Catheter Directed Lysis should *not* be routinely used for intermediate risk PE

Oren Friedman MD

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PERT team

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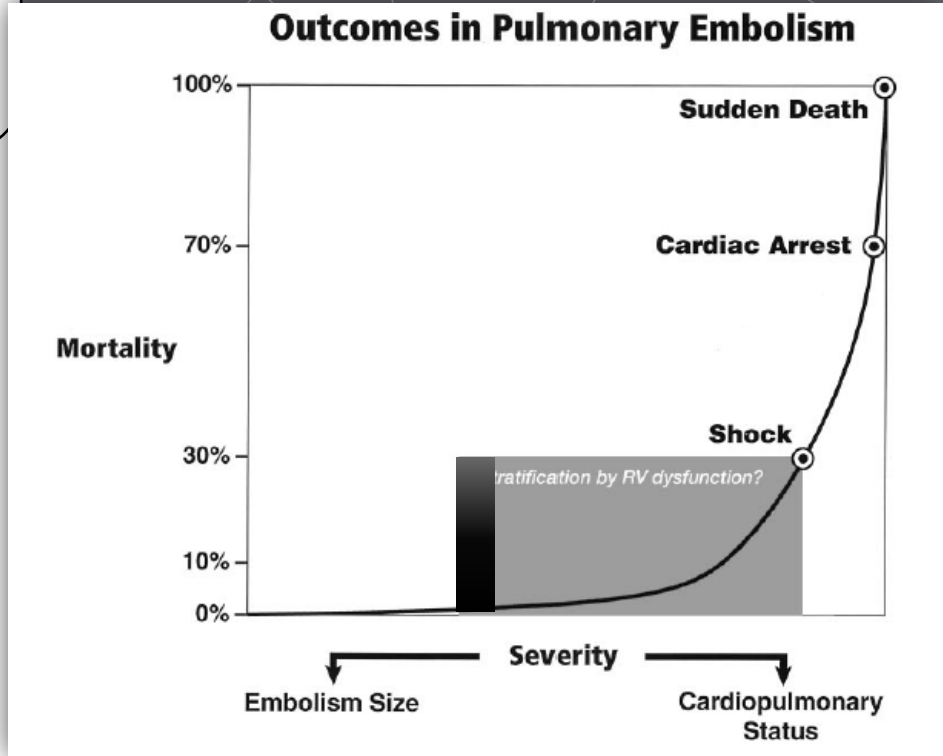
The battle with the captain begins …

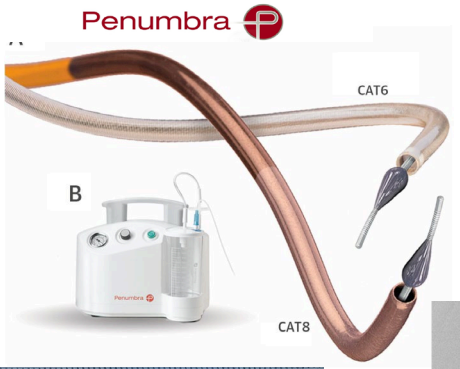
Heparin is a worthy opponent… because it really works

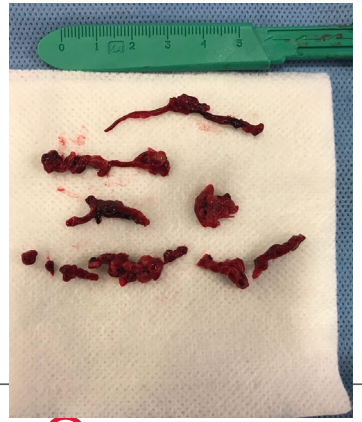
The hardest challenge is risk stratifying intermediate risk PE's; identifying the patients in whom predicted mortality justifies risk of escalating therapy

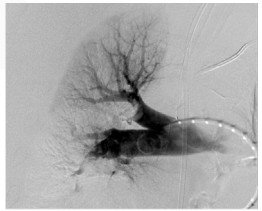


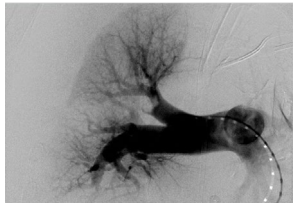
Wood, K. E. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002

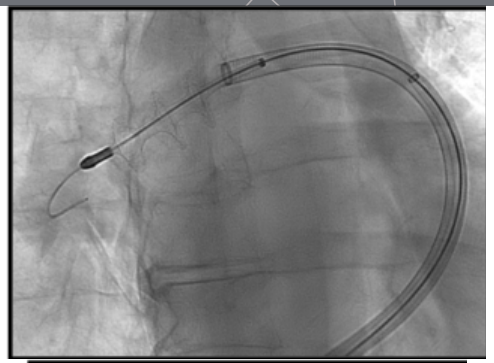
There is an explosion of endovascular devices and treatment options for PE

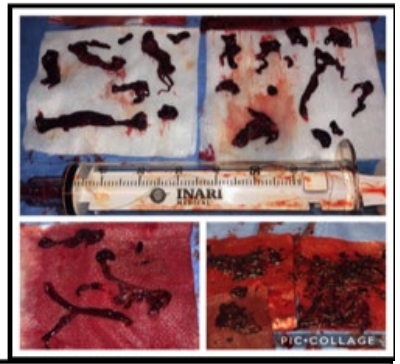


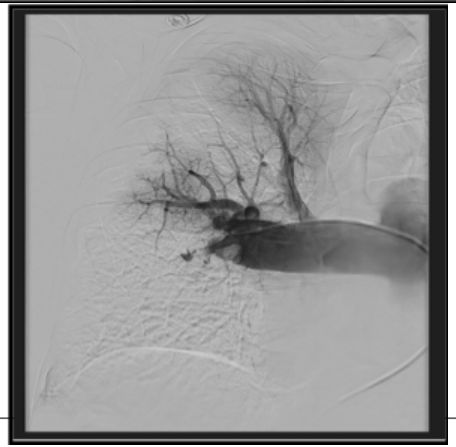


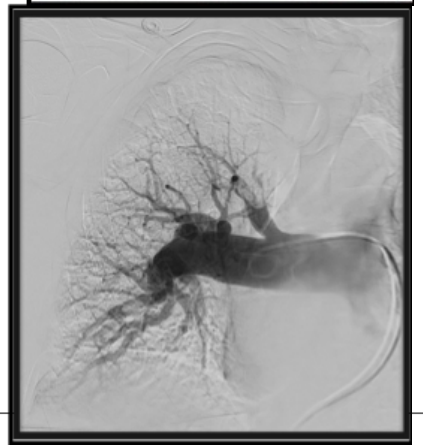












Inari FlowTriever® Courtesy of @carin_Gonsalves Jefferson Radiology

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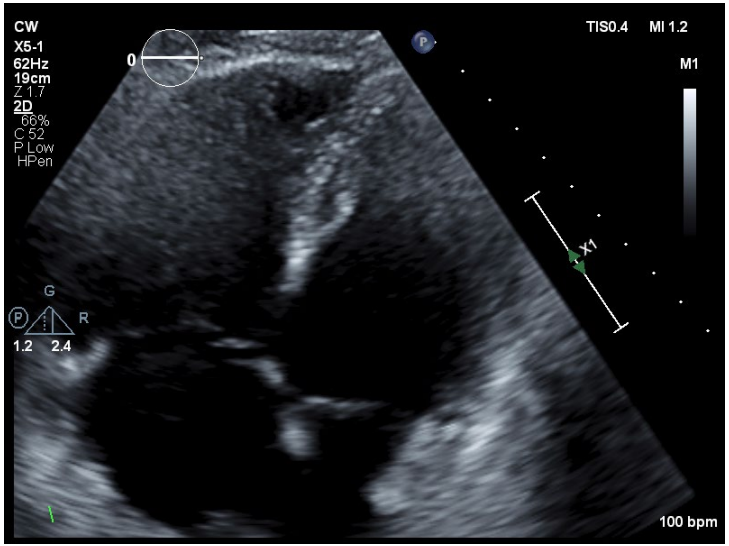
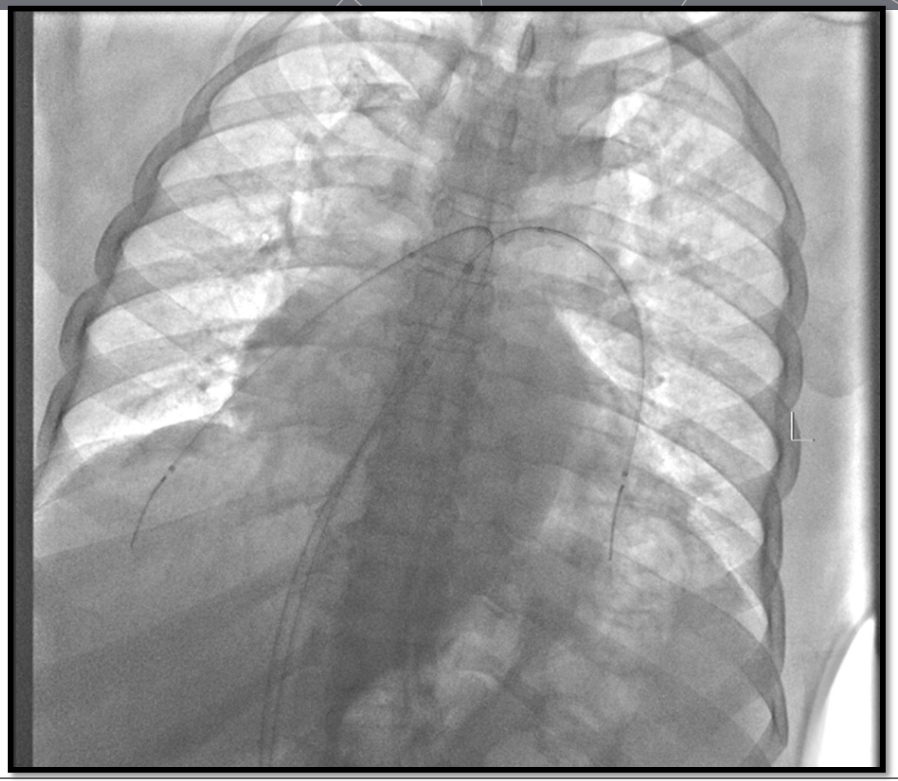
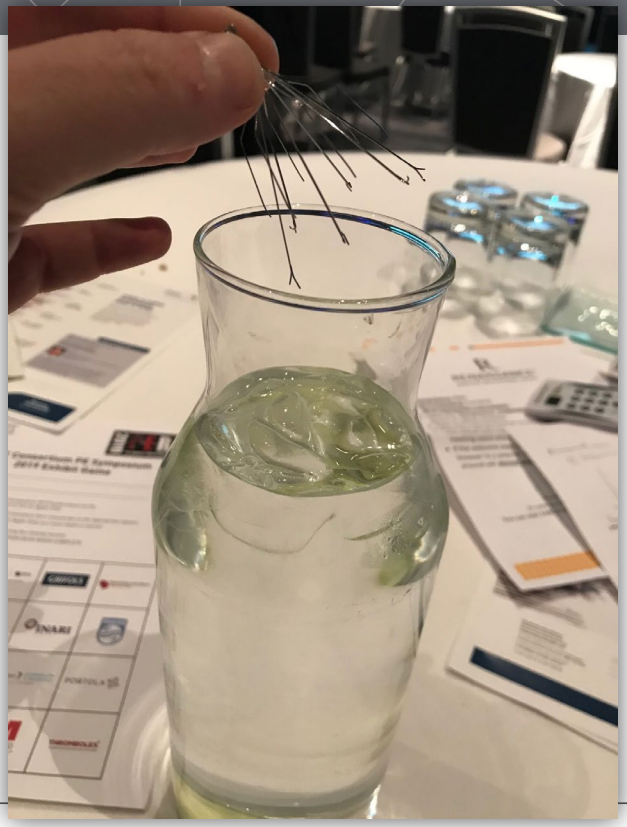
Most often, we are talking about Catheter Directed Low Dose Thrombolysis (CDT)





But, just like “filtered” water…

- CDT is everywhere now
- $$$› UFH
- Bleeding › UFH
- Data is poor
- When is it really useful?
- Is it any better than systemic lysis ?



Myocardial Infarction and pulmonary embolism are not the same disease

Myocardial Infarction

"Time is myocardium"

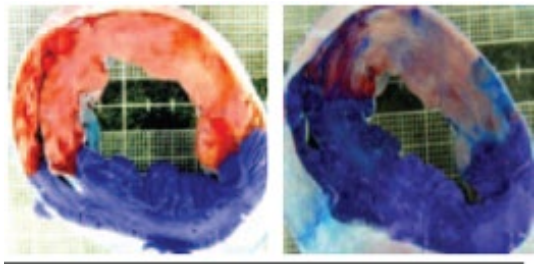


Image Riter Resuscitation 2009

Pulmonary **Embolism**

Infarction (*sometimes*)

Time is not lung

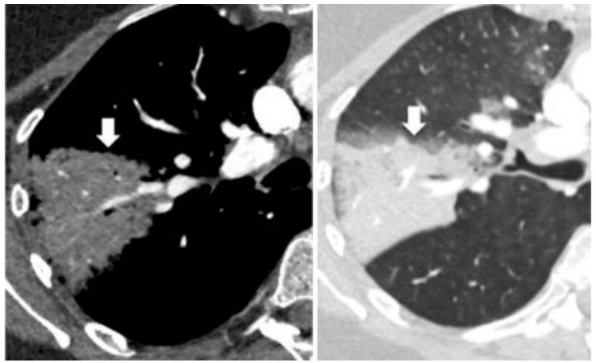
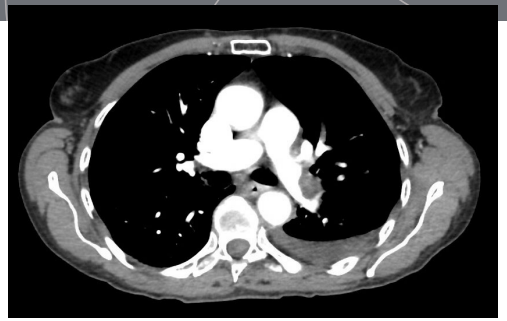
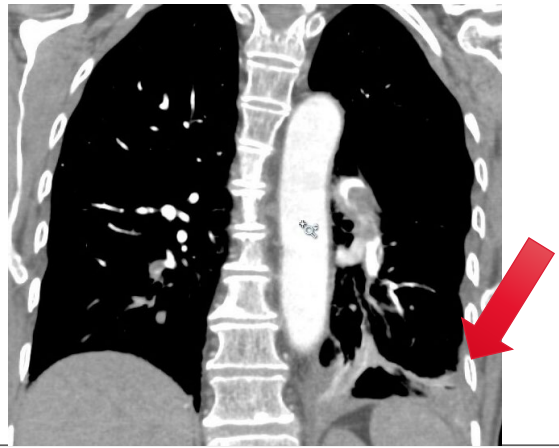
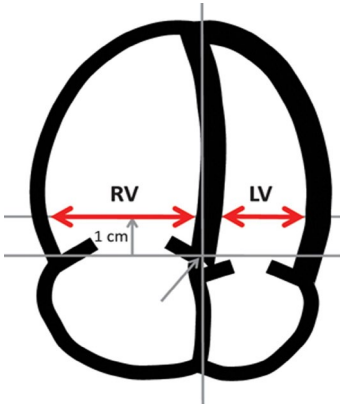


Image Bray Eur Jo Radiology 2014

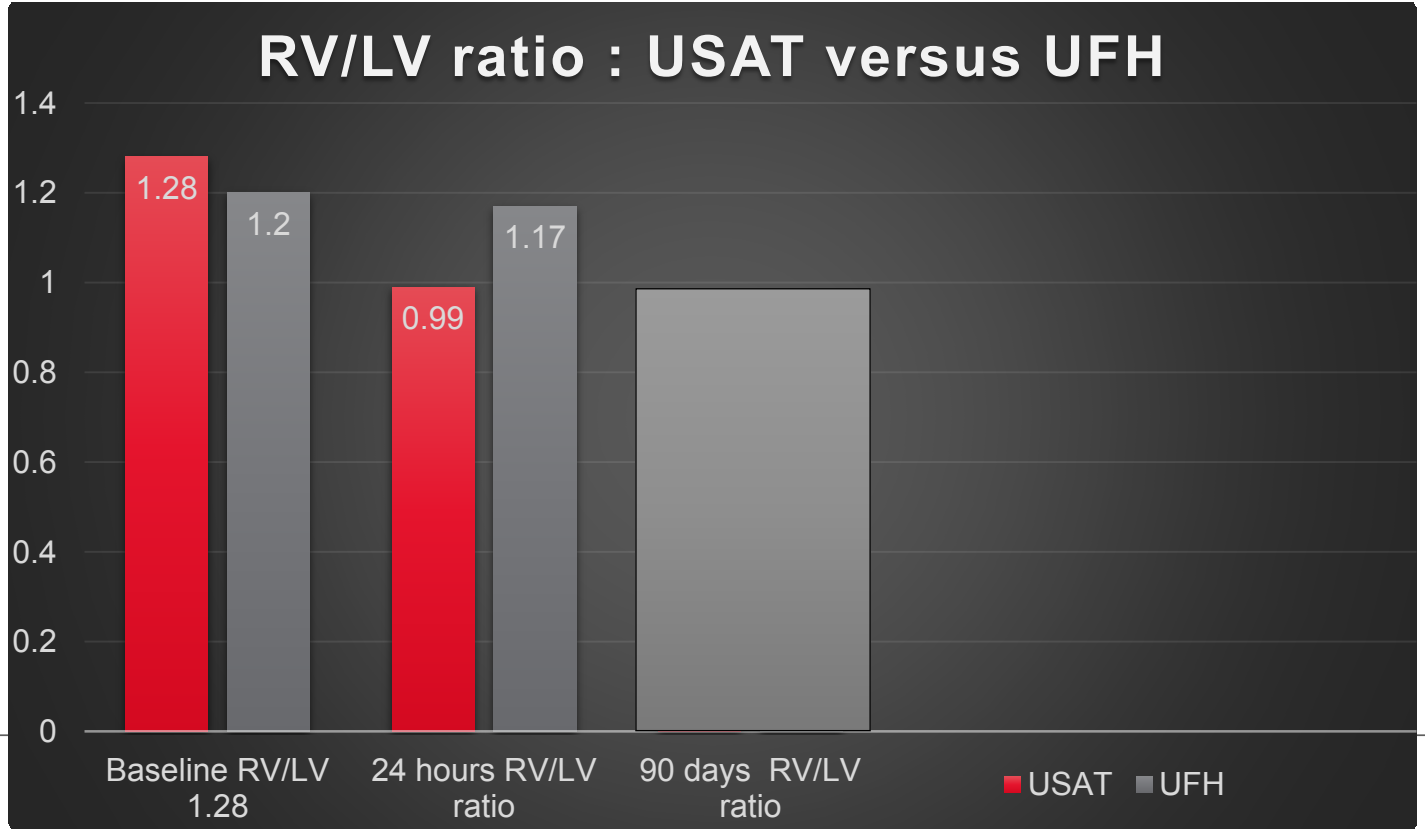




Ultima trial showed us that CDT leads to improvements in RV/LV ratio at 24 hours compared with heparin … but they caught up at 90 days



Data expressed as averages
Data Adapted from ULTIMA



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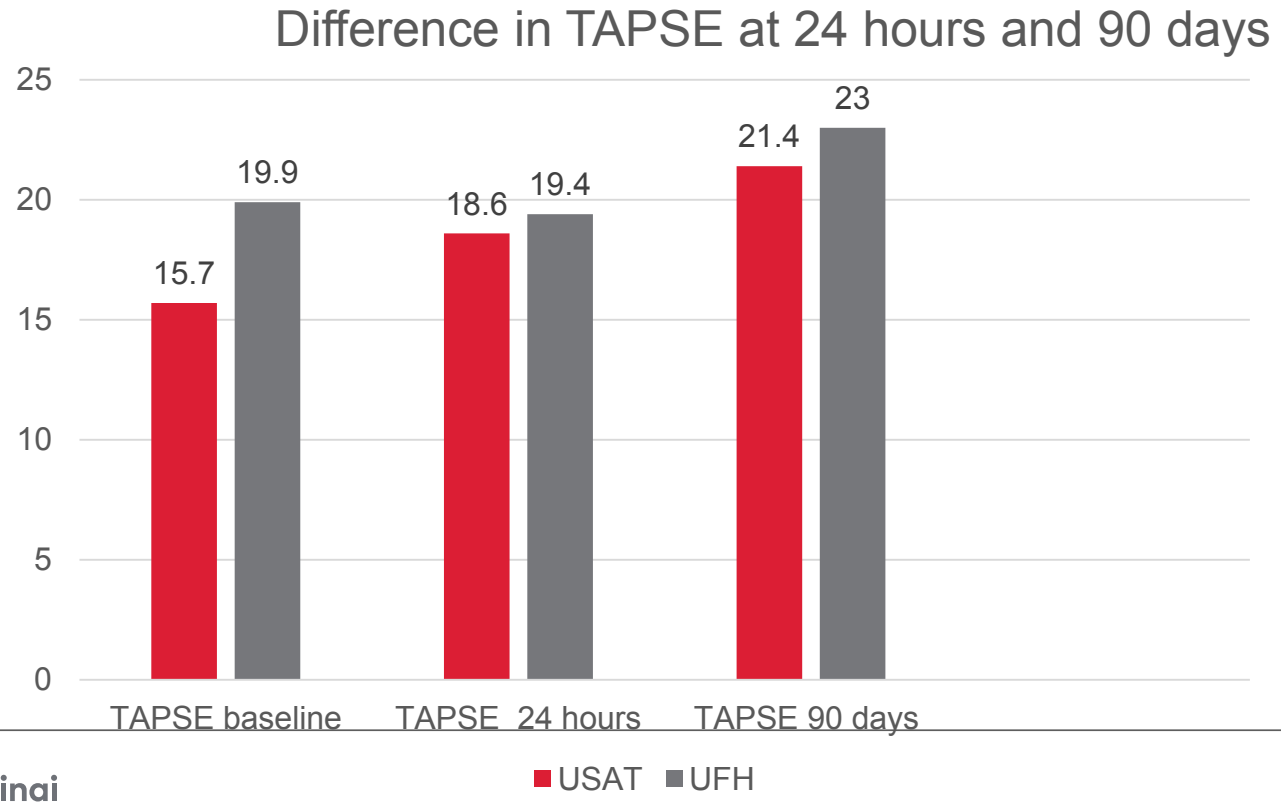
And there was no significant difference in TAPSE at 24 hours or 90 days



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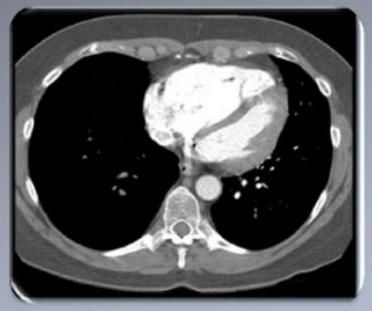
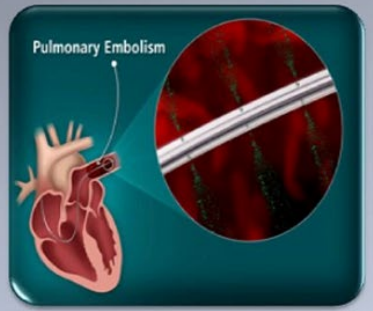
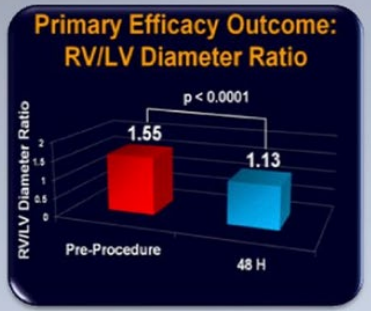
Seattle 2 trial single arm 150 patients







CT-confirmed PE

-Symptoms ≤14 days **AND**

-Massive or submassive PE **AND**

-RV/LV diameter ratio ≥0.9

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis

-tPA 1 mg/h for 24 h (1 device) **OR**

-tPA 1 mg/h for 12 h (2 devices)

TOTAL tPA Dose = 24 mg

Outcomes

-25% decrease in CT-measured RV/LV diameter ratio over 48 h

-30% decrease in pulmonary arterial systolic pressure by the end of the procedure

-30% decrease in pulmonary artery angiographic obstruction over 48 h

-No intracranial hemorrhage

PEITHO: endpoints were driven by a reduction in hemodynamic collapse at the cost of increased bleeds

Endpoint	Tenecteplase (n=506)	Heparin (n=499)	P-Value
1°(combined) endpoint*†	13 (2.6%)	28 (5.6%)	0.015
Death	6 (1.2%)	9 (1.8%)	.43
Hemodynamic Collapse	8 (1.6%)	25 (5%)	0.0002
Major Bleeding	32 (6.3%)	6 (1.5%)	<0.001
Stroke	12	1	
Hemorrhagic	10	1	
Ischemic	2	0	

Mortality rates were awfully low
If we cant prove it with 1k patients, how do we expect anything different with CDT

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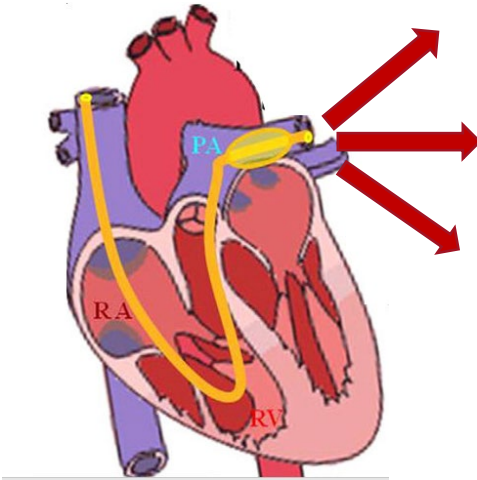
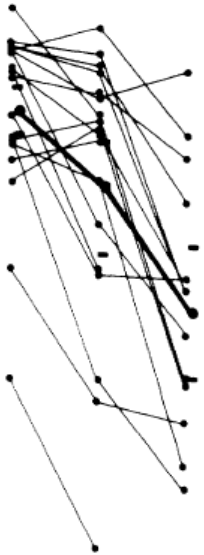
Meyer et al NEJM 2014

IV (systemic) versus PA delivered tPA has the same reduction in clot burden

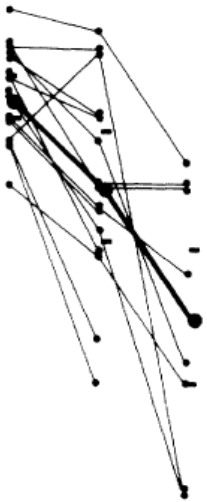


Miller score (angiographic score)

PA



IV



Baseline after 50mg after 100 mg baseline after 50 after 100

THERAPY AND PREVENTION
PULMONARY EMBOLISM

Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism

M. VERSTRAETE, M.D., G. A. H. MILLER, D.M., H. BOUNAMEAUX, M.D., B. CHARBONNIER, M.D., J. P. COLLE, M.D., G. LECORF, M.D., G. A. MARBET, M.D., P. MOMBAERTS, M.D., AND C. G. OLSSON, M.D.

ABSTRACT Eight centers participated in a study in which intrapulmonary and intravenous administration of recombinant tissue-type plasminogen activator (rt-PA) were compared in 34 patients with acute massive pulmonary embolism. All patients received intravenous heparin in a bolus of 5000 IU followed by 1000 IU/hr. After 50 mg rt-PA given over 2 hr the severity of embolism, determined from pulmonary angiograms, declined by 12% in the intrapulmonary drug group ($p < .005$) and 15% in the intravenous drug group ($p < .005$); mean pulmonary arterial pressure fell from 31 ± 7 to 22 ± 6 mm Hg ($p < .005$) and from 31 ± 12 to 21 ± 9 mm Hg ($p < .005$) in the respective groups. After a further 50 mg given over 5 hr (22 patients), the angiographically determined severity of embolism had decreased by 38% from baseline in the intrapulmonary drug group and by 38% in the intravenous drug group. The mean pulmonary arterial pressure further declined to 18 ± 7 and 12 ± 5 mm Hg in the respective groups. Fibrinogen levels dropped to 48% of baseline after 50 mg and to 36% of baseline after 100 mg rt-PA. Some degree of bleeding at puncture and/or operation sites was noted in 16 patients, including four who required a transfusion of two or more units of blood and had been operated on an average of 7.5 days (range 2 to 13) before thrombolytic treatment was started. In seven other patients thrombolytic treatment was initiated an average of 8.5 days (range 3 to 15) after surgery and only very minor or no bleeding was observed. This trial indicates that the intrapulmonary infusion of rt-PA does not offer a significant benefit over the intravenous route and suggests that a prolonged infusion of rt-PA over 7 hr (100 mg) is superior to a single infusion of 50 mg over 2 hr.

Circulation 77, No. 2, 353–360, 1988.

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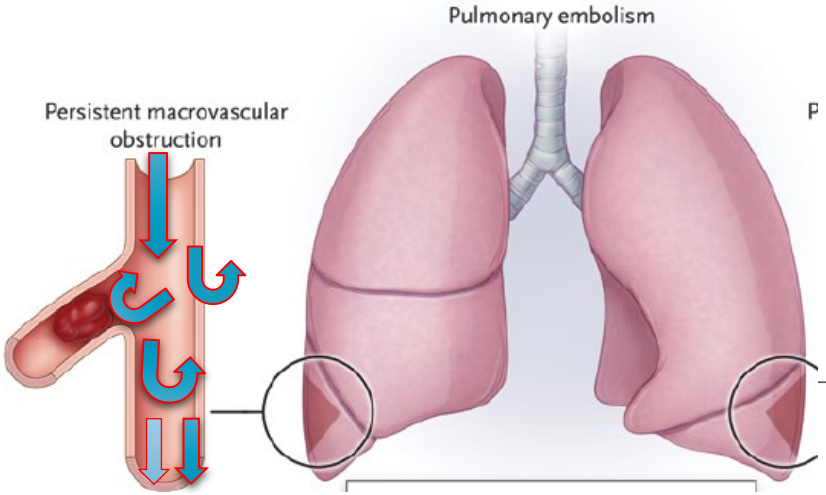
Does an infusion catheter “buried” into clot offer an advantage over systemic lytics

“ Yes please”

Vortex theory (below)

Higher local concentrations *may* be achievable with lower systemic concentrations

Studies “suggest” it dissolves clot safely



“Ehh, Show me the data “

The entire dose of systemic tPA goes right into the lung

Only plausible for short infusions where steady state systemic concentrations are not allowed to equalize

Modern CDT versus systemic lytics have not been directly compared

The lower bleeding rates may just be related to lower total doses of tPA and nothing to do with the catheter

The differences are theoretical

Residual Pulmonary Vascular obstruction - is more common than you think, and is associated with worse outcomes

Timing	RPVO
3 weeks	69%[1]
3months	46-66%[2,3]
6 months	25-52%[4,5,6,7]
9 months	28%[8]
11 months	26%[9]
1 year	25-29%[10,11]

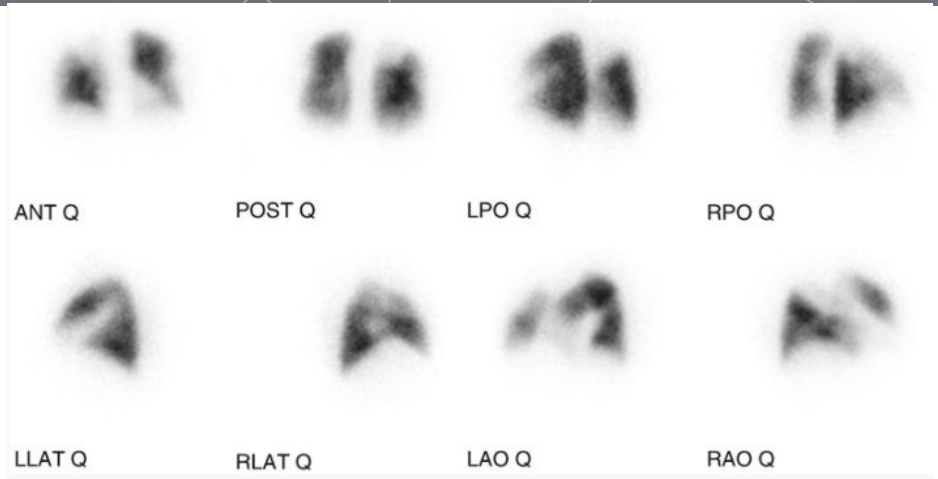
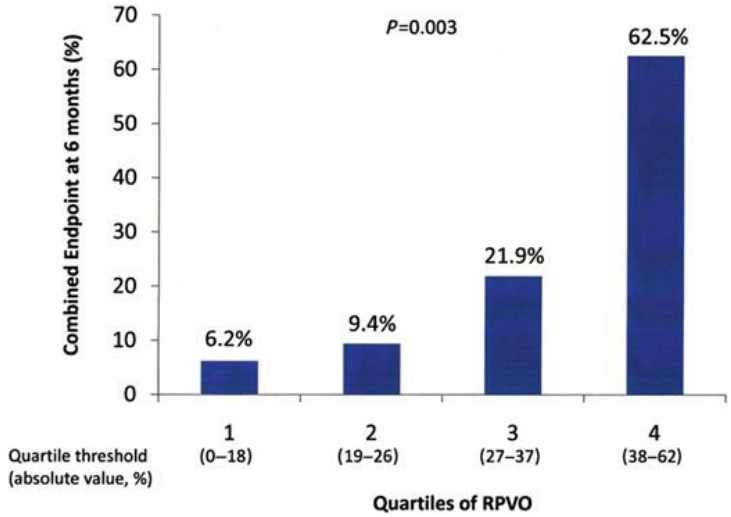


Image Forfia, Gopalan, Auger Its not CTEPH, but it is CTED 2020

1. *Van Es J Thr Hemostat. 2013*
2. *Chopard Am J Cardiol 2017*
3. *Wartski J Nucl med 2000*
4. *Meysman Ann Thorac. Med 2017*
5. *Pesavento Eur Resp Jo 2017*
6. *Kacynska Thromb Res 2008*
7. *Planquette Eur Resp J 2018*
8. *Cosmi Intern Emerge med 2011*
9. *Poli Thromb Haemost 2010*
10. *Sanchez J Thromb. Hemostat 2010*
11. *Lami Thromb Res 2014*

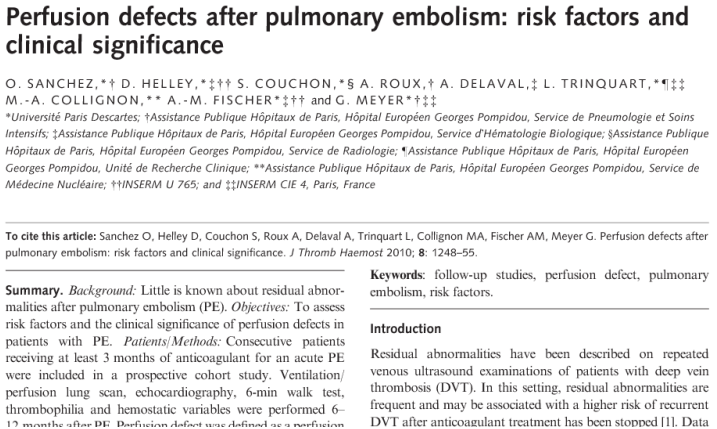
Both early and late RPVO predict poor outcomes

EARLY
416 patients RPVO on discharge associated with death/recurrent PE/CHF
↓ NYHA class at 6months



Meneveau Eur Heart Jo 2013

LATE
254 patients
- 29% patients had residual defects on VQ scan at median follow up of 12 months associated with ↑dyspnea, ↓ 6MWD, ↑PAP



Perfusion defects after pulmonary embolism: risk factors and clinical significance

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*Université Paris Descartes; †Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Pneumologie et Soins Intensifs; ‡Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service d'Hématologie Biologique; §Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Radiologie; ¶Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Unité de Recherche Clinique; **Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Médecine Nucléaire; ††INSERM U 765; and ‡‡INSERM CIE 4, Paris, France*

To cite this article: Sanchez O, Helley D, Couchon S, Roux A, Delaval A, Trinquart L, Collignon MA, Fischer AM, Meyer G. Perfusion defects after pulmonary embolism: risk factors and clinical significance. *J Thromb Haemost* 2010; **8**: 1248–55.

Summary. *Background:* Little is known about residual abnormalities after pulmonary embolism (PE). *Objectives:* To assess risk factors and the clinical significance of perfusion defects in patients with PE. *Patients/Methods:* Consecutive patients receiving at least 3 months of anticoagulant for an acute PE were included in a prospective cohort study. Ventilation/perfusion lung scan, echocardiography, 6-min walk test, thrombophilia and hemostatic variables were performed 6–12 months after PE. Perfusion defect was defined as a perfusion

Keywords: follow-up studies, perfusion defect, pulmonary embolism, risk factors.

Introduction

Residual abnormalities have been described on repeated venous ultrasound examinations of patients with deep vein thrombosis (DVT). In this setting, residual abnormalities are frequent and may be associated with a higher risk of recurrent DVT after anticoagulant treatment has been stopped [1]. Data

Sanchez J Thromb Haemost 2010

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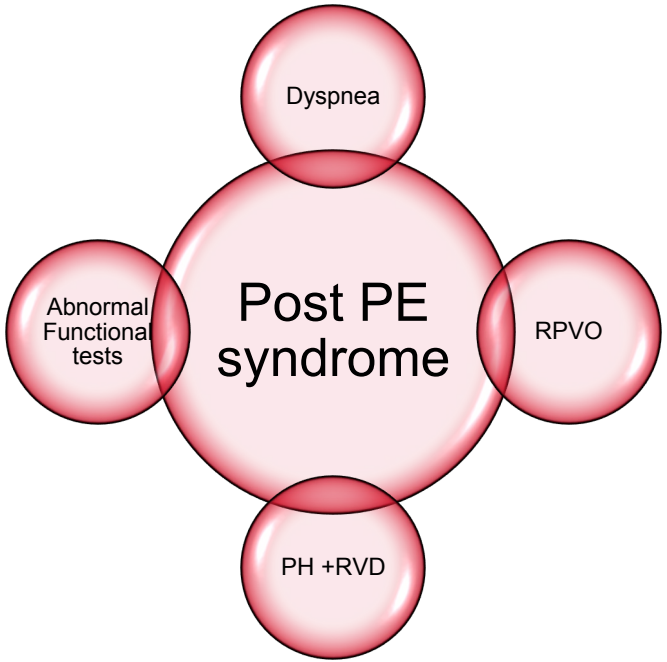
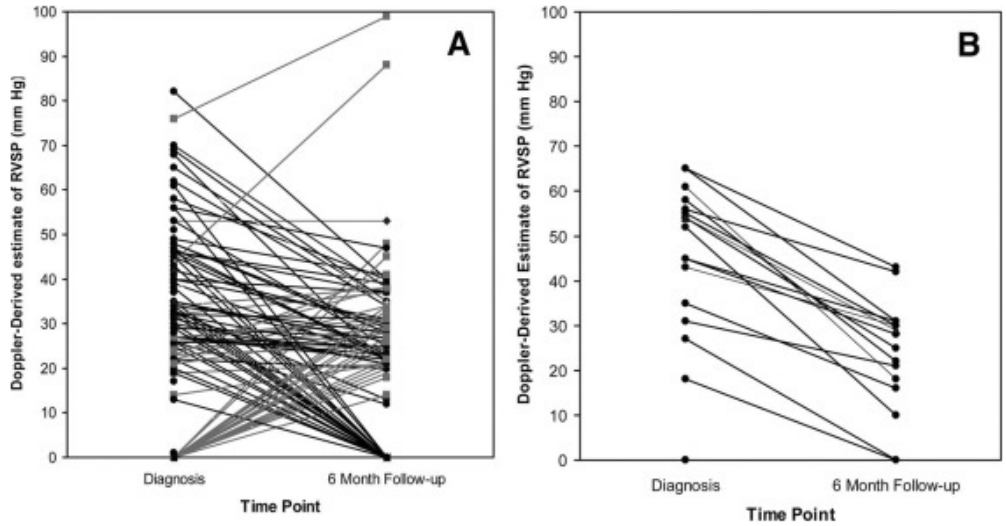
Post PE syndrome can occur in up to 50% of patients



Can up front CDT reduce the incidence of this poorly understood phenomenon of post PE syndrome ?

In this small non randomized trial 6 month resolution of pulmonary hypertension after intermediate risk PE was more consistent in the tPA group

Heparin only tPA



In patients with repeat CT or VQ at 6 months 26% had radiologic evidence of unresolved filling defects

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Kline Chest 2009

But… there was no reduction in CTEPH or pulmonary hypertension or RVD in the lysis group of PEITHO

TABLE 4 Findings in Patients With Echocardiographic Long-Term Follow-Up

	Tenecteplase (N = 144)	Placebo (N = 146)	p Value
Right ventricular end-diastolic diameter >30 mm	34 (23.6)	22 (15.1)	0.058
Missing data	12 (8.3)	11 (7.5)	
Right/left ventricular end-diastolic diameter >0.9	34 (23.6)	22 (15.1)	0.834
Missing data	12 (8.3)		
Hypokinesia of the right ventricular free wall (any view)	6 (4.2)		0.740
Missing data	4 (2.8)	4 (2.7)	
Tricuspid annulus plane systolic excursion reduced	14 (9.7)		07
Mean, mm Hg	4.8	23.9 ± 5.	
Median, mm Hg	24.0 (20.0-27.0	4.0 (21.0-26.0	0.551
Missing data,	19 (13.2)		
Tricuspid systolic velocity >2.6 m/s	22 (15.3)		0.412
Missing data	11 (7.6)	14 (9.6)	
Systolic pulmonary artery pressure, mm Hg			
Mean	31.6 ± 12.3	30.7 ± 10.2	0.527
Median	30.0 (24.0-35.0)	30.0 (25.0-35.0)	
Missing data	33 (22.9)	39 (26.7)	

RV size

RV function

PH

Summary and Disclaimer

It is still not clear which intermediate risk patients benefit from systemic tPA and by extension CDT

It is not clear there is any difference between CDT and systemic administered tPA

Clinical trials of CDT only show proof of improved RV/LV ratio but it looks like the heparin group catches up

Residual clot obstruction is bad and is part of the post PE syndrome

Up front systemic lysis does not decrease RVD, PH, or mortality so how can we expect CDT to be any different

Disclaimer: My practice is very similar to Vic and I do recommend CDT for many high intermediate risk patients

Cedars Sinai PERT

?

Oren Friedman
Pulm Crit

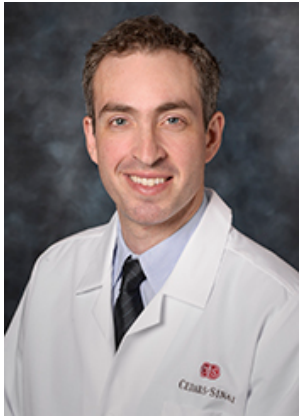
Suhail Dohad
Cardiology

Gabe Lipshutz IR

Siddharth Singh Echo
Cardiology

Danny Ramzy
CT surgery

Aaron Weinberg
Pulm Crit



Jonathan Steinberger IR