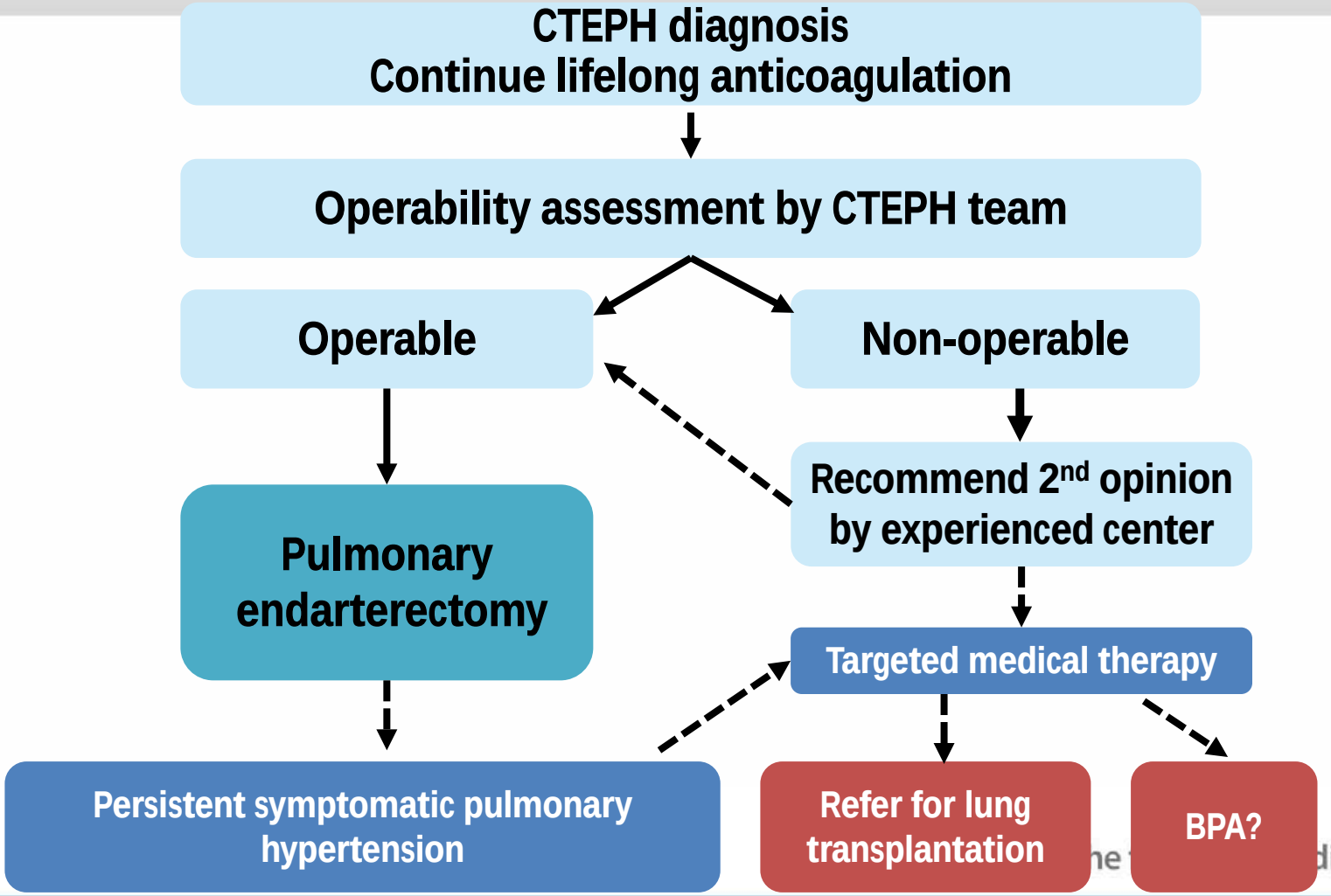
N=786 patients with PAH enrolled in QuERI database.

*P<0.0001 versus academic center.

McLaughlin VV, et al. *Chest*. 2013;143:324-332.

Treatment for CTEPH

Modified Treatment Algorithm for CTEPH

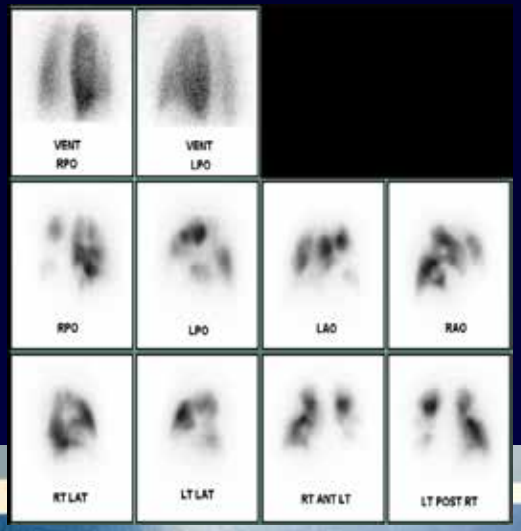


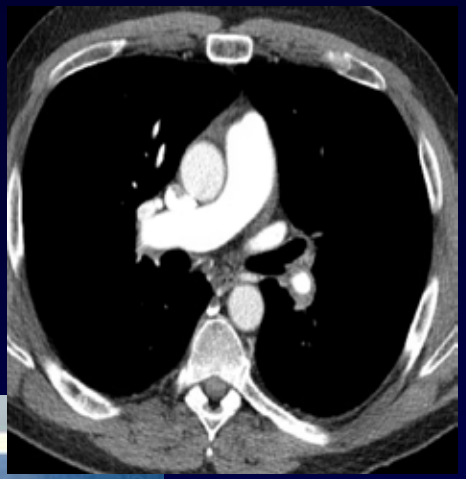
dicine, today.

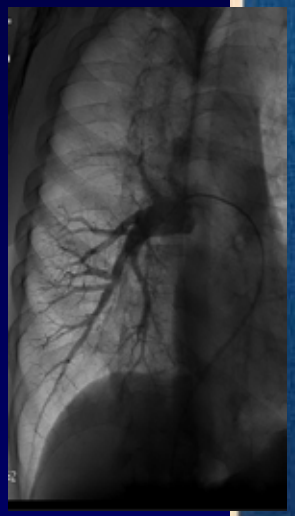
Kim NH, et al. *J Am Coll Cardiol.* 2013;62:D92-D99.

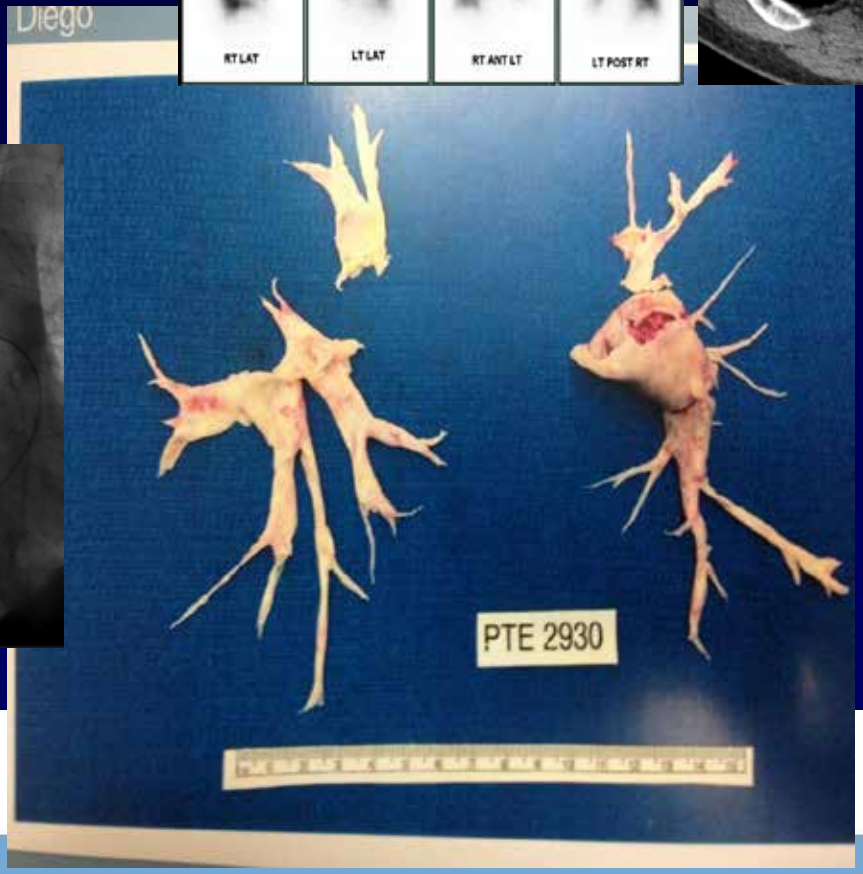
Criteria for Operability of CTEPH Lesions

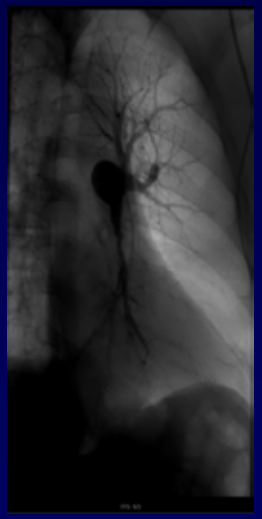
- 10% to 50% of patients may be deemed ineligible for PTE
  - Subjective and dependent on center experience
  - High-volume, experienced surgeon may be capable of distal endarterectomy
- Screen not just for the presence of proximal disease, but the potential for concomitant microvascular disease
  - Compare PVR to angiographic burden











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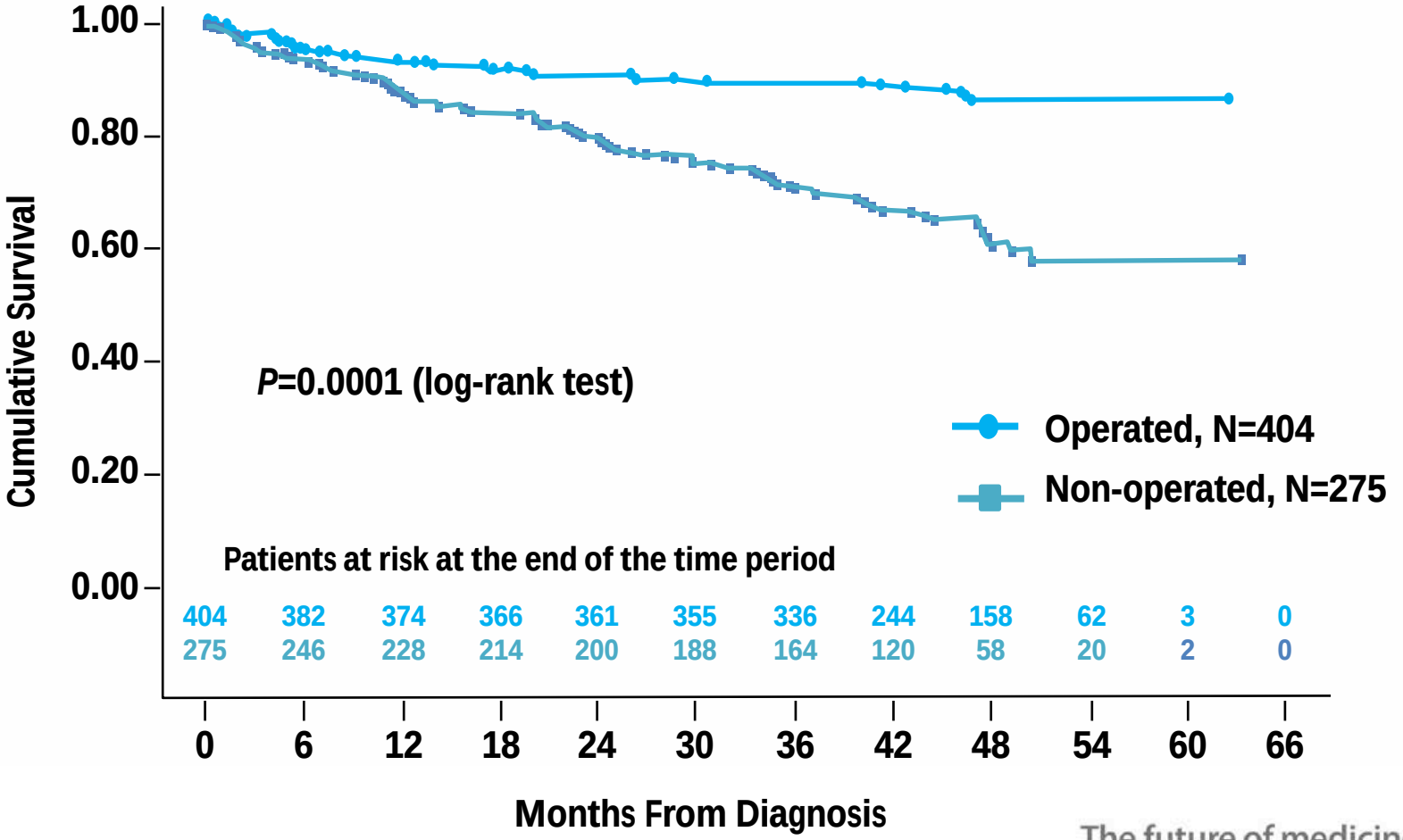
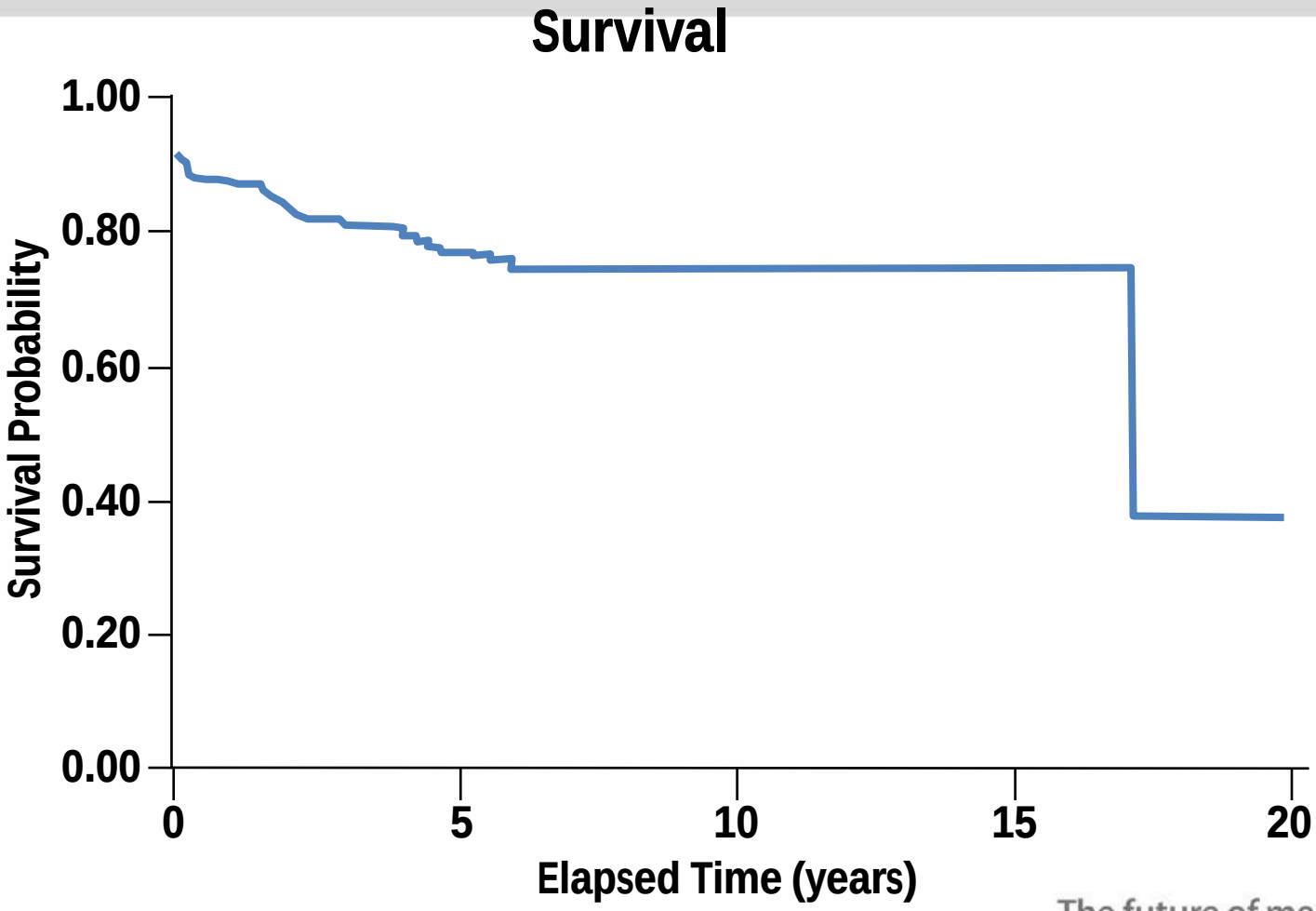
CTEPH Survival: Operated vs Non-operated Patients



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

Delcroix M, et al. *Circulation*. 2016;133:859-871.

Survival Following Successful PTE



The future of medicine, today.

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

Archibald CJ, et al. *Am J Respir Crit Care Med*. 1999;160:523-528.

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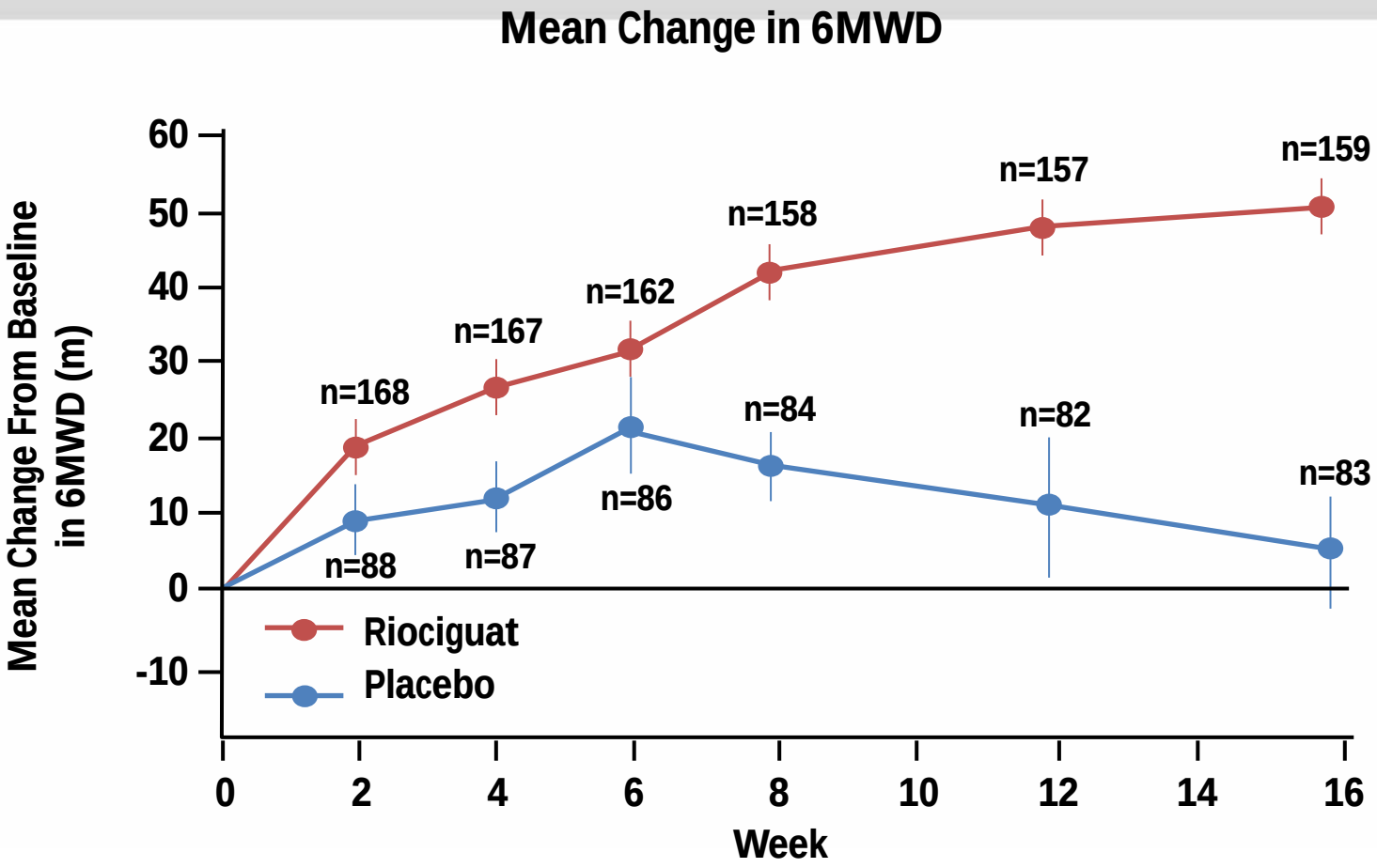
Therapeutic Options for Patients With CTEPH Who Are Not Considered Suitable Surgical Candidates or With Persistent PH Following PTE

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

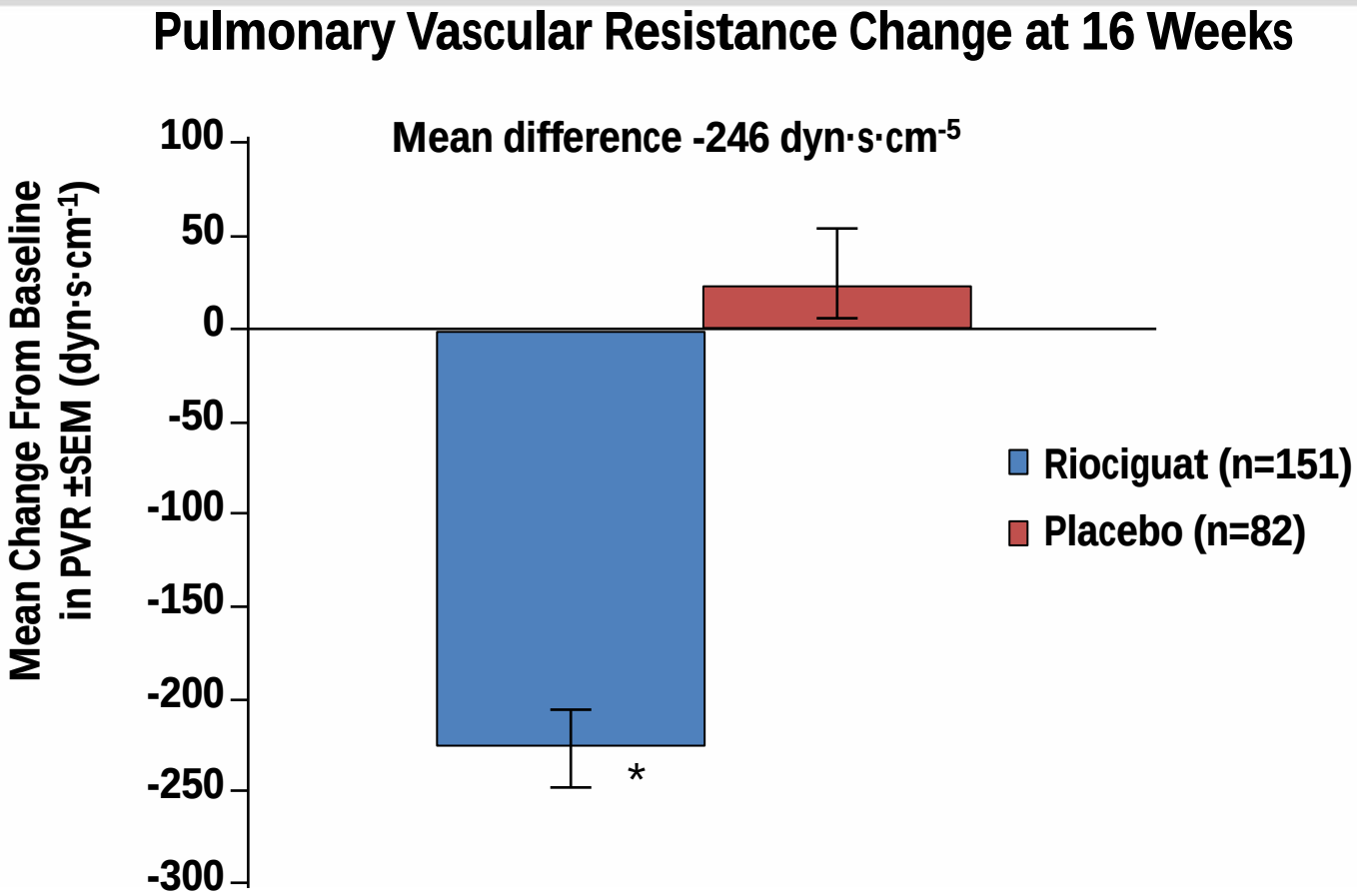


N=263. Double-blind placebo-controlled trial. Patients were not allowed to be on other PAH-specific therapy.

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

Ghofrani HA, et al. *N Engl J Med*. 2013;369:319-329.

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.
*P<0.0001 versus placebo.

Ghofrani H, et al. *N Engl J Med*. 2013;369:319-329.

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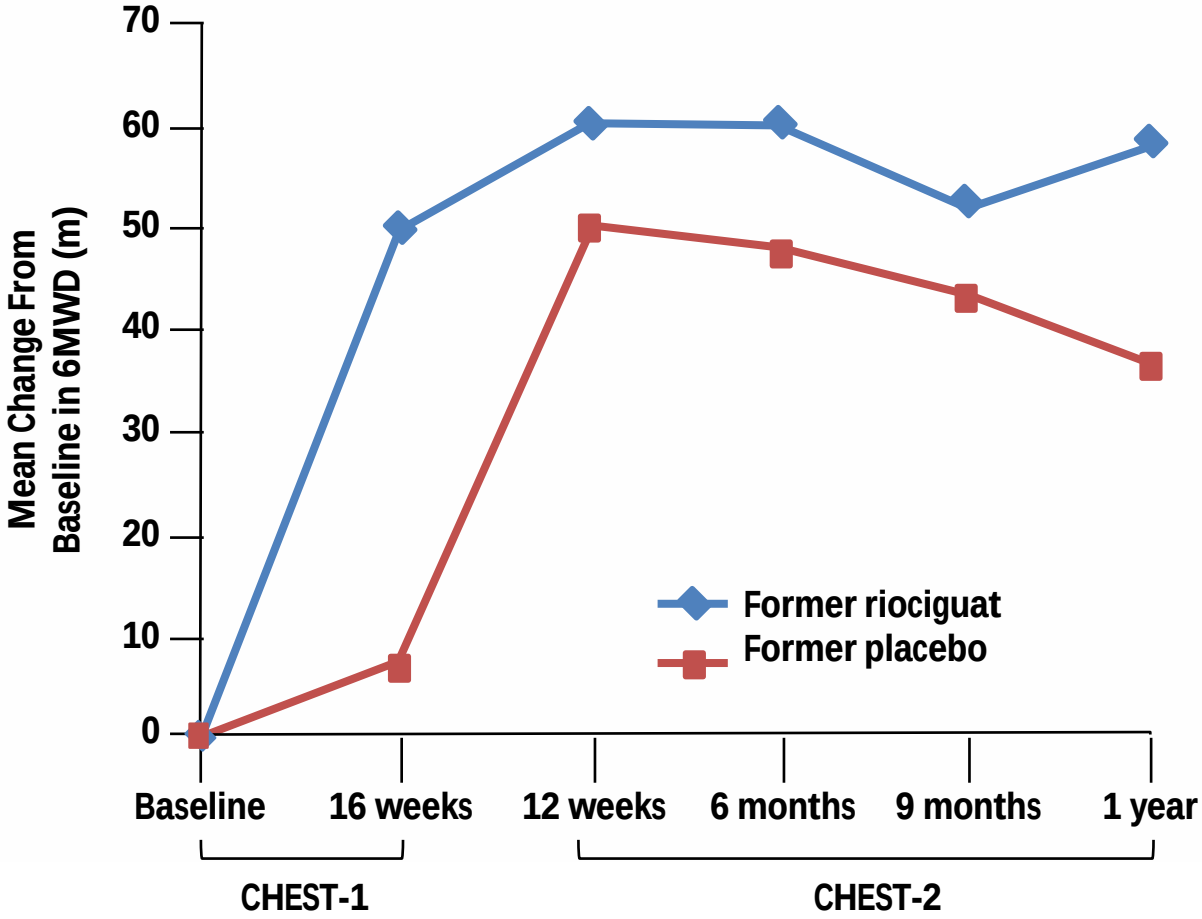
CHEST-2: Change in 6MWD Using Long-term Riociguat for Inoperable CTEPH

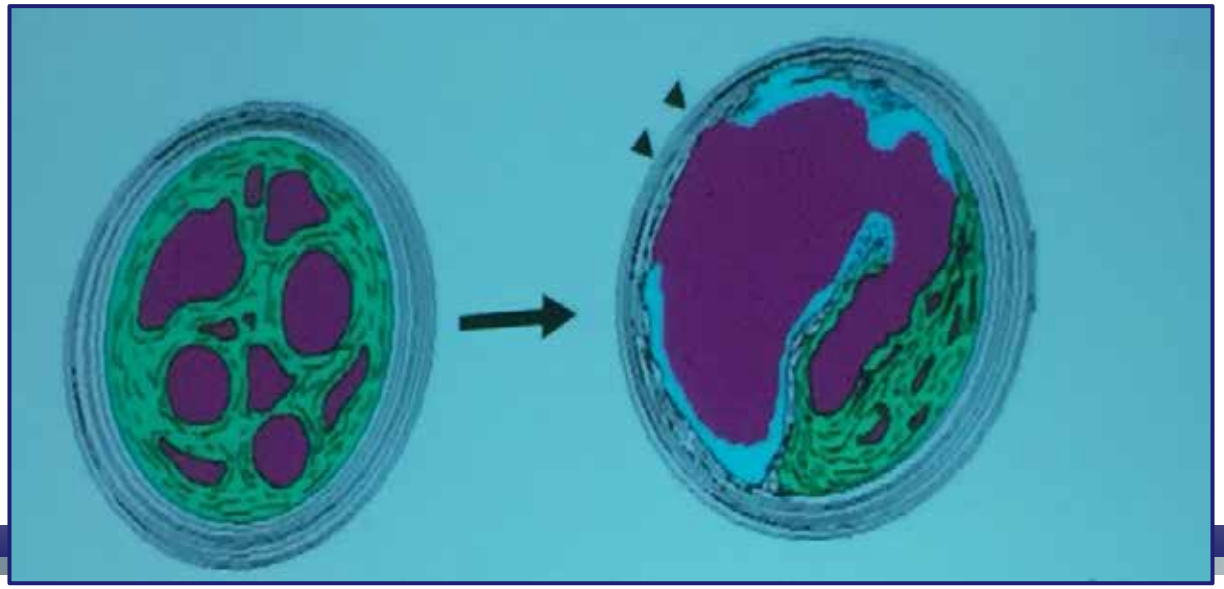


The future of medicine, today.

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

Simonneau G, et al. *Eur Respir J.* 2015;45:1293-1302.

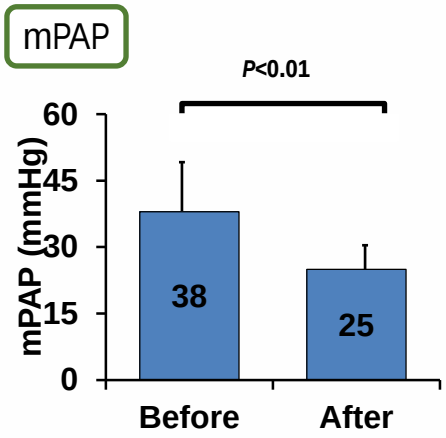
Balloon Pulmonary Angioplasty (BPA) in CTEPH

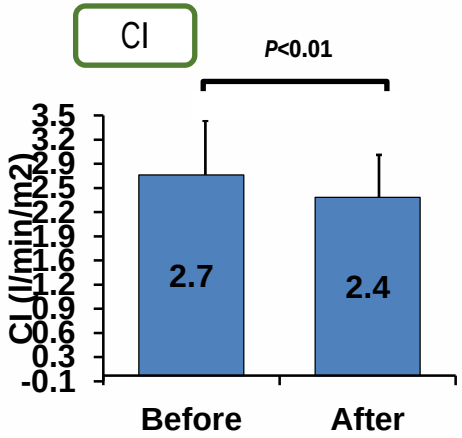


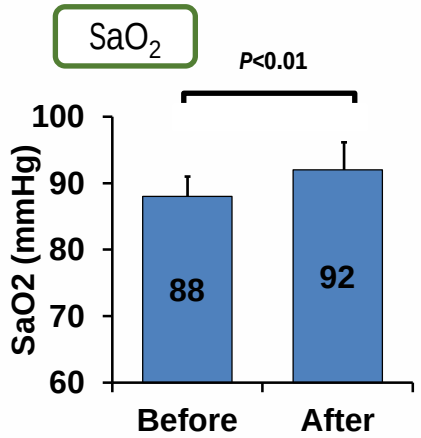
- Organized thrombi is forced on one side of the vessel enlarging the lumen
- BPA causes local dissection of the media with thinning (arrowheads) of the vascular wall leading to the expansion of the luminal diameter over time
- Experience using this technique is largely confined to Japan
- Experts suggest that this technique may be appropriate for patients with residual PH following PTE

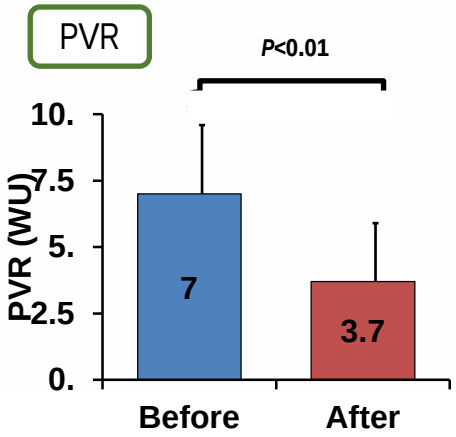
Kitani M, et al. *Circ Cardiovasc Interv.* 2014;7:857-859.

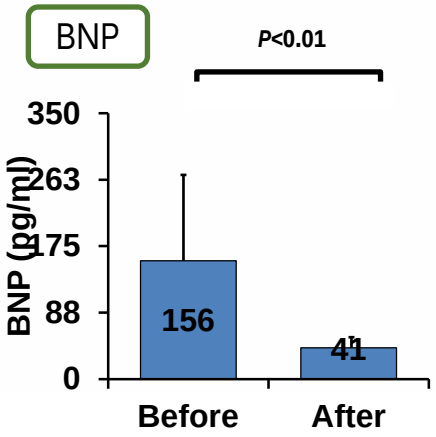
Efficacy of Balloon Pulmonary Angioplasty in Patients With Inoperable CTEPH

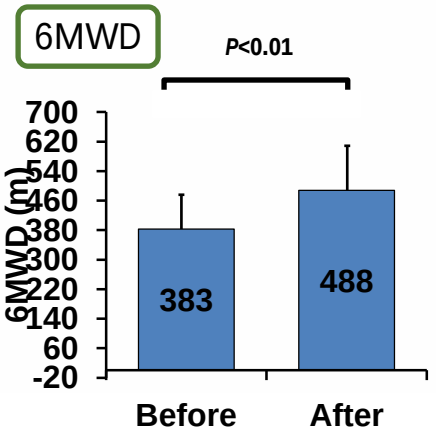












N=72 inoperable CTEPH patients undergoing BPA. Mean follow-up period = 21 months.

Aoiki T, et al. American Thoracic Society. San Francisco CA. May 13-18, 2016. A1229.

Complications of BPA in Patients With Inoperable CTEPH

Complications (%)	N = 372*
Pulmonary arterial dissection	27 (7)
Hemoptysis	64 (17)
Use of NPPV	31 (8)
Oral intubation	1 (<1)
Death associated with the procedures	0 (0)

N=72 inoperable CTEPH patients undergoing BPA.
* Total number of procedures during study period

Aoki T, et al. American Thoracic Society. San Francisco CA. May 13-18, 2016. A1229.

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

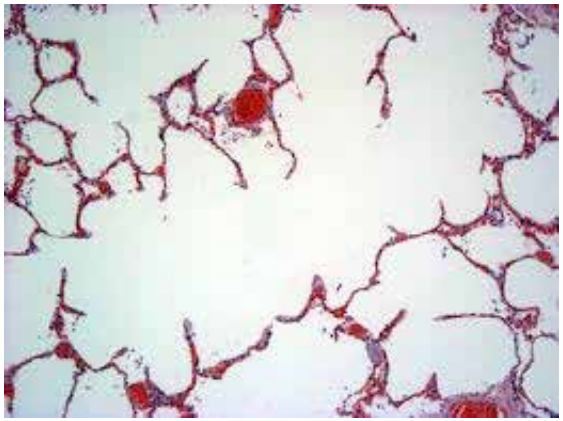
PTE in appropriate candidates can be curative; accordingly, patients should be first considered for surgery

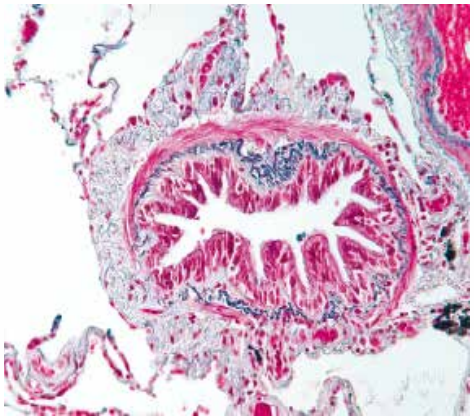
Medical therapy should be reserved for patients with CTEPH deemed inoperable or for those patients with residual symptomatic PH following PTE

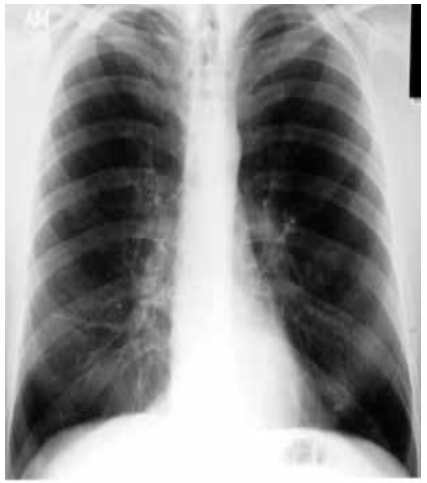
Emphysema

Emphysema

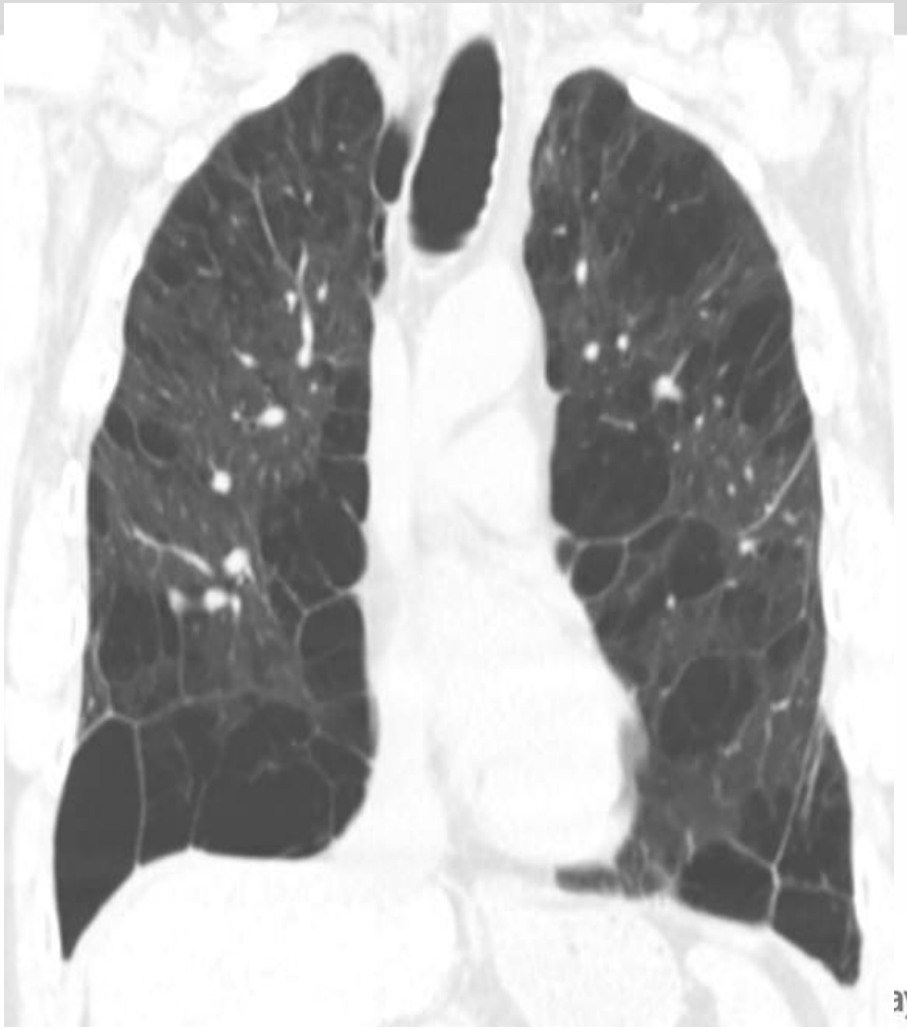
Permanent destruction and enlargement of the air-spaces distal to the terminal bronchiole
Loss of elastic recoil and gas exchange surface
Early closure of the small airways during exhalation
Air-trapping and hyperinflation
Flat diaphragm and respiratory muscle disadvantage

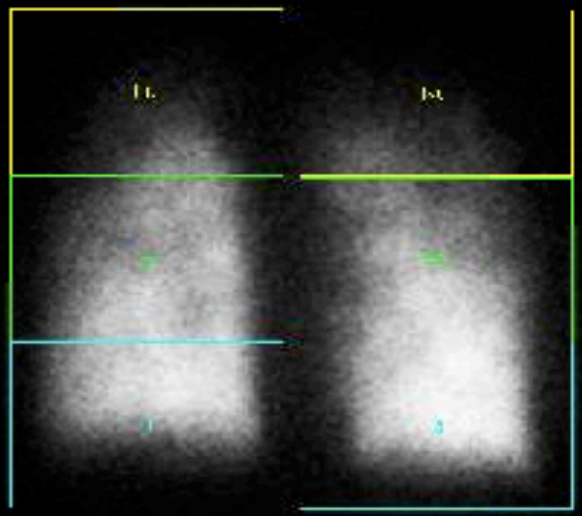


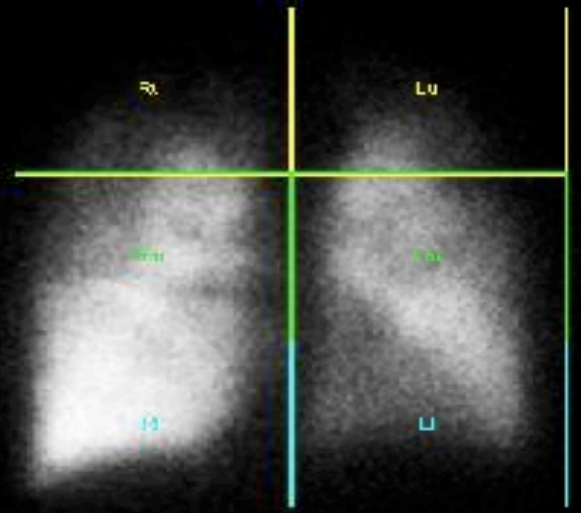




Emphysema: Heterogeneous and Upper Lobe Predominant Vs Homogenous







	Posterior Kct				Geometric Mean Kct				Anterior Kct			
	Left		Right		Left Lung		Right Lung		Right		Left	
	%	Kct	%	Kct	%	Kct	%	Kct	%	Kct	%	Kct
Upper Zone:	4.5	31.37	4.3	29.63	4.3	29.31	4.4	28.95	4.4	30.27	4.0	27.39
Middle Zone:	22.8	157.96	21.9	151.43	22.0	151.12	25.0	171.75	28.1	194.79	20.9	144.59
Lower Zone:	19.9	137.38	26.6	184.24	15.3	104.83	29.1	199.47	31.2	216.96	11.6	79.99
Total Lung:	47.2	326.71	52.8	365.30	41.6	285.26	58.4	401.16	63.6	441.01	36.4	251.96

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

Fein AM. Lung volume reduction surgery: answering the crucial questions. Chest. 1998 Apr;113(4 Suppl):277S-282S.

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**

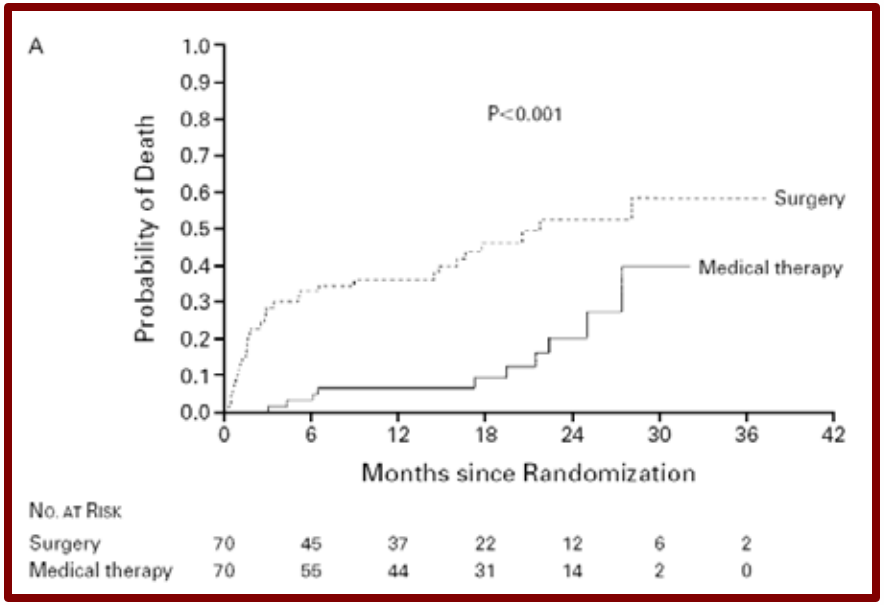
Patients were **well matched** regarding: age, race, gender, distribution of emphysema, perfusion ratio (to the upper lobes), PFT (FEV1 ~ 27%, DLCO 28% predicted), PaO2, PaCO2 and respiratory symptoms scores.

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).

A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema (NETT) National Emphysema Treatment Trial Research Group. N Engl J Med 2003;348:2059-73.

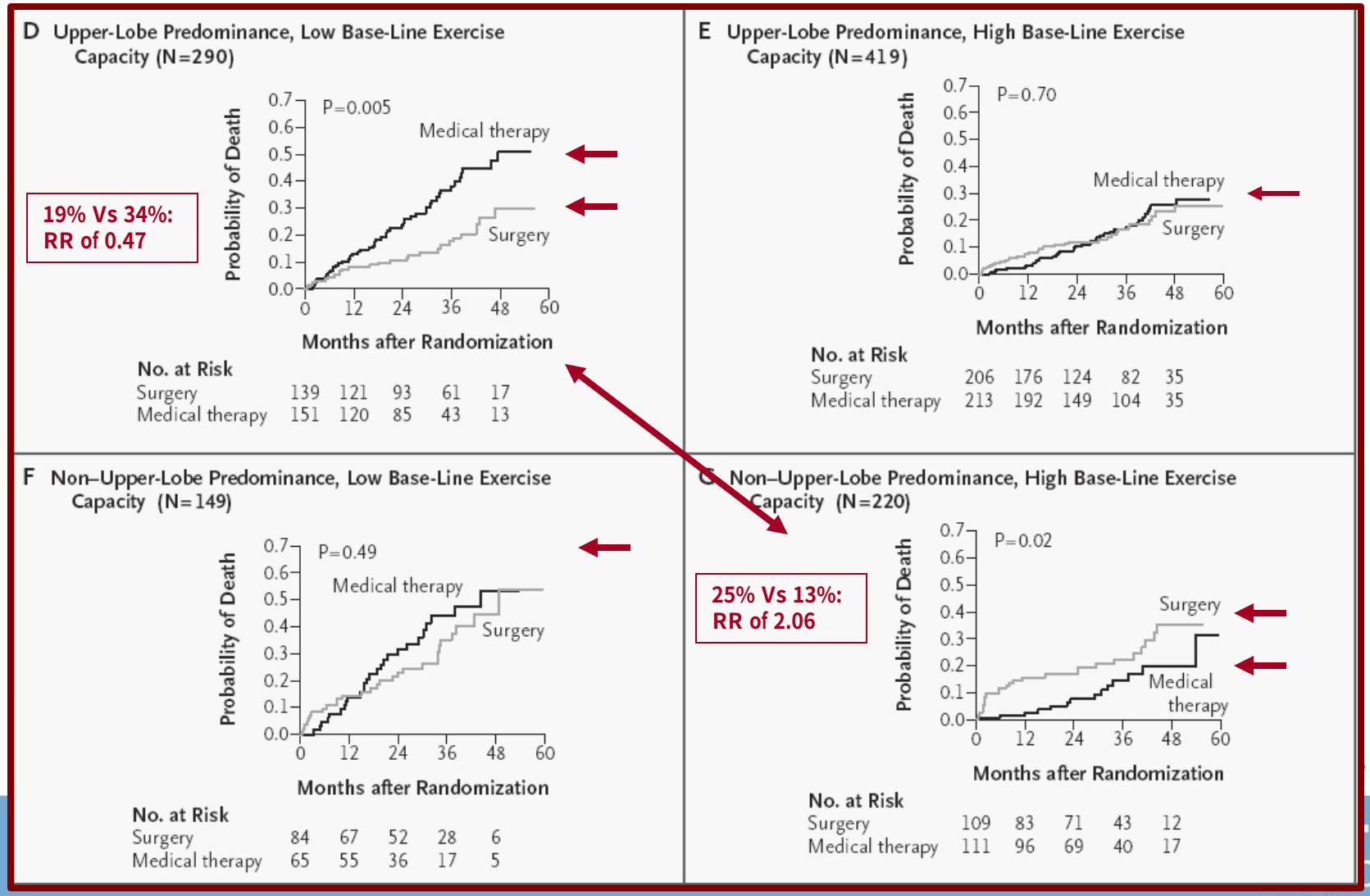
High Risk of Death (NETT)

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



NETT

Subgroup analysis (overall mortality was 26% for both groups at 29 months)



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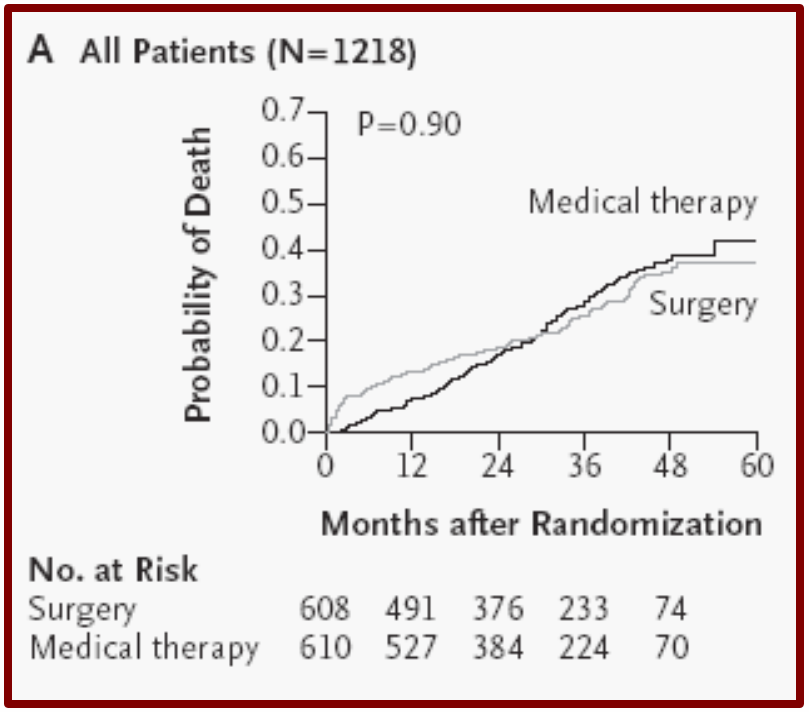
Early mortality and Morbidity

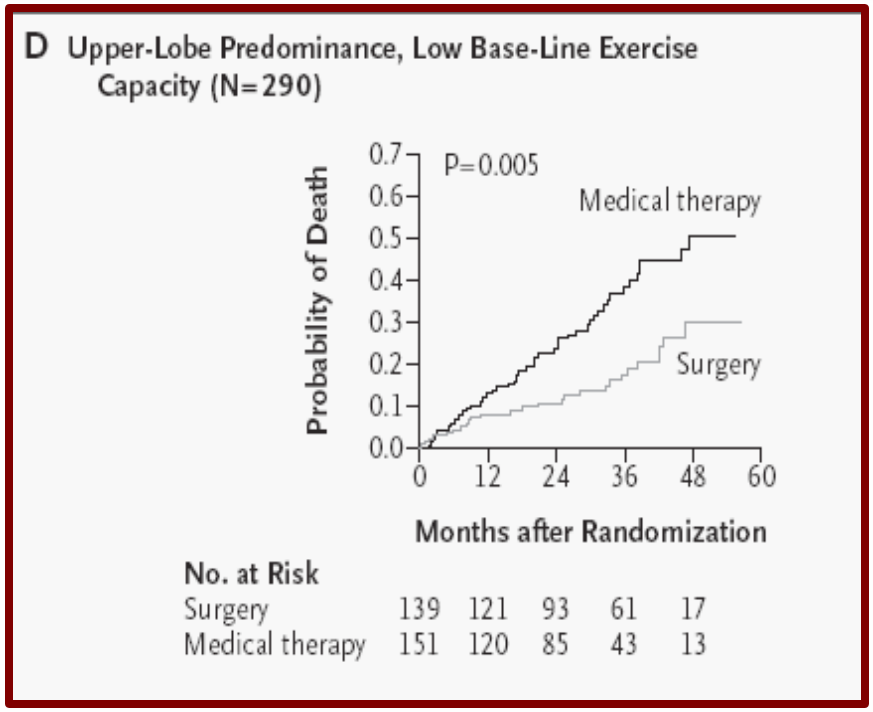
90-day mortality was 5.2% in the surgical group compared to 1.5% for the medical group

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 0.82-0.85

RR of death at 4.3 years 0.57

The future of medicine, today.

Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, Deschamps CC, Martinez FJ, Sciurba FC, Tonascia J, Fishman AP; National Emphysema Treatment Trial Research Group. **Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group.** Ann Thorac Surg. 2006 Aug;82(2):431-43.

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

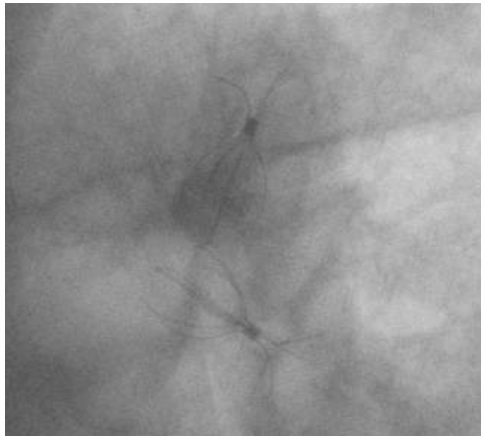
- Age < 75 years
- Severe dyspnea
- 6 months of smoking cessation
- FEV1< 45%
- DLCO > 20%
- TLC > 100%
- RV > 150%
- Heterogeneity of emphysema on CT imaging

- **Post pulmonary rehabilitation 6MWT > 140 m**
- **Low exercise capacity (< 40 W for men and < 25 W for women)**
- **PaO2 > 45 mm Hg**
- **PaCO2 < 60 mm Hg**
- **Mean PAP < 35 mm Hg (systolic < 45 mm Hg)**
- **LVEF > 40%**

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

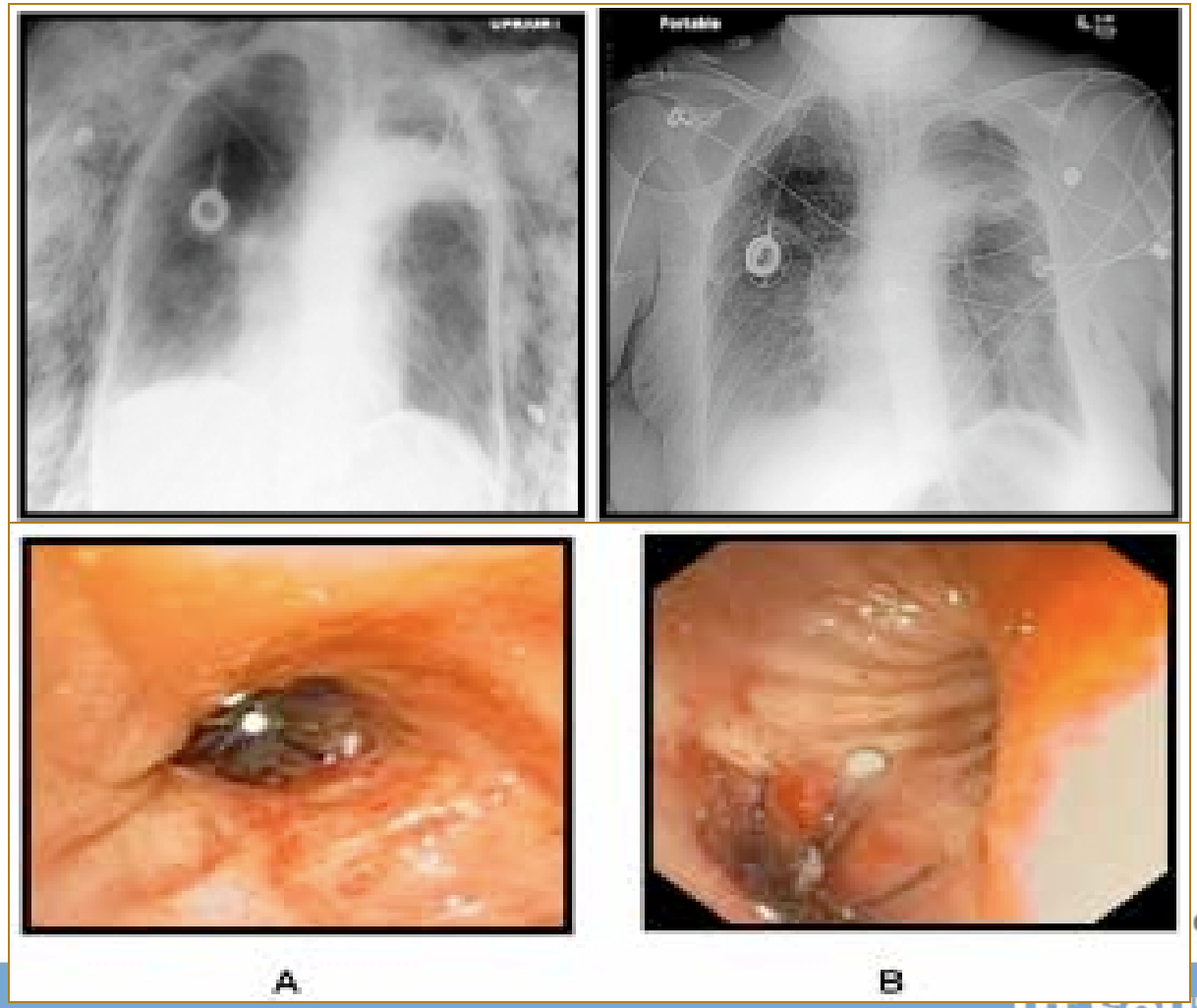
Intrabronchial unidirectional valves in the airways



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



of medicine, today.

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Abu-Hijleh M, Blundin M. Emergency Use of an Endobronchial One-Way Valve in the Management of Severe Air Leak and Massive Subcutaneous Emphysema. *Lung.* 2010 Jun;188(3):253-7.

STELVIO Study: EBV

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.)

NEJM, 2015

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.*

Variable	EBV Group (N = 34)	Control Group (N = 34)	Between-Group Difference	P Value
Change in FEV_1				
Milliliters (95% CI)	161 (80 to 242)	21 (–9 to 52)	140 (55 to 225)	0.002
Percentage (95% CI)	20.9 (11.1 to 30.7)	3.1 (–0.4 to 6.6)	17.8 (7.6 to 28.0)	0.001
Response rate — %	59	24	—	0.003
Change in FVC				
Milliliters (95% CI)	416 (201 to 631)	69 (–50 to 187)	347 (107 to 588)	0.005
Percentage (95% CI)	18.3 (9.3 to 27.3)	4.0 (–0.7 to 8.6)	14.4 (4.4 to 24.3)	0.005
Change in distance on 6-min walk test				
Meters (95% CI)	60 (35 to 85)	–14 (–25 to –3)	74 (47 to 100)	<0.001
Percentage (95% CI)	19.6 (10.4 to 28.9)	–3.6 (–6.9 to –0.4)	23.3 (13.6 to 32.9)	<0.001
Response rate — %	59	6	—	<0.001

Statistical and clinical significance

STELVIO Study: EBV

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

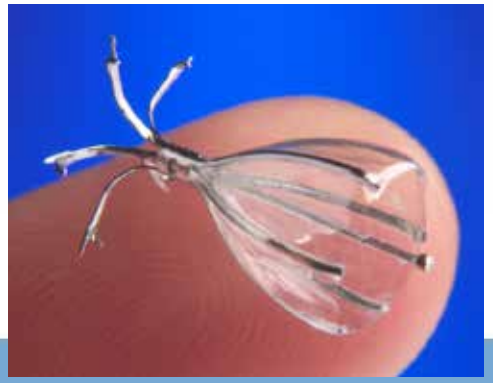
Event	EBV Group (N=34)	Control Group (N=34)	P Value†
	no. (%)		
Total no. of serious events	23	5	<0.001
Pulmonary events			
Death	1 (3)‡	0	1.00
COPD exacerbation with hospitalization	4 (12)	2 (6)	0.67
Pneumonia	2 (6)	1 (3)	1.00
Pneumothorax	6 (18)	0	0.02
Resolved ≤14 days after onset, without drainage	1 (3)	0	1.00
Resolved ≤14 days after onset, with drainage	2 (6)	0	0.49
Required temporary valve removal	1 (3)§	NA	NA
Required permanent valve removal because of recurrent pneumothorax	1 (3)	NA	NA
Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax	1 (3)	NA	NA

At the expense of more complications (Pneumothorx!)

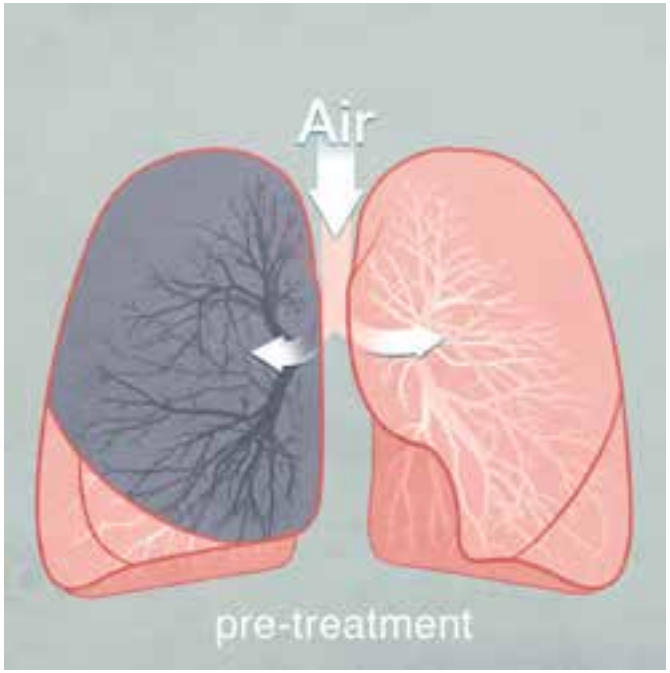
NEJM, 2015

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%, $PaCO_2$ < 55 mm Hg

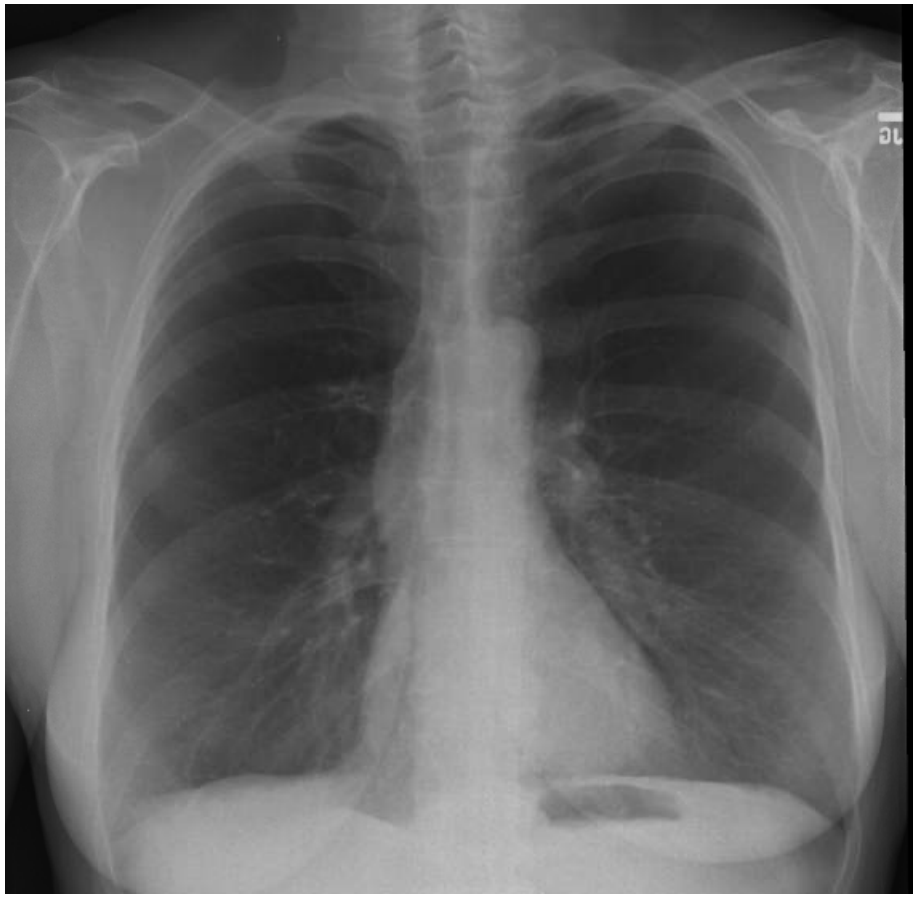


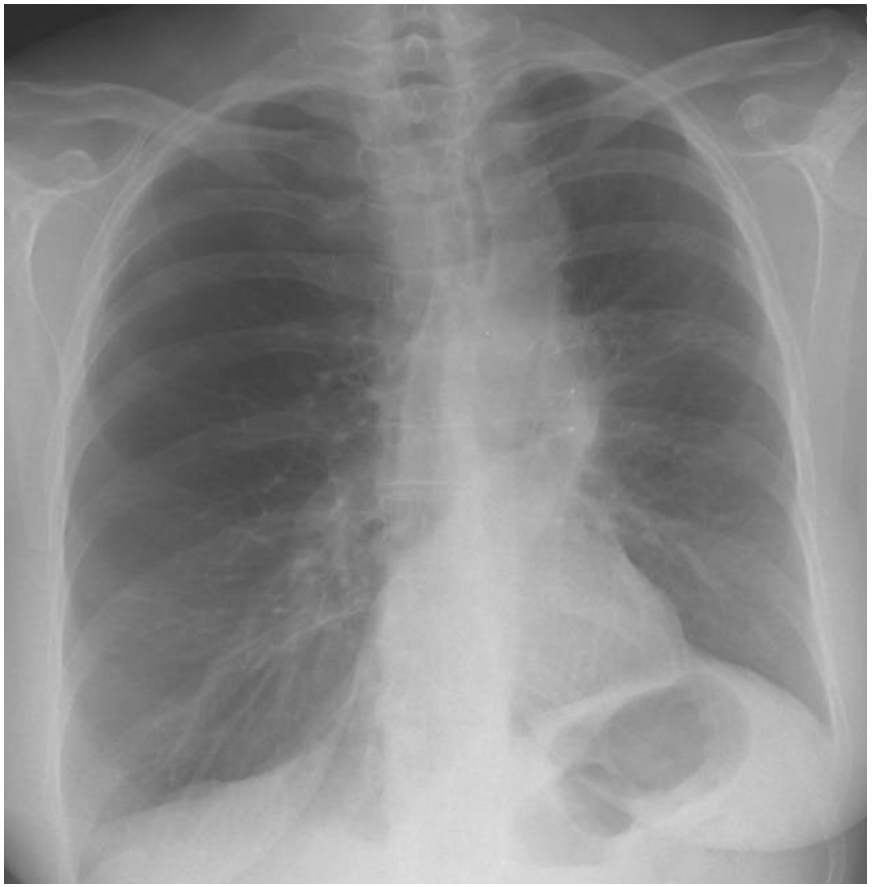
Available protocols
EMPROVE study: IBV



EMPROVE: patient information

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

700 LUNG TRANSPLANTS

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