



Ultrasound Accelerated Thrombolysis of Massive and Sub-massive Pulmonary Emboli

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EJGH



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Presenter Disclosure

- Financial:
 - T. Engelhardt has no financial disclosures
 - A. Taylor and L. Simprini at MedStar Research Institute received a grant from EKOS Corporation to independently analyze study CTA images
- Approved Uses:
 - The device used in this presentation has received European approval (CE Mark) for the treatment of pulmonary embolism (PE)
 - The device discussed in this presentation has been cleared by the US FDA for placement in the PA for use with solutions
- Unapproved/Unlabeled Uses:
 - This presentation includes information on uses of drug and device that have not been approved or cleared by the US FDA for PE treatment

Pulmonary Embolism

- Annual incidence
 - United States: >600,000; Europe >1,000,000
- Up to 200,000 deaths in the US annually
 - More die of PE in the US than AIDS, motor vehicle accidents & breast cancer combined
- PE categories
 - **Massive (5% of PE patients): 58% 90-day mortality rate**
Patients present in hemodynamic collapse with cardiogenic shock; high early mortality rate due in part to right ventricular failure
 - **Sub-massive (40% of PE patients): 22% 90-day mortality rate**
Presenting with thrombosis usually in one or both of the left and right pulmonary arteries, hemodynamic compensation and maintenance of adequate systolic arterial blood pressure albeit with right heart strain consistent with imminent right heart failure
 - **Minor (55% of PE patients): 15% 90-day mortality rate**
Presenting with small clots in the distal pulmonary vessels, pleuritic chest pain, mild tachycardia and possibly hemoptysis

High Risk

Intermediate Risk

ACCP Treatment Guidelines (2008)¹

- **Massive PE**
 - Recommend aggressive treatment
 - IV thrombolytics
 - Endovascular embolectomy or pharmacomechanical interventions
 - Surgical embolectomy
- **Sub-massive PE**
 - Recommend consideration of IV thrombolytics

Why Aggressively Treat Sub-massive PE?

- RV/LV ratio > 0.9 is an independent predictor of mortality^{1,2,3,4,}
- Mortality risk increases 11 fold with a pulmonary obstruction index $>60\%$ ⁵
- Patients with persistent RV dysfunction at discharge were 8 times more likely to have recurrent PE, and had 4 times the mortality rate of patients in whom RV dysfunction had regressed at discharge⁶
- At 1 year post PE, 44% of sub-massive PE patients with right heart dysfunction at hospital discharge will have chronic PHT⁷
- RV hypokinesis on baseline echocardiography was associated with a 57% higher mortality rate at 3 months, even though 89% of the patients were hemodynamically stable⁸
- Anticoagulation interrupts the clotting cascade preventing thrombus propagation but does not resolve existing clot
 - Compared to anticoagulation alone, systemic thrombolysis can reverse right ventricular dilatation within 24 hours of treatment^{9,10}

1. Quiroz, Circ 2004; 109:2401-2404
2. Frémont, Chest 2008; 133:558-362
3. Schoef, Circ 2004; 110:3276-3280
4. Kucher, Arch Intern Med 2005; 165:1777-1781
5. Van der Meer, Radiology 2005; 235:798-803

6. Grifoni, Arch Intern Med 2006; 166:2151-215
7. Ribeiro, Circ 1999;99:1352-1330
8. Goldhaber, The Lancet 1999;353: 9162
9. Becattini, Thromb Res 2010; 125:e82-86
10. Konstantinides, Am J Cardiol 1998;82:966-970

Systemic Fibrinolytic Treatment

- Improves right ventricular function¹
- Increases pulmonary perfusion
- Lowers incidence of recurrent PE

- However –

- Increases bleeding complications¹
 - Major bleeding rates <1% to 21.7%
 - ICH 0%-3%

1. Goldhaber, N Engl J Med 1998;339:93-104.

Ultrasound Accelerated Thrombolysis



Mechanism of Action

- Ultrasound energy causes fibrin strands to thin and loosen, exposing plasminogen receptor sites
- Thrombus permeability and thrombolytic penetration are dramatically increased
- Ultrasonic pressure waves force drug deep into the clot
- Drug acts faster, clearing clot sooner with lower drug dose & no hemolysis

Goal of Ultrasound Accelerated Thrombolysis

- Accelerates thrombolysis
 - Rapid reversal of right ventricular dilation and reduction in pulmonary clot burden
 - Improves pulmonary perfusion
 - Reduces right heart load
- Lower drug dose (≤ 20 mg rt-PA)
 - Significantly lower risk of bleeding

Single Center Experience

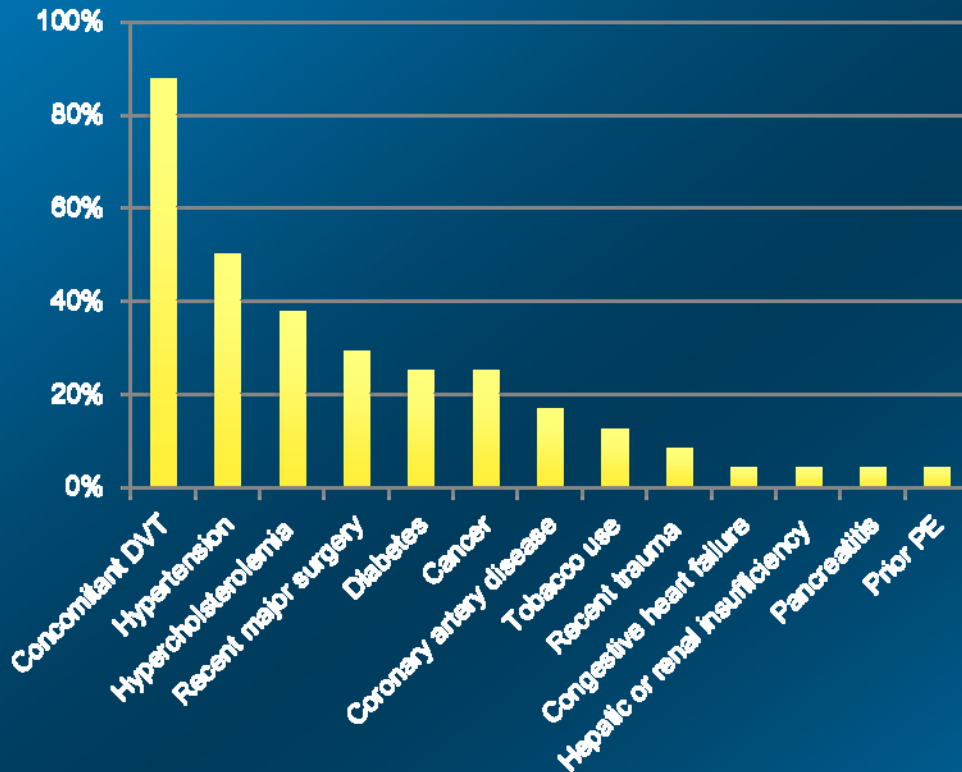
- Based on our experience, we treat both massive and sub-massive PE patients with the same therapy
 - rt-PA with simultaneous low-intensity ultrasound delivered via the EkoSonic Endovascular device
- From February 2009 to July 2010, we treated 27 PE patients with ultrasound accelerated thrombolysis
 - Retrospective data analysis on 24 consecutive patients with pre- and post-treatment contrast-enhanced CT imaging
 - Clinical history
 - RV/LV ratio reduction
 - Clot burden reduction
- Optimum drug dose identified
 - 20 mg rt-PA maximum dose over 12 hours resulted in good clinical outcomes with no bleeding complications

Patient Demographics

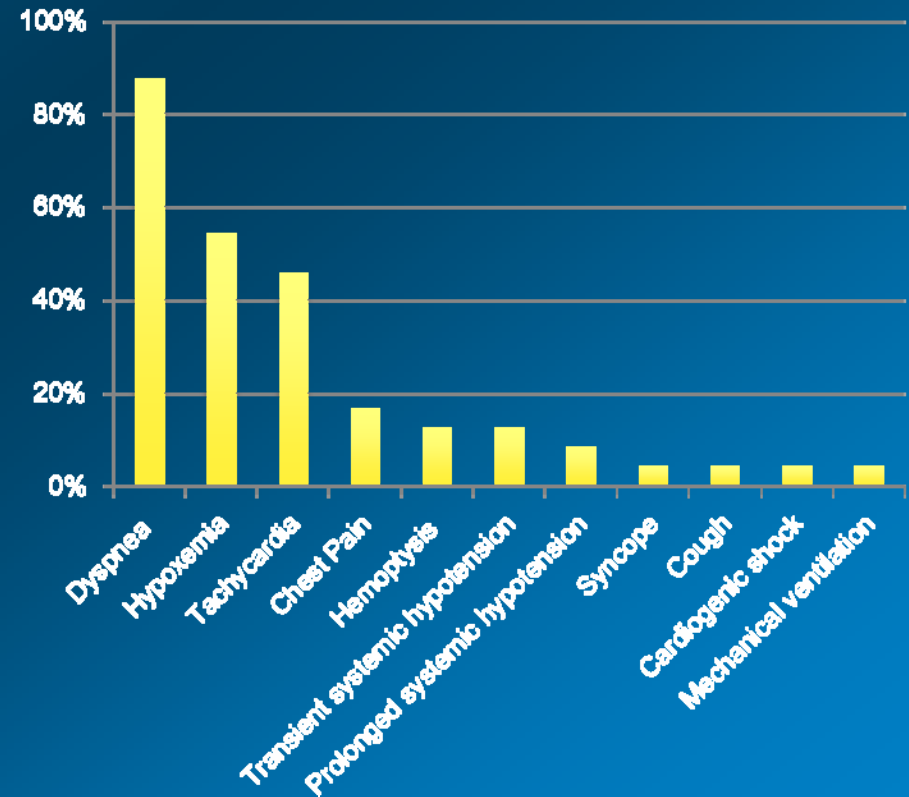
Mean Age (Range): 61.7 ± 15.9 (32-85)

Male (%): 11 (46%)

Comorbidities



Symptoms and Hemodynamic Status



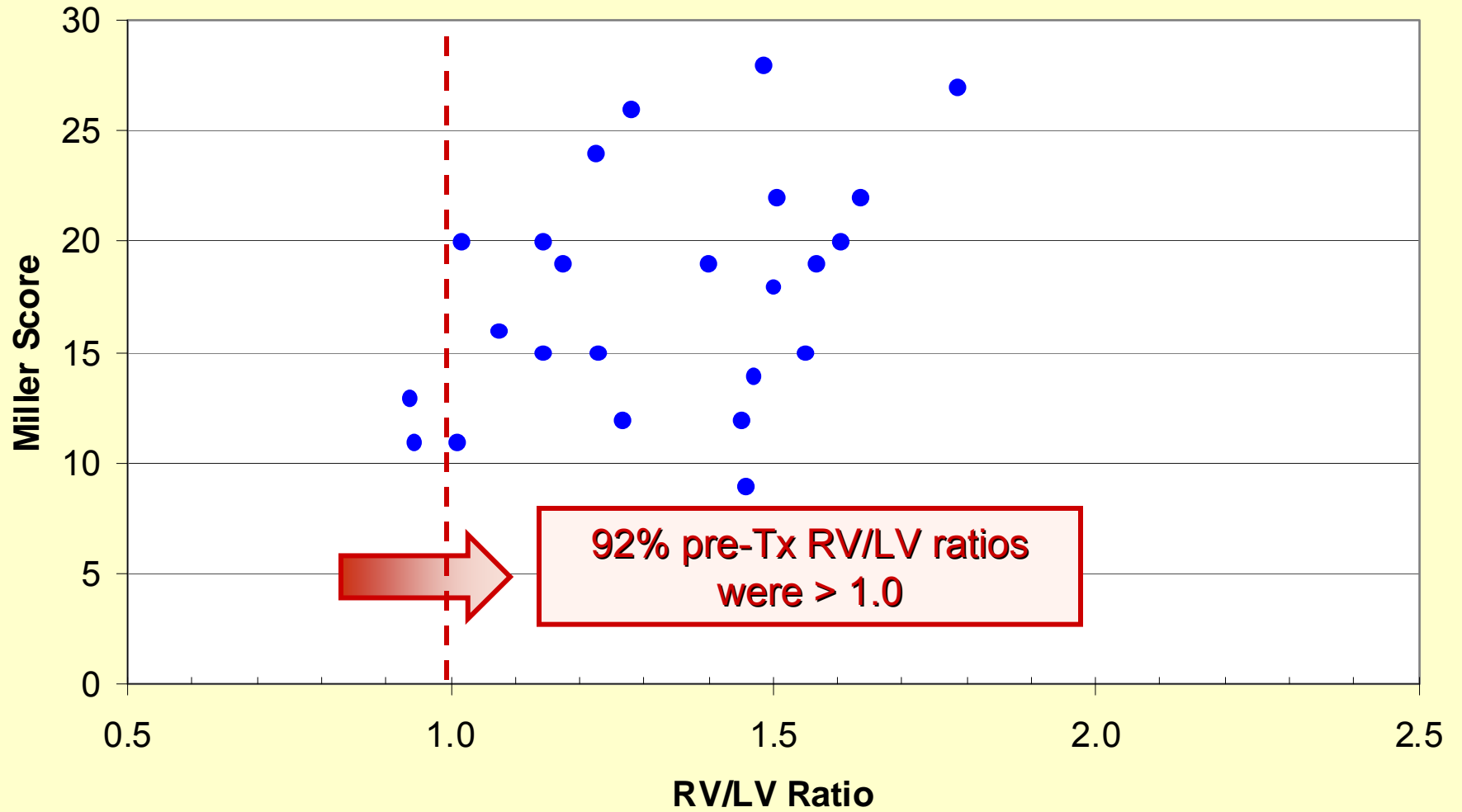
Excellent Results with EKOS

- All patients survived to hospital discharge
- <48hr median time to follow-up CT
- Significant reduction in RV/LV ratio and Modified Miller Score*

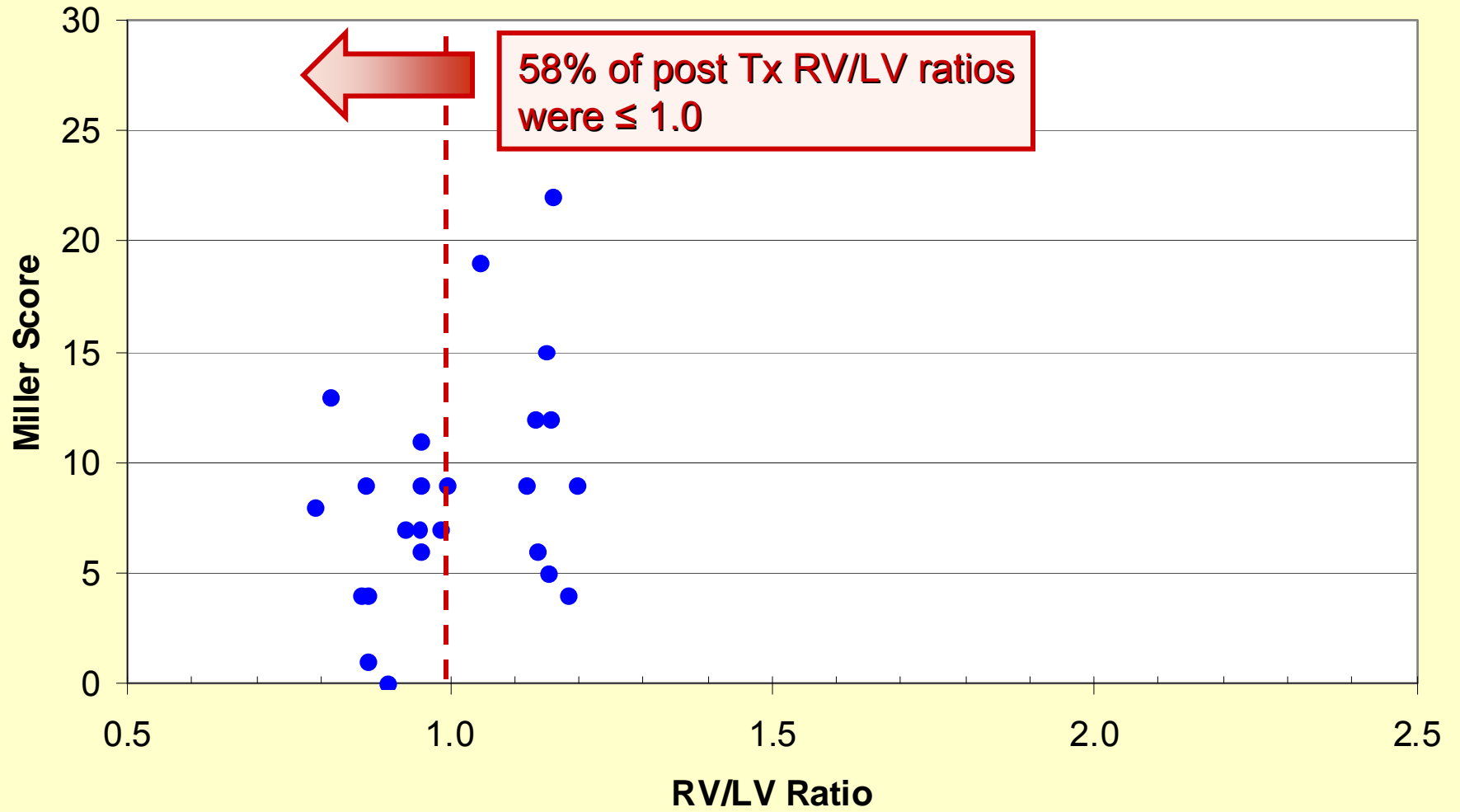
Parameter	Pre-treatment	Post-treatment	P-value
RV/LV Ratio	1.33 ± 0.24	1.00 ± 0.13	p<0.001
Mean RV End Diastolic Diameter	51.0 ± 8.0	43.7 ± 6.4	
Mean LV End Diastolic Diameter	39.1 ± 5.7	43.8 ± 6.7	
Modified Miller Score	17.8 ± 5.3	8.7 ± 5.1	p<0.001

- Symptoms (dyspnea, difficulty speaking, etc.) resolved in 2-3 hours after initiation of treatment

RV/LV Ratio vs. Miller Score
N = 24 PE patients, Pre-Treatment



RV/LV Ratio vs. Miller Score
N = 24 PE patients, Post-Treatment



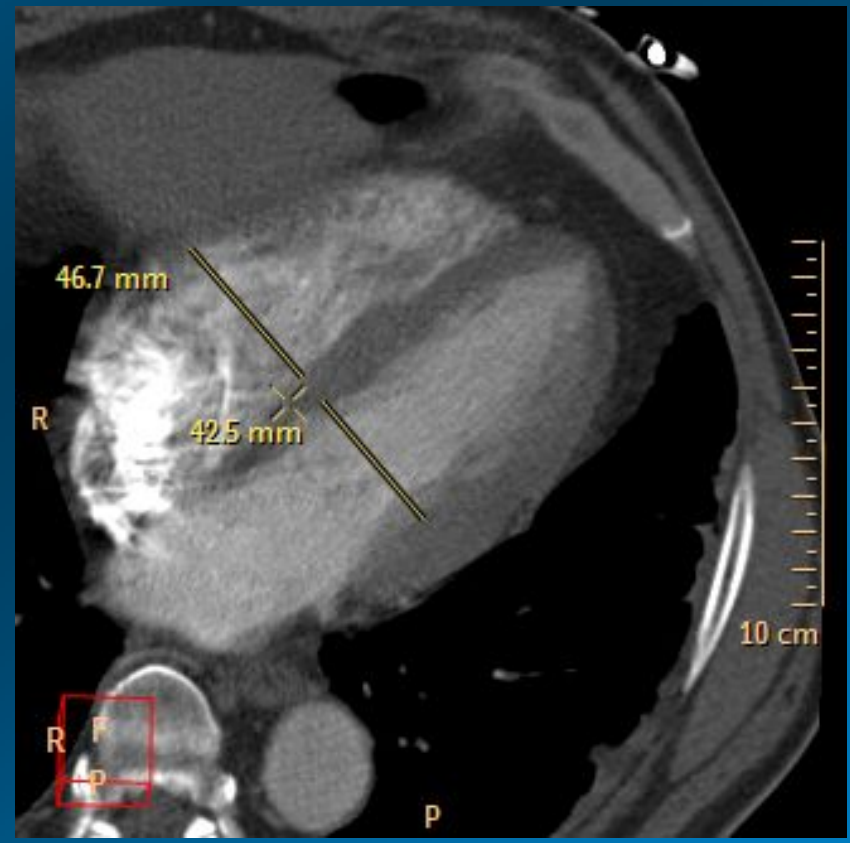
Complications

- Bleeding
 - No ICH or systemic bleeding complications
 - Initial high dose group (n=13)
 - Average dose: 45 mg rt-PA
 - 4 patients with **puncture site bleeding** requiring transfusion
 - Low dose group (n=11)
 - Average dose: **20mg rt-PA**
 - **No bleeding complications**
- 1 patient had suspected recurrent PE
- No other complications were recorded

Case 1

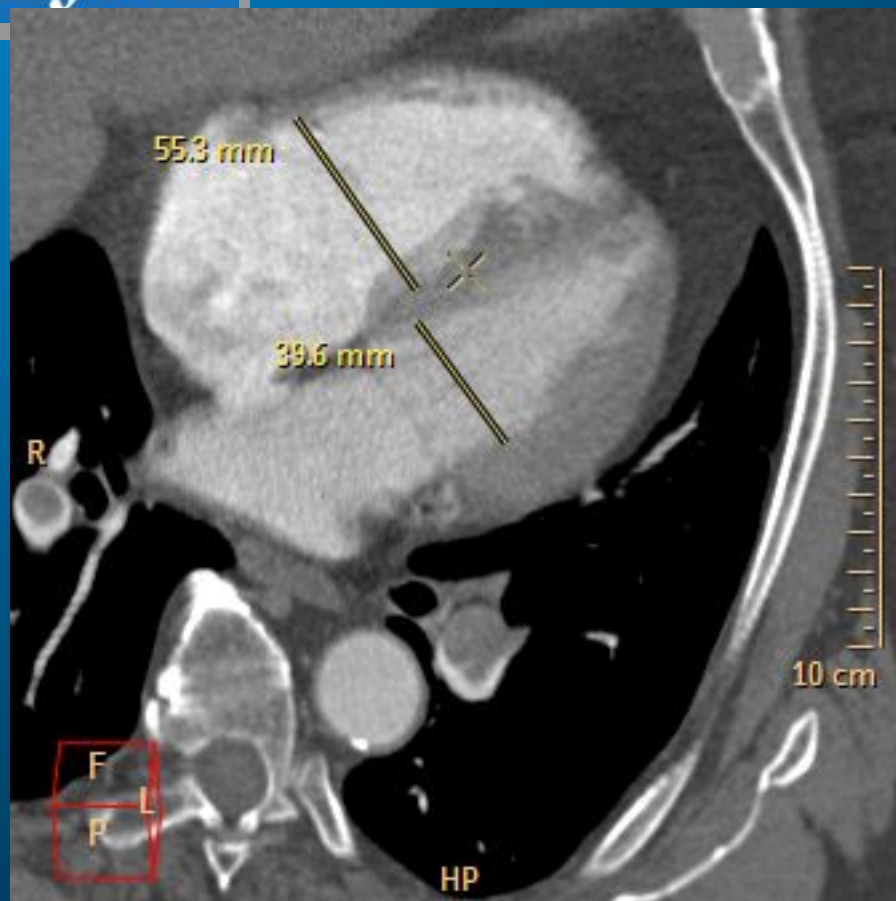


Pre-EKOS
(RV/LV = 1.64)

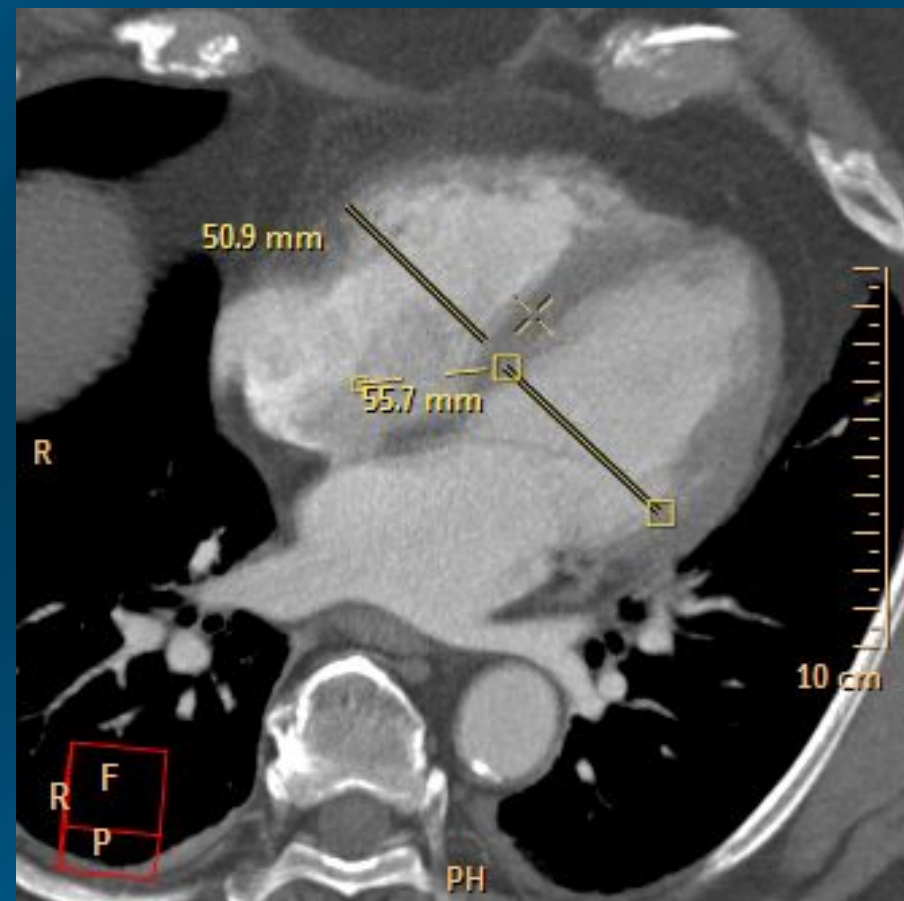


Post-EKOS
(RV/LV = 1.10)

Case 2

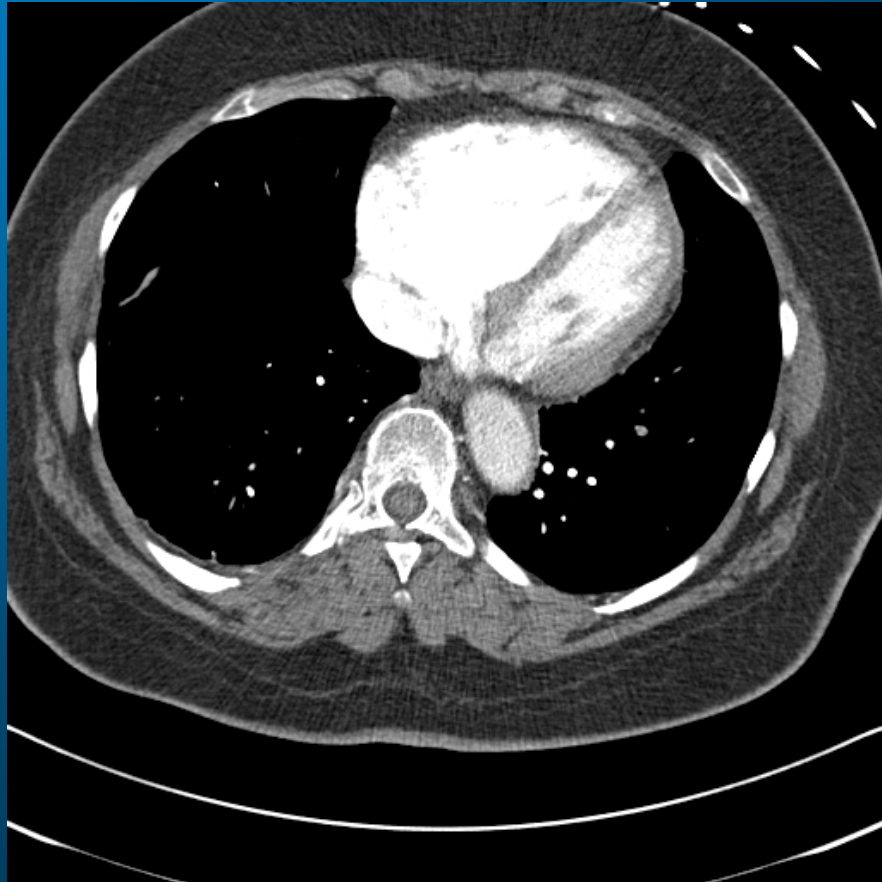


Pre-EKOS
(RV/LV = 1.40)

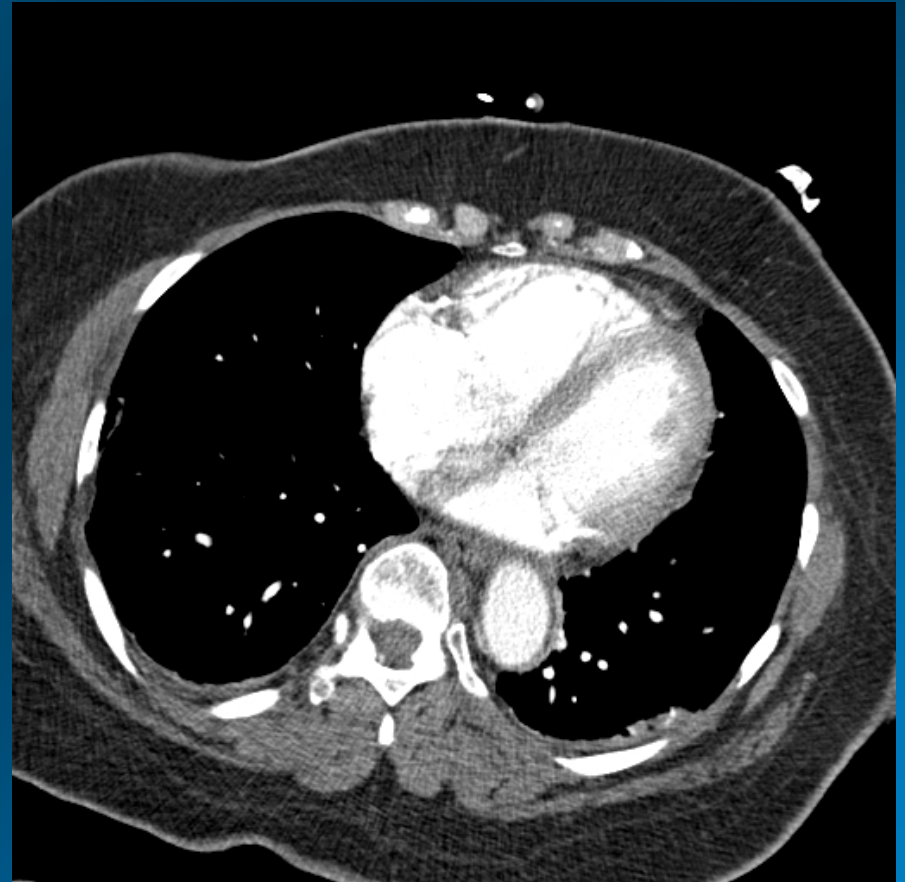


Post-EKOS
(RV/LV = 0.91)

Case 3



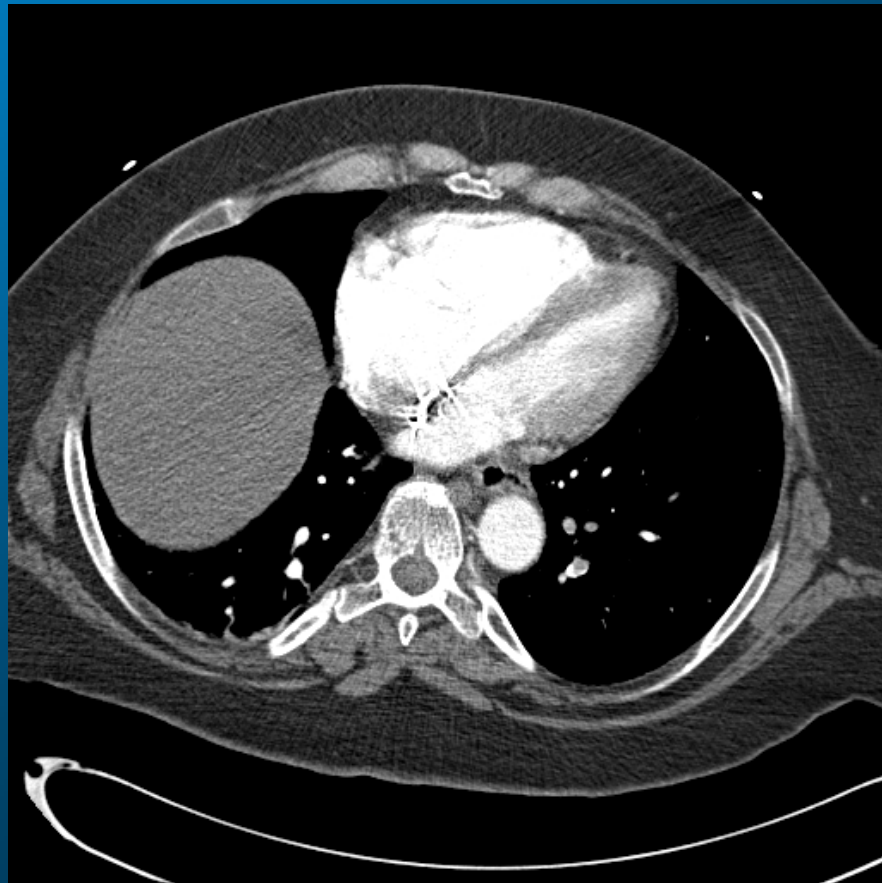
Pre-EKOS



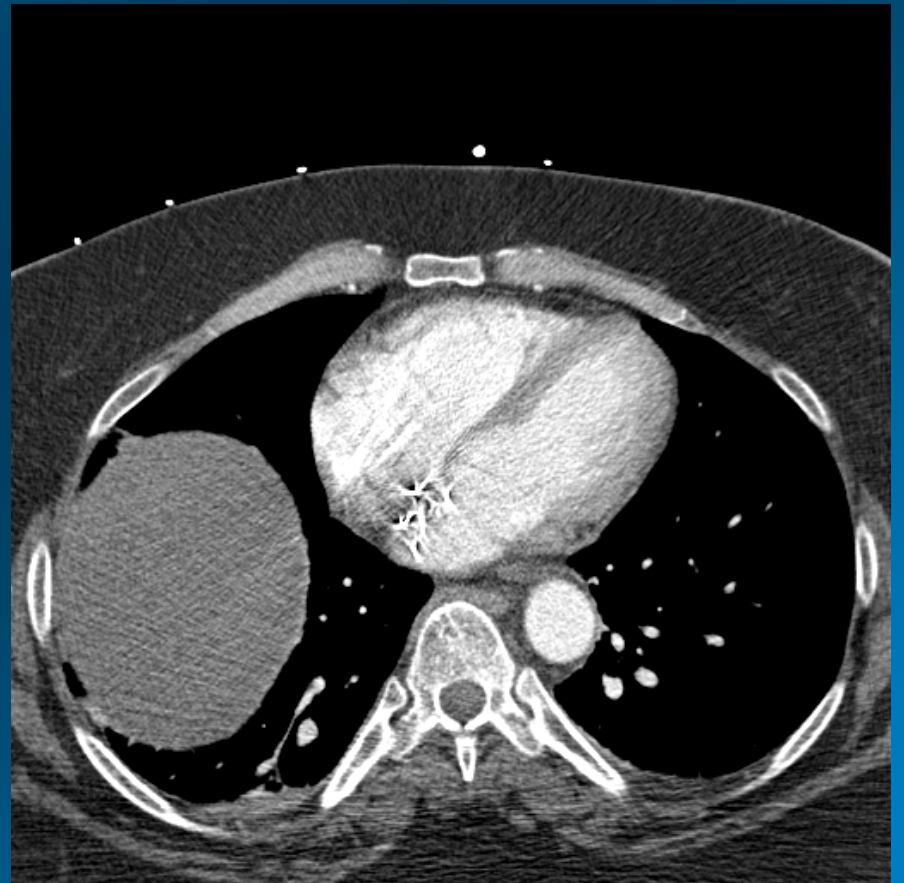
Post-EKOS

Case 4

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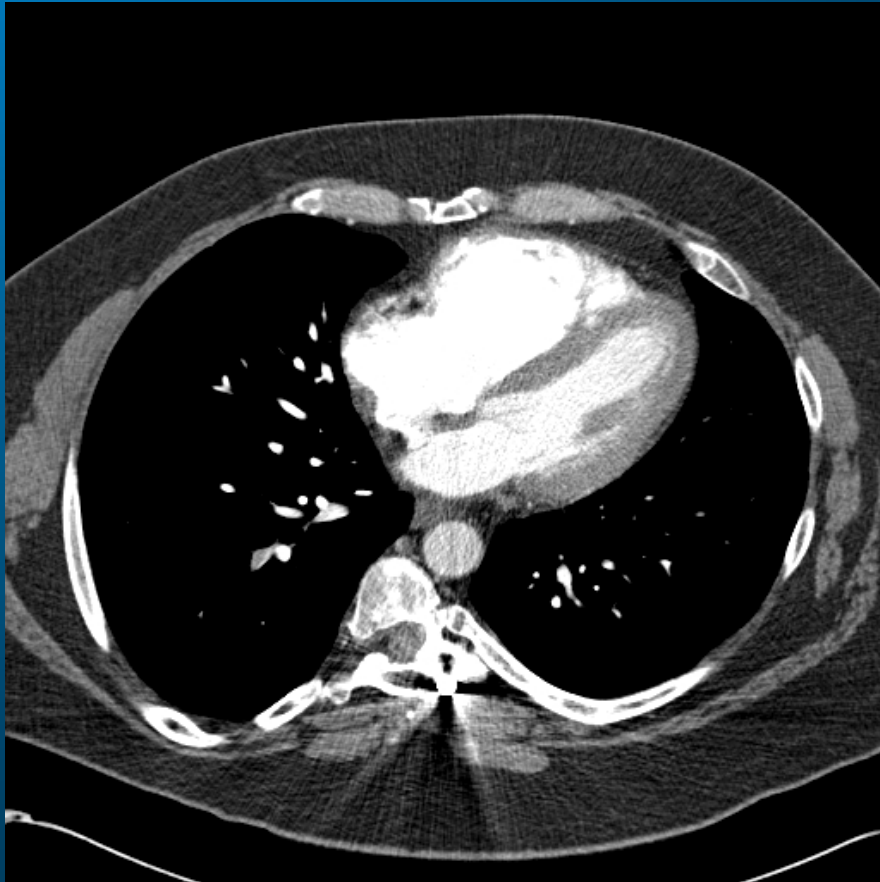


Pre-EKOS

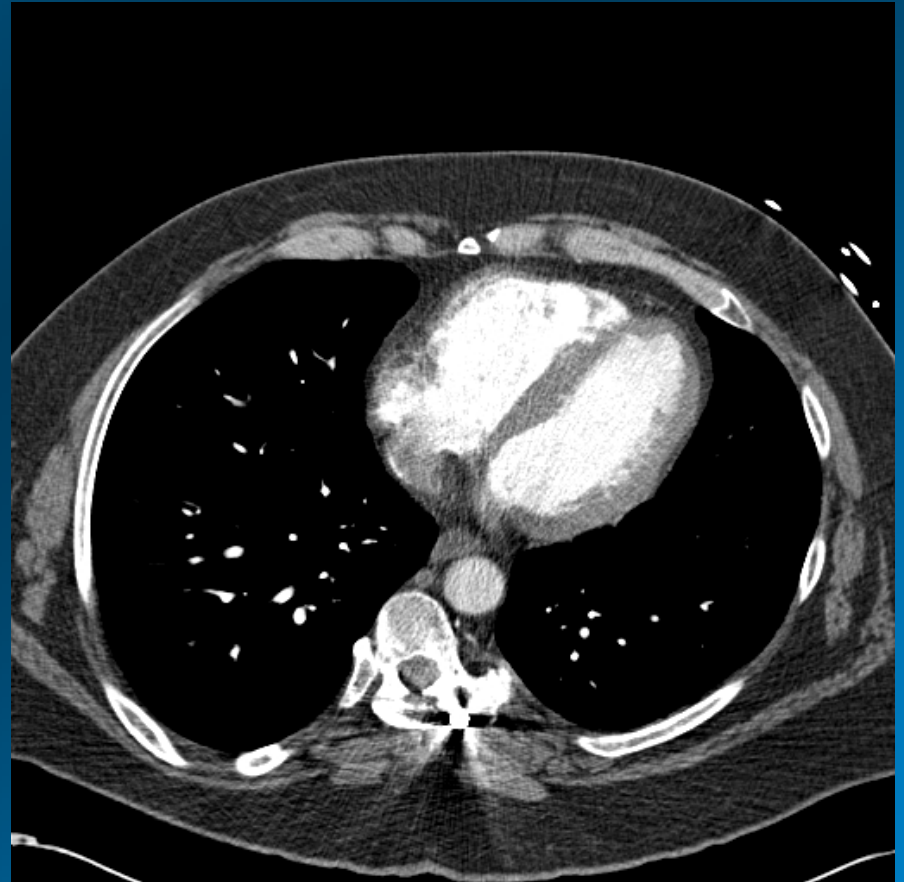


Post-EKOS

Case 5



Pre-EKOS



Post-EKOS

Conclusions

- RV dysfunction is main cause of death, usually within several hours of acute embolic event
 - Anticoagulation halts propagation but does not clear existing thrombus
 - Endogenous fibrinolysis may often be incomplete
 - Up to 33% of patients have ongoing RV dysfunction at 7 days
- Systemic thrombolysis restores right heart function but is associated with risk of bleeding complications
- Low dose USAT rapidly improved right ventricular dilatation and pulmonary clot burden in patients with intermediate and high risk PE
 - Patients survived acute pulmonary embolism episode
 - No bleeding complications with low dose (<20 mg rt-PA)
 - Patients discharged with resolved right heart dysfunction
 - Significantly reducing recurrent PE and mortality