How Should We Treat High-Risk PE in 2020?

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Disclosure

- No Financial Disclosures
- I am
  - An Internist
  - A Cardiologist and believe BOTH ventricles matter
  - An Interventional Cardiologist
  - A Vascular and Endovascular Specialist
  - A PERT TEAM BELIEVER!!

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Right Ventricle Axioms
the forgotten and unloved ventricle

- " the RV is a ventricle too"
- " we are in fact not reptiles and have 4 chambered hearts "
- " if you think it's just a conduit, wait until it fails "

My favorite pulmonologist
Chad E. Miller, MD

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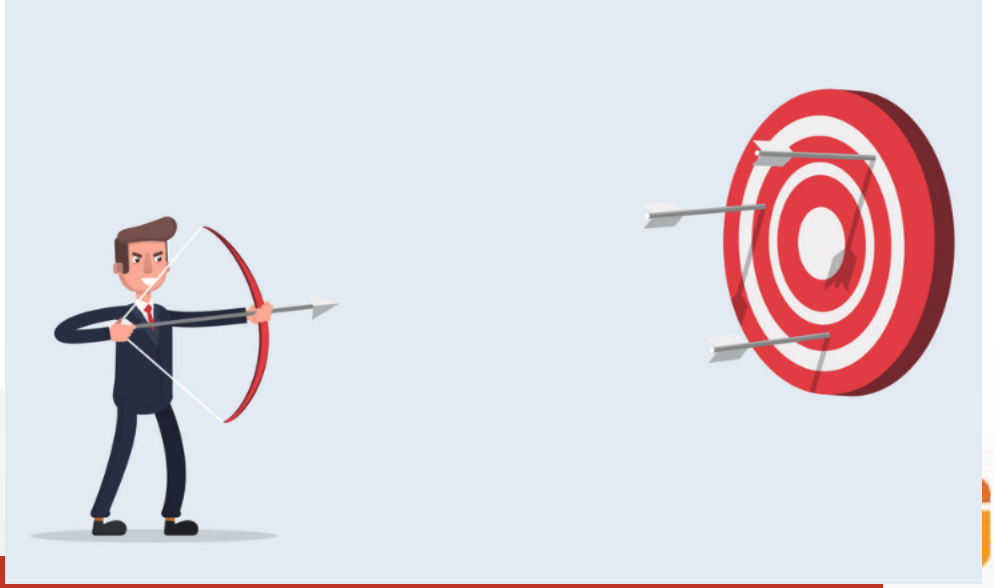
Objective

- Discuss best practices for modern, evidence-based treatment of high-risk PE
- MCS: Who and when?
- Lytics, Surgery, Endo
- MCS with AC alone



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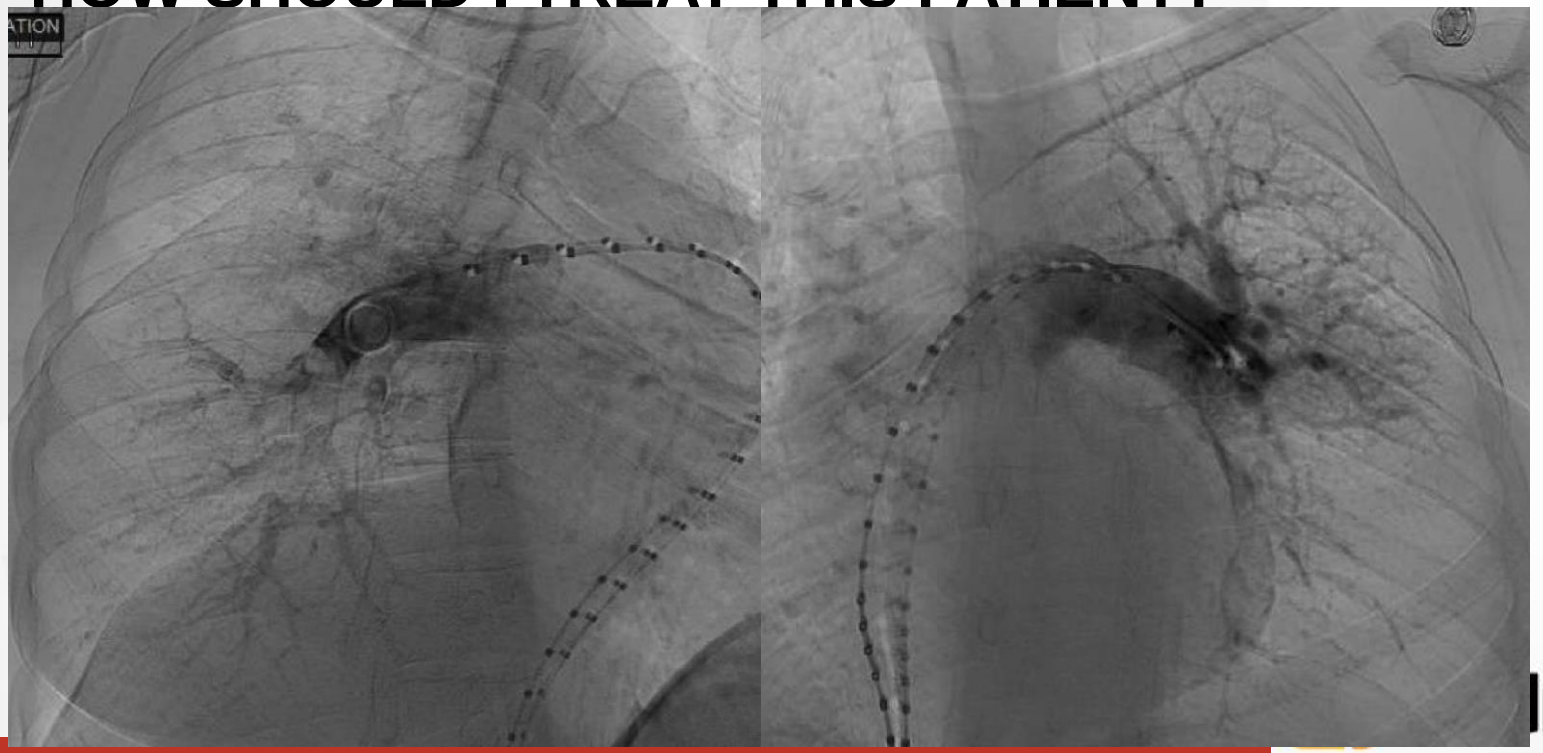
Know Thy Enemy

- 50 yr female with syncope, BP 90/50 mmHg
- RA: 14 PA: 52/17; 31 mmHg PCWP: 14mmHG
- **Fick CO/CI: 3.6/1.9**
- **TD CO/CI: 2.53/1.34**
- **HOW SHOULD I TREAT THIS PATIENT?**



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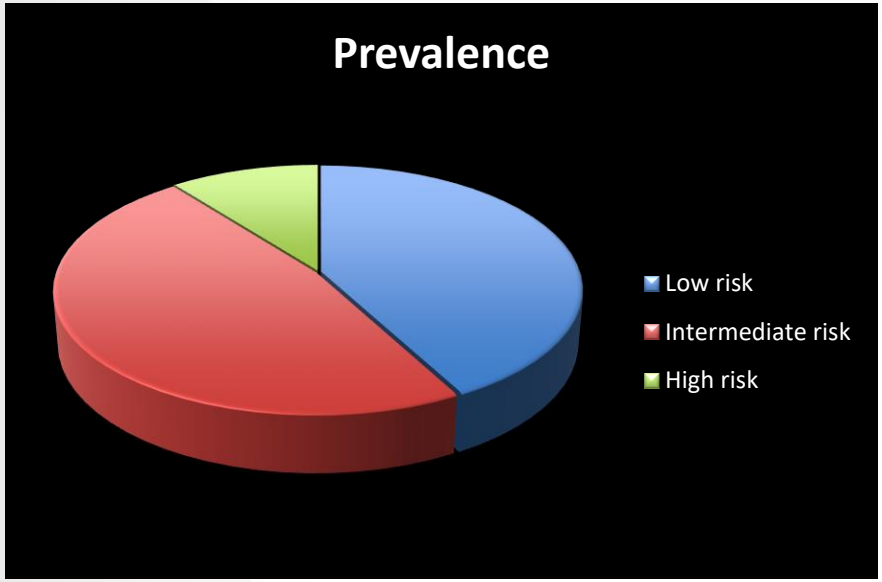
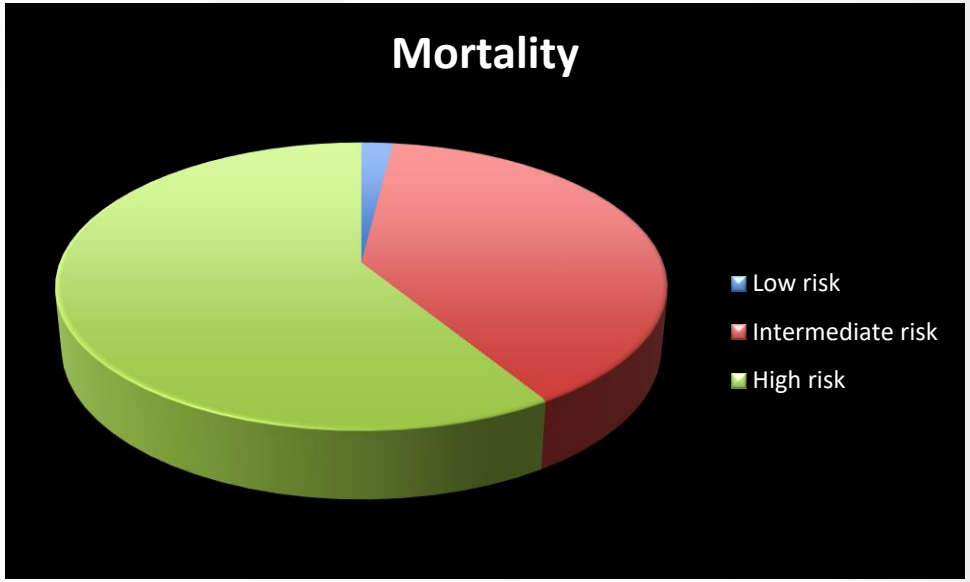
Prevalence and Impact





RISK	PREVALENCE	MORTALITY
Low	40%	1%
Intermediate	40-45%	5-20%
High	5-15%	>30%

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Risk of Mortality

American Heart Association Definitions of Massive, Submassive, and Low-Risk PE and Associated Mortality

PE Classification	Definition	Mortality
Massive	Acute PE with sustained hypotension (< 90 mm Hg systolic) > 15 minutes or requiring inotropic support	25%–65% (62)
Submassive	Systolic pressure > 90 mm Hg and either: (a) RV dysfunction (CT, BNP/proBNP, ECG changes) or (b) myocardial necrosis (elevated troponins)	3% (20)
Low risk	Absence of hypotension, RV dysfunction, and myocardial necrosis	<1% (20)

Note.—BNP = brain natriuretic peptide, ECG = electrocardiography.

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Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123(16):1788–1830.

PE Categories

- **Massive:**
  - **Acute PE with sustained hypotension** (systolic blood pressure 90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia,hypovolemia, sepsis, or left ventricular [LV] dysfunction)**pulselessness**, or **persistent profound bradycardia** (heart rate 40 bpm + shock)

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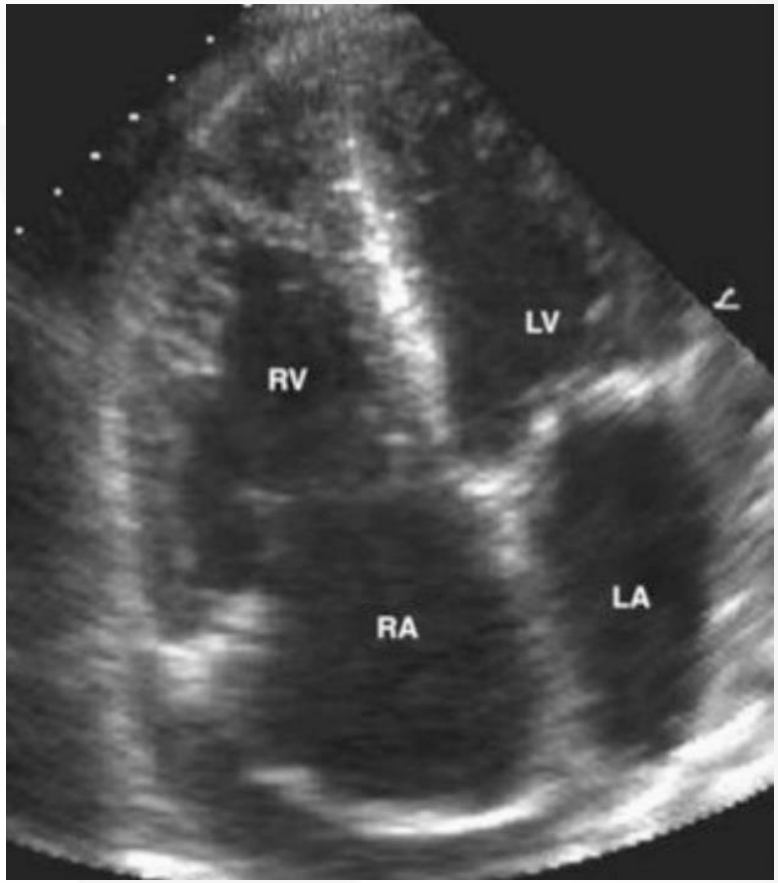
Pathophysiology

- PA pressure does not increase until > 30% of the pulmonary circulation is obstructed
- PA pressure goes up→ RV Dilates→tachycardia and increased contractility+ sympathetic activation.
- RV dilation increases intramural pressure increases→ reducing coronary blood flow→ decrease in contractility of the chamber→ Cannot get blood into lungs to left side of heart→ Hypotension
- RV dilation→ Bowing of the intraventricular septum and decreased filling of the left ventricle (LV)→Hypotension



McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 1971;28(3):288–294.
Piazza G, Goldhaber SZ. Management of submassive pulmonary embolism. Circulation 2010;122(11):1124–1129.

Pathophysiology of PE

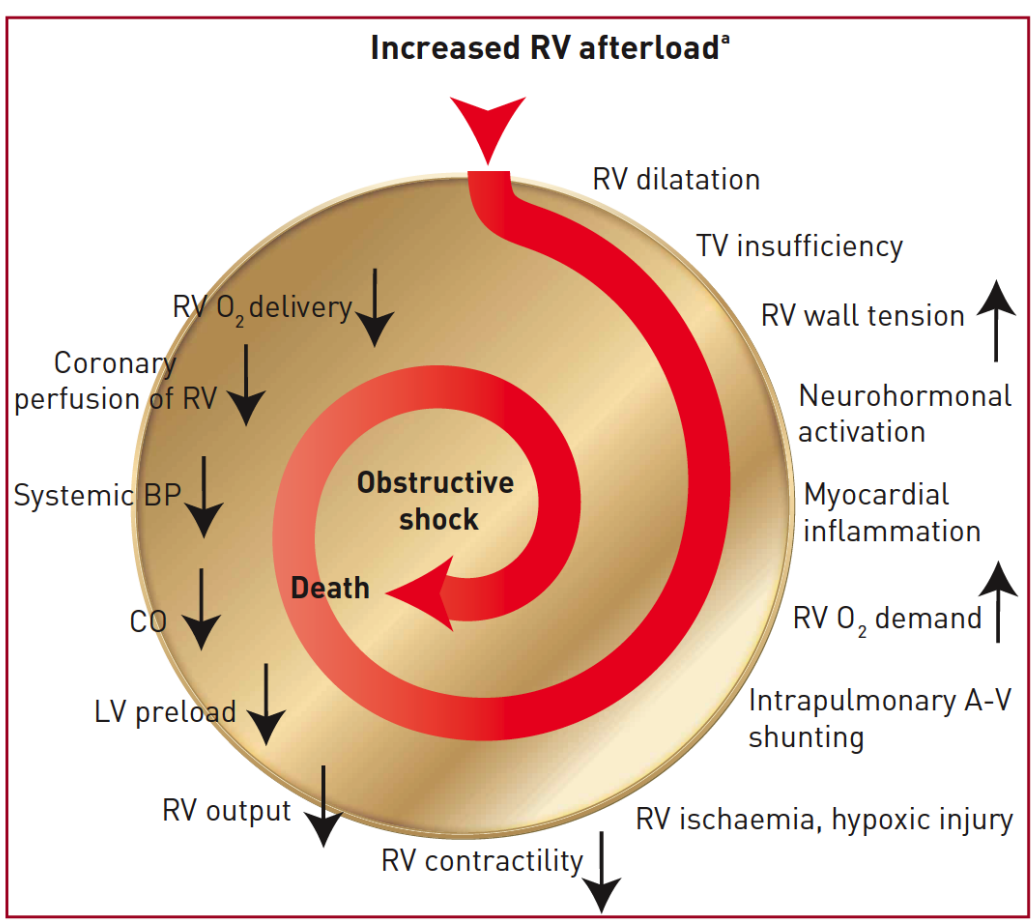


FIGURE 2 Key factors contributing to haemodynamic collapse and death in acute pulmonary embolism (modified from Konstantinides *et al.* [65] with permission). A-V: arterio-venous; BP: blood pressure; CO: cardiac output; LV - left ventricular; O2: oxygen; RV: right ventricular; TV: tricuspid valve. [a]The exact sequence of events following the increase in RV afterload is not fully understood.

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Definition of Cardiogenic Shock

TABLE 1 Definition and signs of cardiogenic shock

Hemodynamic criteria
1. Systolic blood pressure (SBP) of less than 90 mm Hg for >30 minutes, or use of vasopressors/inotropes to maintain SBP greater than 90 mm Hg
2. Reduced cardiac output (<1.8 L/min/m^2), or 2.0-2.2 L/min/m^2 with vasopressor/inotropic support, in presence of elevated pulmonary capillary wedge pressure
Signs of tissue hypoperfusion
1. Tachycardia
2. Pale, cool, and clammy peripheries, prolonged capillary refill time
3. Oliguria
4. Altered mental status/confusion
5. Elevated lactate
6. Mixed venous saturation of less than 65%

DEFINITION

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Clin Cardiol. 2019 Feb 26. doi: 10.1002/clc.23168. [Epub ahead of print]

Should PERT teams be like trauma teams?

The Golden Hour

The time following a traumatic injury when prompt medical treatment has the highest likelihood to prevent death

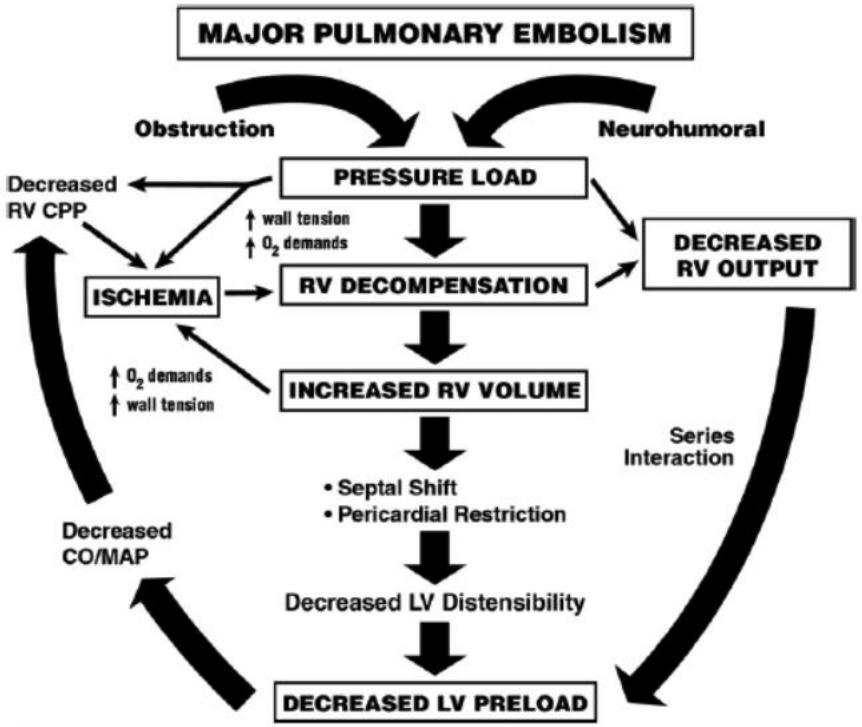

Fig. 2. Pathophysiology of PE. (*From* Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002;121;877–905; with permission.)

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What to Do!

- **Sound the alarm!**
- **Mobilize Team**
- **Stabilize the patient**

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Treatment of MASSIVE PE

- Stay Calm
  - Resist Intubation
- Upfront Stabilization Principles
- +/-Mechanical Circulatory Support
- Options for Definitive Therapy
  - Lytics
  - Surgery
  - CDT
    - Maceration of clot
    - Embolectomy
    - Lytic Infusion
  - AC alone

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Massive PE: Treatment

- **Volume administration is seldom helpful, and potentially harmful**
  - Excessive CVP elevation will over-distend the right ventricle→ LV diastolic compression of the left ventricle→ Decreased CO
  - The ideal CVP is probably in the mild-moderately elevated range (8-15mmHg?)

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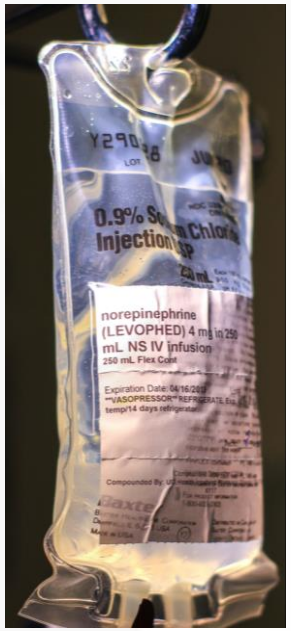
https://emcrit.org/pulmcrit/eight-pearls-for-the-crashing-patient-with-massive-pe/

Massive PE: Treatment

- **Consider starting norepinephrine early to maintain an adequate blood pressure**
- **For treatment failure, consider inhaled nitric oxide**
  - iNOPE trial
    - Inhaled nitric oxide failed to increase the proportion of patients with a normal troponin and echocardiogram but
    - Increased the probability of eliminating RV hypokinesis and dilation on echocardiography



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Ann Am Thorac Soc. 2014 Jun;11(5):811-22. doi: 10.1513/AnnalsATS.201312-446FR.
https://emcrit.org/pulmcrit/eight-pearls-for-the-crashing-patient-with-massive-pe/

Massive PE: Treatment

- Avoid Intubation if possible
- Immediately determine contraindications to thrombolysis using a checklist
  - IF Lytics, stop heparin
    - Heparin causes no acute improvement in hemodynamics, but increases risk of hemorrhage when combined with thrombolysis
- For thrombolytic candidates, pursue thrombolysis early OR PLACE ON ECMO

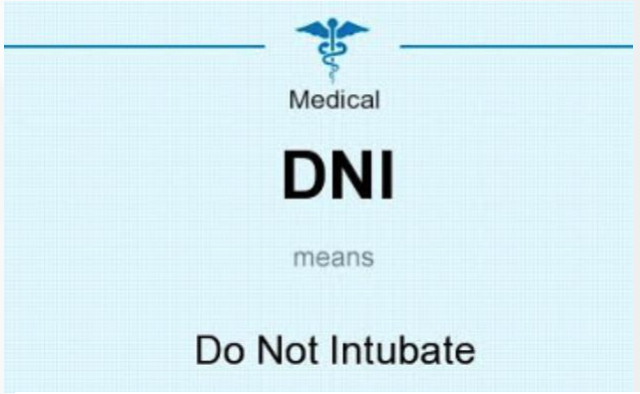

Table 2: Contraindications to Thrombolytic Therapy

Absolute Contraindications
Any prior intracranial hemorrhage
Known intracranial malformation or neoplasm
Ischemic stroke <3 month
Suspected dissection
Recent surgery
Recent head trauma
Bleeding diathesis
Relative Contraindications
>75 years of age
Current anticoagulants
Pregnancy
Cardiopulmonary resuscitation >10 minutes
Recent internal bleed (2–4 weeks)
Uncontrolled hypertension (180/110 mmHg)
Remote ischemic stroke
Major surgery within 3 weeks

Modified from Jaff et al.[39]

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Castillo C[1], Tapson VF. Cardiol Clin. 2012 May;30(2):233-41. doi: 10.1016/j.ccl.2012.03.003.

Massive PE: Treatment

- **IF LYTICS**
  - **Plan for failure: Know how to code an arresting PE patient**
  - Lytics and continue compressions
  - Do not pause compressions to intubate
    - LMA, Glidescope
  - Get pressor drip going, assume repeat loss of pulse
  - 35% of PE patients in MAPPET study survived w CPR

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J Am Coll Cardiol. 1997 Nov 1;30(5):1165-71.

https://emcrit.org/pulmcrit/eight-pearls-for-the-crashing-patient-with-massive-pe/

MCS and ECPR

- ECPR: initiation of venoarterial ECMO (VA-ECMO) for cardiac arrest patients requiring ongoing cardiopulmonary resuscitation (CPR)
- Observational studies
  - Improvements in ROSC, mortality, and neurologic outcomes with ECPR;
  - NO RCTS
  - Class IIb recommendation in patients with cardiac arrest with ongoing CPR after 10 min.

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AHA guidelines 2015

Mechanical Circulatory Support

- Support is based on prior considerations:
  - Bridge to Decision (ie: ECPR)
  - Bridge to Recovery (AC alone)
  - Bridge through a procedure (Embolectomy)
  - Bridge to Destination (RVAD?)

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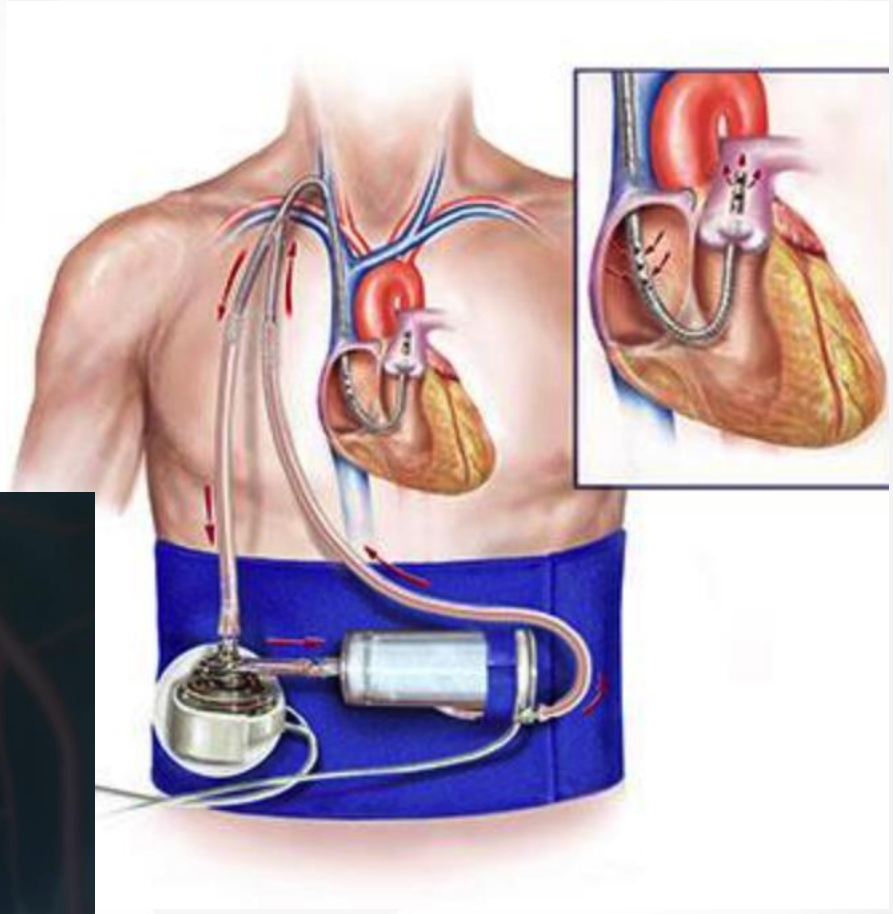
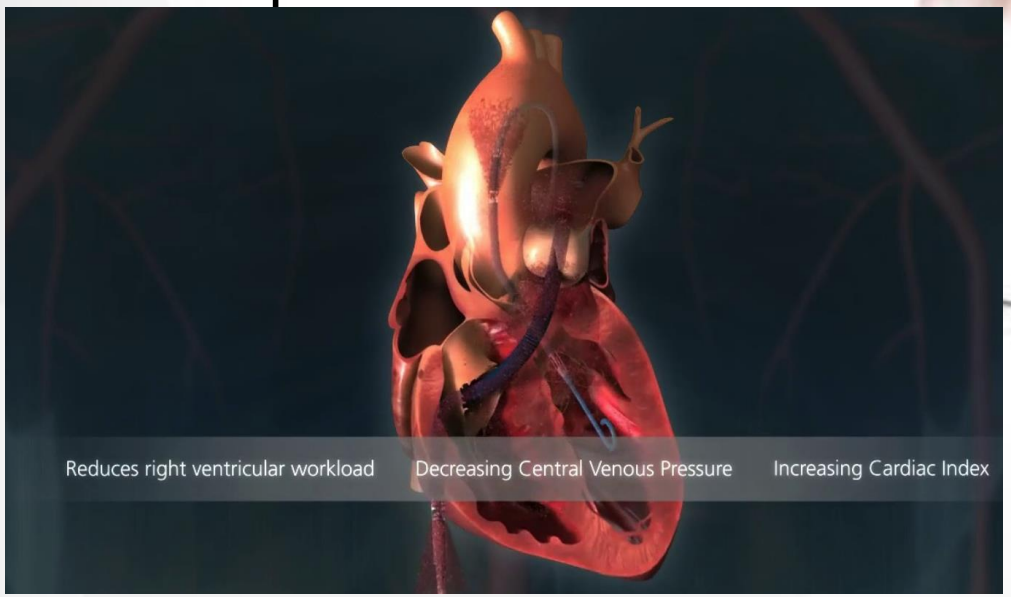
‘Alternative’ MCS for RV

- Protek Duo
  - 2 sites
  - IJ and PA
  - Oxygenator capable
  - Bypass RV
- RV IMPELLA
- ECMO preferred





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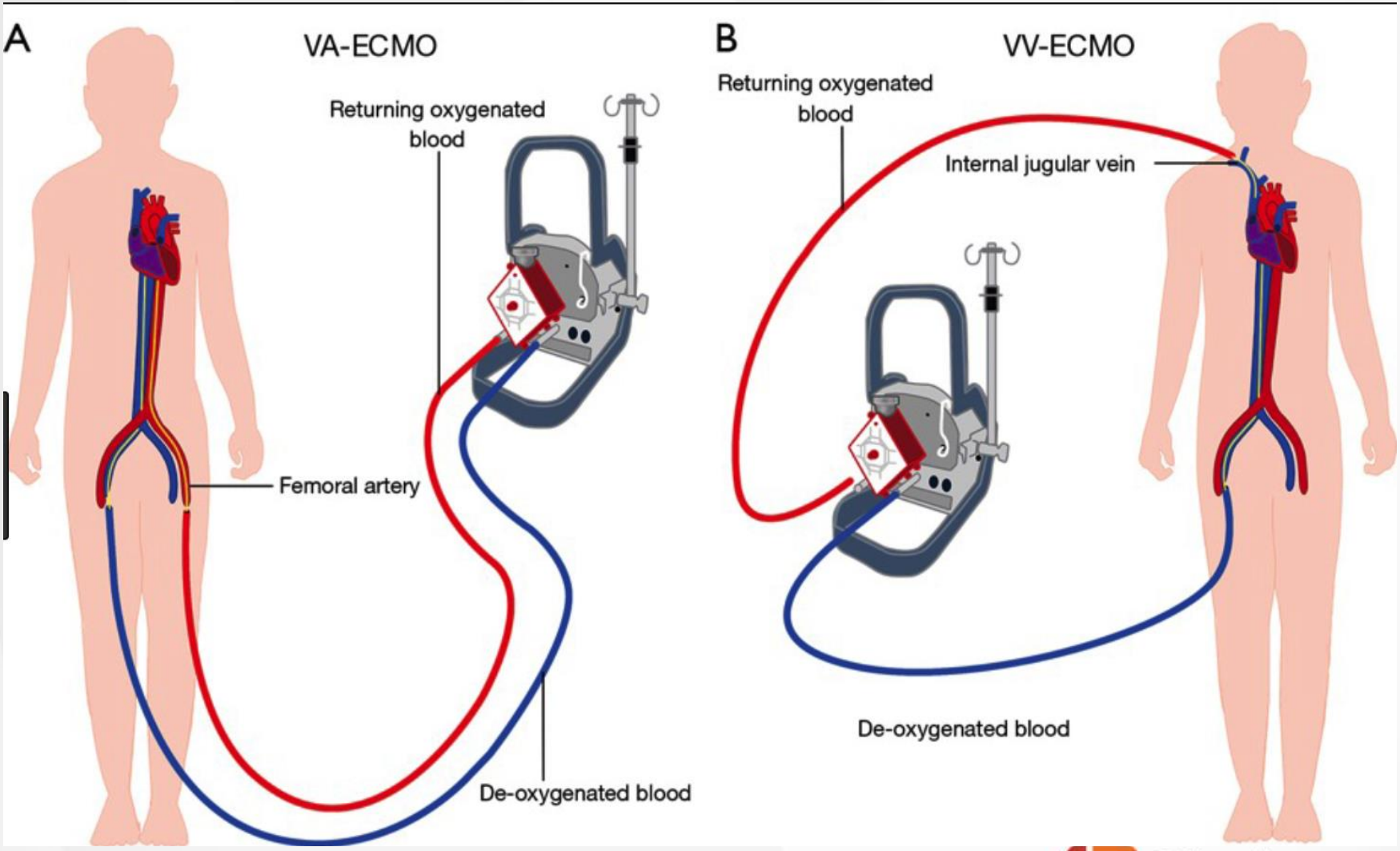
ECMO



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ECMO

- Extracorporeal Life Support Organization (ELSO) Registry
  - 87,000 pts
  - 12,566 adults to VA ECMO
- Hospital Mortality Rates: 50-60%
  - 6 month Survival 30%

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Circ Cardiovasc Interv. 2017;e004337:10.

ECMO Data

- 12 studies
  - 7 Retrospective
  - 2 meta-analysis
  - 3 prospective
- Pts with reversible causes do better
- eCPR patients do poorly
  - Older age,female gender, higher BMI, lactate, reduced PT time, vent time

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Piedmont ECMO INCLUSION

- Acute cardiac insufficiency with reversible cause
- **Acute RV failure with reversible cause (PE)**
- Prolonged vasodilatory shock
- Refractory Cardiac arrest in previously healthy patient with limited co-morbidities and arrest time <60 min
- Witnessed arrest
- Severe potentially reversible respiratory failure
- RESP score 1-2
- Hypoxic respiratory failure with mortality>80% as defined by PAO2/FIO2 <0.80 on FIO2 >0.90, Murray Score 3-4

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Piedmont ECMO EXCLUSION

- Unknown arrest time
- End Tidal CO2 <18 after 8 minutes of BCLS/ACLS
- Pre-existing terminal condition or malignancy
- Severe neuro disease, CNS injury or recent hemorrhage
- Recent Systemic TPA
- Known irreversible heart/lung disease (CM or COPD when not tx or LVAD candidate)
- Poor functional status

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Mechanical Circulatory Support and PE

- eCPR
- Need time to decide in hypotensive PE patient
- BEFORE Lytics
- TEAM Approach
  - MCS:IC and/or CTS
  - PERT TEAM
    - ED
    - Interventionalist
    - CT Surgeon
    - Pulmonary

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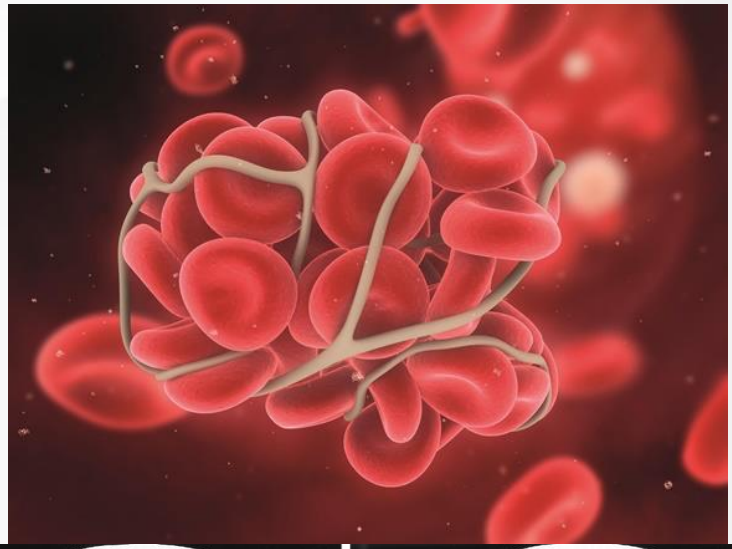
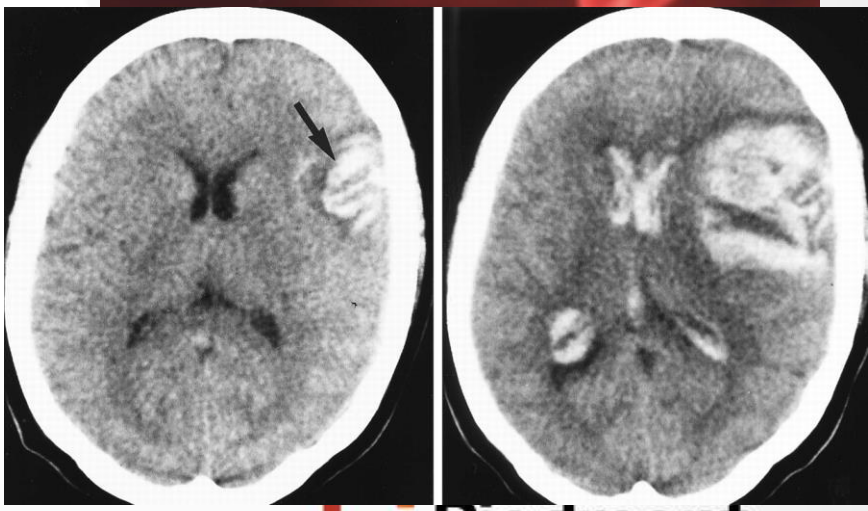
Treatment of Massive PE: Lytics

- Systemic Thrombolytics
  - Alteplase, tenecteplase
  - Ease of Administration
  - ICH Risk
  - Usually reserved for massive PE





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Treatment of Massive PE-Lytics

- RCT
- **8 patients**
  - 1,500,000 IU + heparin vs. heparin alone
- Time of onset of shock:
  - SK group (2.25 +/- 0.5 hrs) vs. heparin (1.75 +/- 0.96 hrs)
- 4 pts in SK group survived up to 2 years
- 4 pts in heparin group died within 1-3 hrs in ED with autopsy proven PE

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Streptokinase and Heparin versus Heparin Alone in Massive Pulmonary Embolism: A Randomized Controlled Trial. J Thromb Thrombolysis. 1995;2(3):227-229

Treatment of PE: Lytics and ICH

TABLE 4: Rate of intracranial hemorrhage (ICH) among patients with PE treated with to heparin +/- thrombolysis

	Dose	ICH rate, Heparin + Placebo	ICH rate, Heparin + Lytics
PIOPED 1990	40-80 mg alteplase	0/4	0/9
Levine 1990	0.6 mg/kg alteplase	0/25	0/33
Dalla-Volta 1992	100 mg alteplase	0/16	1/20
Konstantinides 2002	100 mg alteplase	0/138	0/118
Fassulo 2011	100 mg alteplase	0/35	0/37
Sharifi 2012	50 mg alteplase	0/60	0/61
All Alteplase v. Placebo		**0/278**	**1/278 (0.4%)**
Levine 1990	0.6 mg/kg alteplase	0/25	0/33
Sors 1994	0.6 mg/kg alteplase	No placebo arm	0/36
Wang 2010	50 mg alteplase	No placebo arm	0/65
Sharifi 2012	50 mg alteplase	0/60	0/61
Sharifi 2014	50mg alteplase	No placebo arm	0/98
All Alteplase Reduced Dose			**0/293 (0%)**
Becattini 2010	30-50 mg tenecteplase	0/30	1/28
Meyer 2014	30-50 mg tenecteplase	1/499	10/506
Kline 2014	30-50 mg tenecteplase	0/43	1/40
All Tenecteplase v. Placebo		**1/572**	**12/574 (2.1%)**

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TREATMENT OF MASSIVE PE

- Lytics
- Surgery
  - If lytics contraindicated (absolute/relative)
  - Stable for OR
    - ECMO

Table 2: Contraindications to Thrombolytic Therapy

Absolute Contraindications
Any prior intracranial hemorrhage
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Ischemic stroke <3 month
Suspected dissection
Recent surgery
Recent head trauma
Bleeding diathesis
Relative Contraindications
>75 years of age
Current anticoagulants
Pregnancy
Cardiopulmonary resuscitation >10 minutes
Recent internal bleed (2–4 weeks)
Uncontrolled hypertension (180/110 mmHg)
Remote ischemic stroke
Major surgery within 3 weeks

Modified from Jaff et al.[39]

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Treatment of PE:

Surgical Embolectomy

- Massive or Failed Lysis
- Single Center Study
  - October 1999-February 2004
  - 47 patients
  - 12 (26%) of 47 patients were in cardiogenic shock
  - 6 (11%) of 47 were in cardiac arrest.
  - Results
    - 3 (6%) operative deaths, 2 with cardiac arrest; 2 of these 3 patients required RVAD
    - Median length of stay was 11 days (range, 3-75 days).
    - Median follow-up was 27 months (range, 2-50 months);
    - 6 (12%) late deaths, 5 of which were from metastatic cancer.
    - Actuarial survival at 1 and 3 years' follow-up was 86% and 83%, respectively.

TABLE 2. Indications for surgical embolectomy (n = 47)

Indication	N (%)
Contraindications to thrombolysis	21 (45%)
Recent surgical intervention	10 (21%)
Active bleeding	3 (6%)
Stroke	4 (9%)
Other	4 (9%)
Failed medical treatment	5 (10%)
Failure of thrombolytics	4 (9%)
Failure of catheter embolectomy	1 (2%)
Large RA-RV thrombus	5 (10%)
RV hemodynamic dysfunction	15 (32%)
Large PFO	1 (2%)

RA-RV, Right atrium–right ventricle; *PFO*, patent foramen ovale.

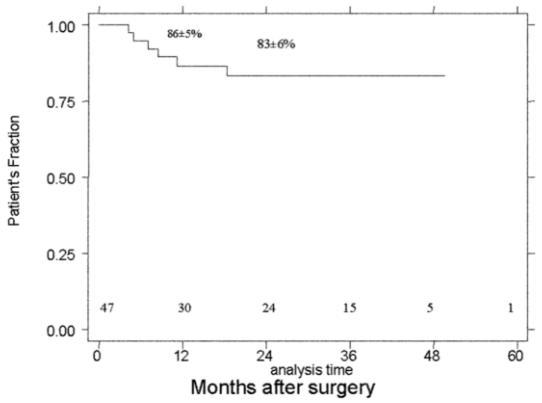

Figure 3. Kaplan-Meier survival curve after surgical pulmonary embolectomy (n = 47 patients, including the 3 operative deaths).

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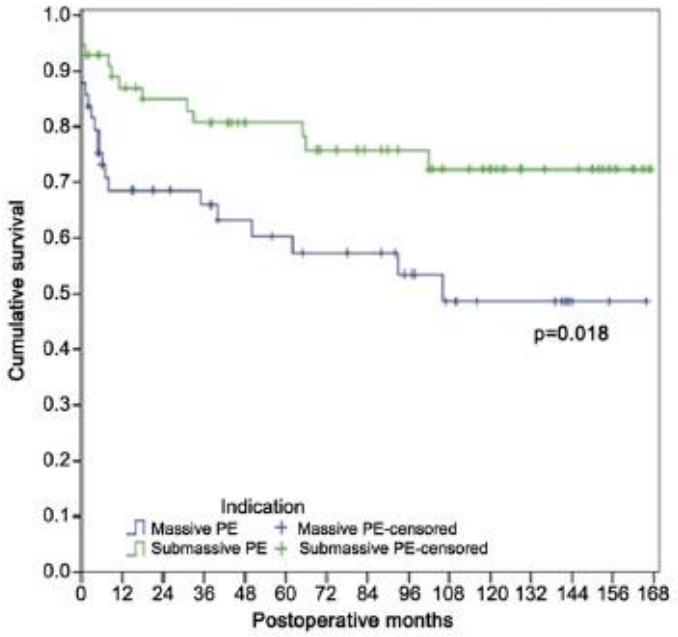
Leacche M et al. J Thorac Cardiovasc Surg 2005;129: 1018-23

Treatment of PE: Surgical Embolectomy

- Mortality
  - 1985-2005 (20%)
  - <1985 (32%)
- Single center studies
  - 115 pts
  - Mortality 3.6%
  - 1-year survival 80.4%
- Stable pts do better
- Morbidity



Number at risk

Starting month	0	24	48	72	96	120	144
Massive PE	47	27	22	18	12	7	2
Submassive PE	54	40	34	27	21	14	7

Fig 3. Kaplan-Meier survival curves comparing massive pulmonary embolism (PE) group (blue line) and submassive PE group (green line), n = 105 (p = 0.018). Blue hatch marks indicate massive PE censored; green hatch marks indicate submassive PE censored.

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Ann Thorac Surg 2015;100:1245–52

Treatment of Massive PE-Surgery

- Viable Option in Experienced Centers

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Treatment of Massive PE-CDT

- ACP recommends CDT in massive PE:
  - Contraindications to thrombolysis
  - Failed thrombolysis
  - Shock that is likely to cause death before systemic thrombolysis can take effect.

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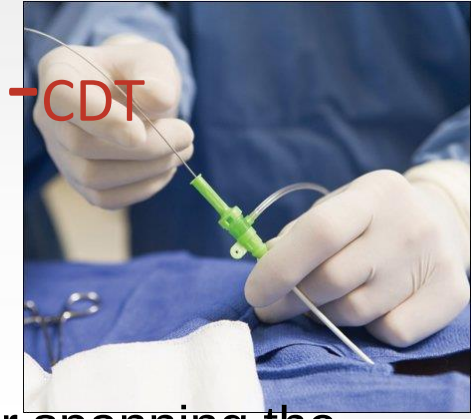
Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149(2):315–352.

Treatment of Massive PE-CDT



- 594 patients Meta-Analysis
- “Modern” techniques
  - <10-F fragmentation and/or aspiration
  - Fibrinolytic infusion through a multisidehole catheter spanning the thrombus.
- Clinical success: 86.5%
  - Stabilization of hemodynamics
  - Resolution of hypoxia
  - Survival to hospital discharge
- 96% of patients: CDT with no prior systemic tPA infusion
- 33% mechanical treatment alone without local thrombolytic infusion
- Success enhanced with:
  - Local and extended thrombolytic therapy
- Major procedural complications occurred in 25 patients
  - Angiojet related

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J Vasc Interv Radiol 2009;20(11):1431–1440.

Treatment of Massive PE-CDT

- CDT with *mechanical fragmentation*
  - 111 patients
  - Normalized PAP@30–90-d
  - Major complication rate: 4.5%
    - 7 deaths: 3 progressive RV failure and 1 ICH
- ECMO Support

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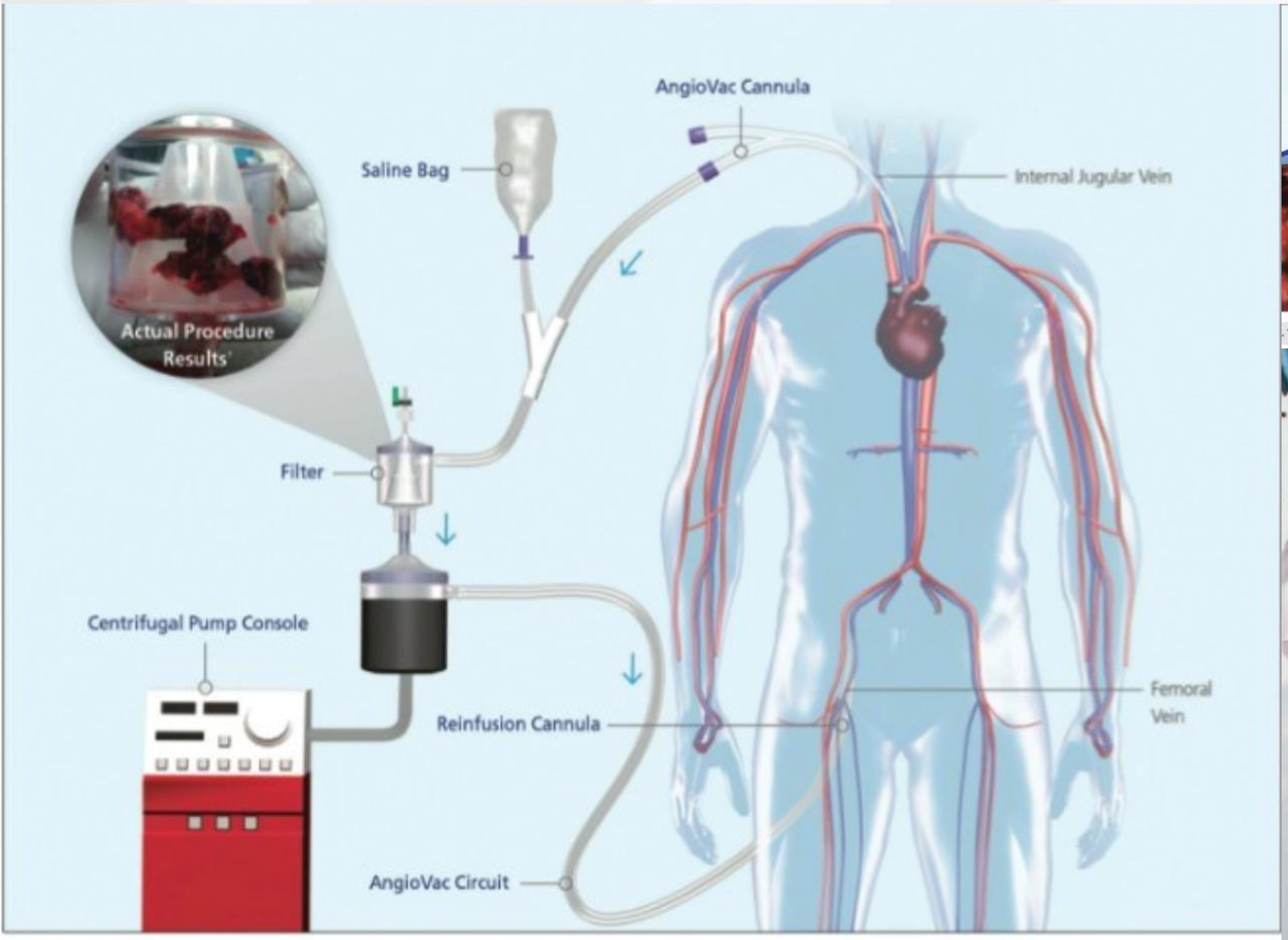
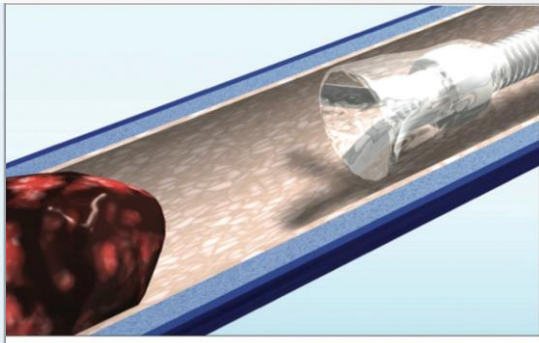
Arch Bronconeumol 2011;47(1):17–24.

Treatment of PE: AngioVac





. The 22F coil-reinforced AngioVac venous drainage cannula.

Figure 1. An extracorporeal circuit is created outside the body consisting of an outflow line, a centrifugal pump, a filter and an inflow line. †An individual experience may not be indicative of all procedure results.

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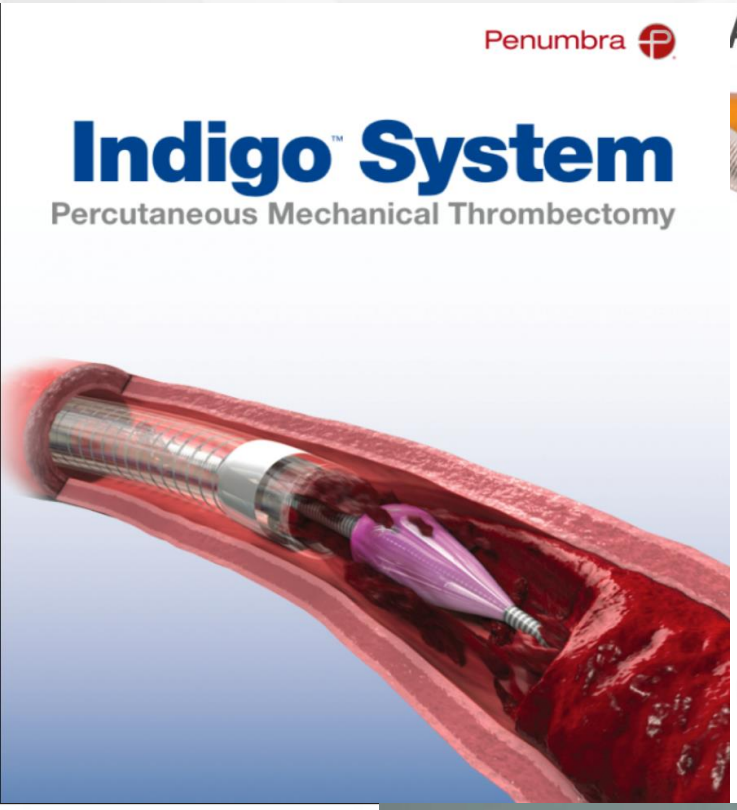
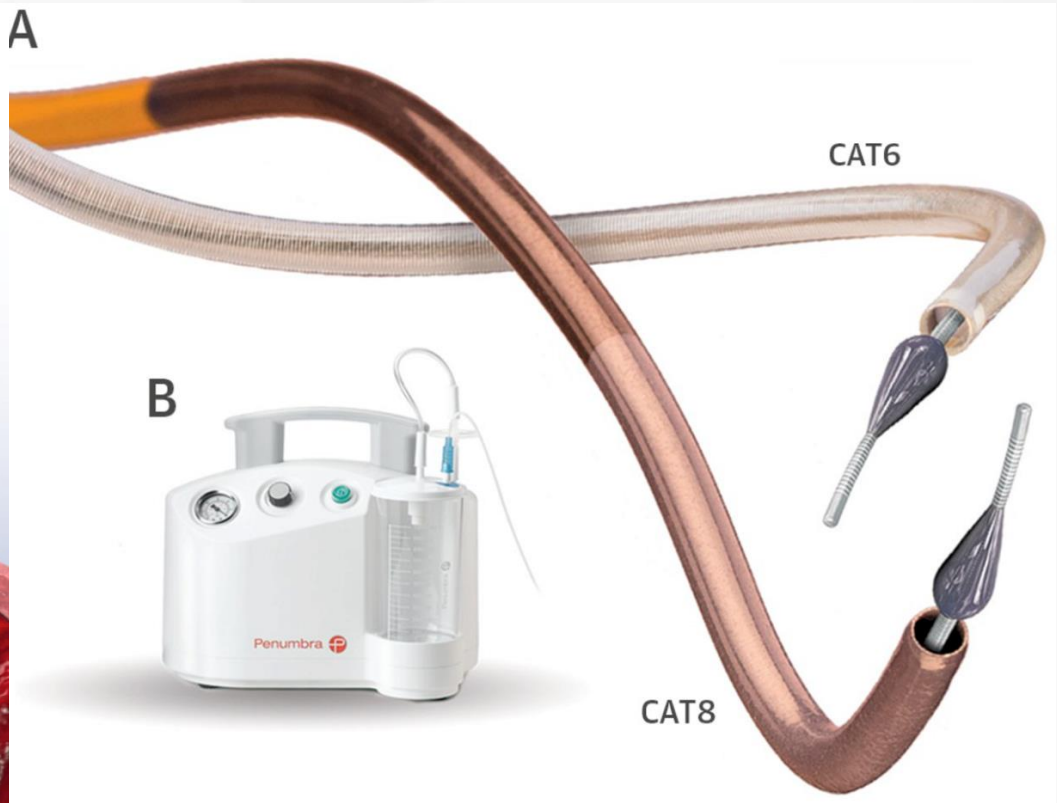
Treatment of PE: Aspiration Thrombectomy





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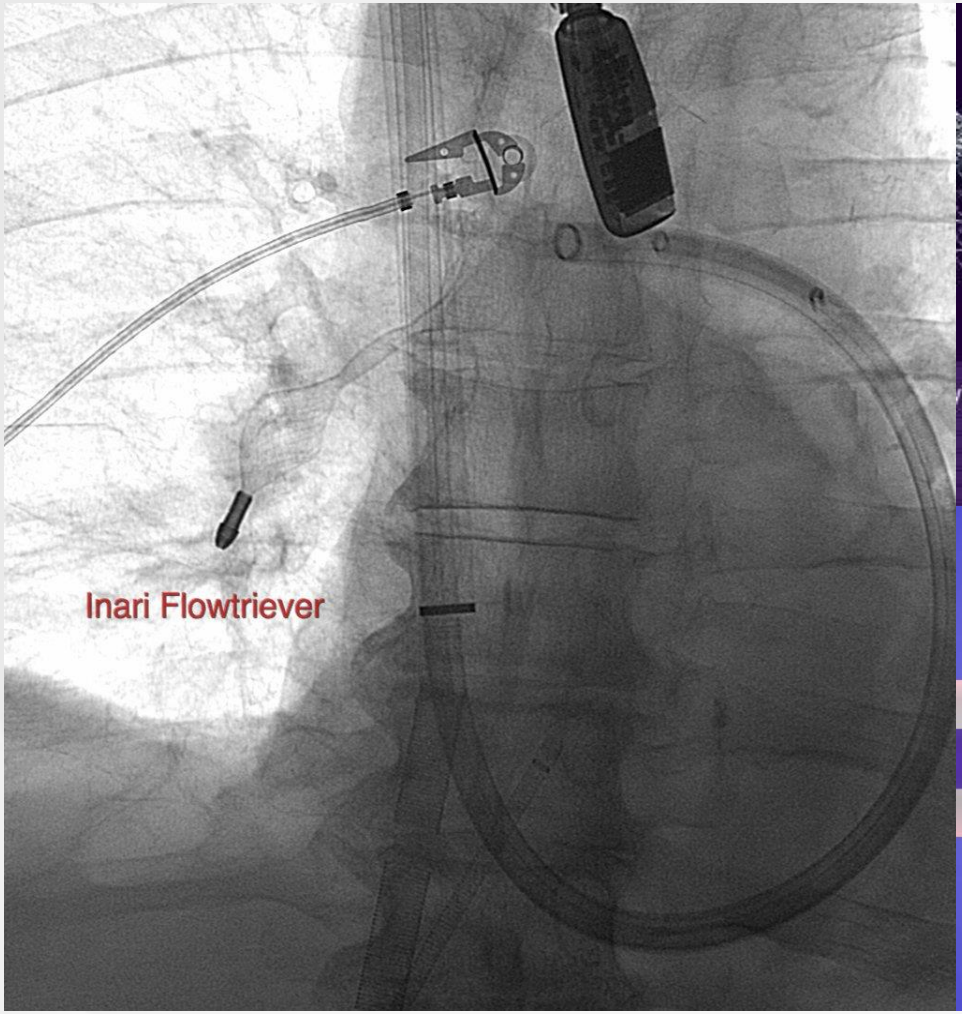
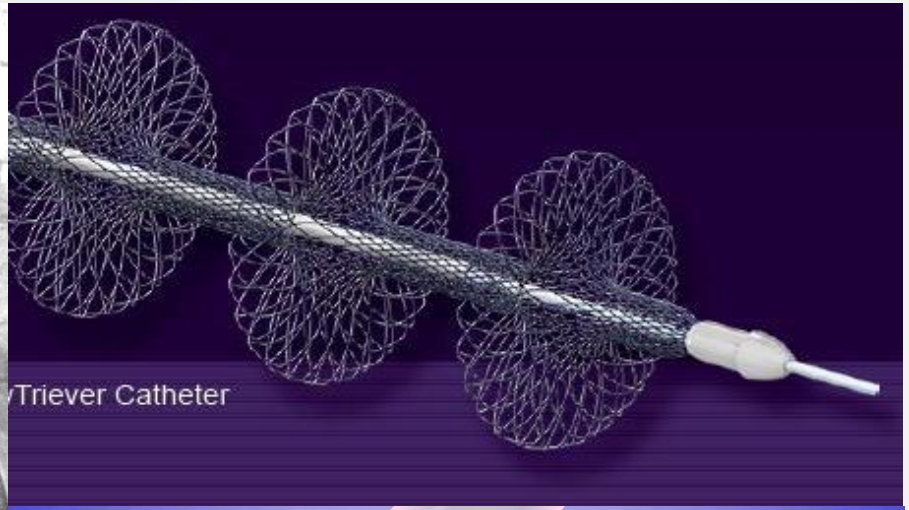
Treatment of PE-Remove it





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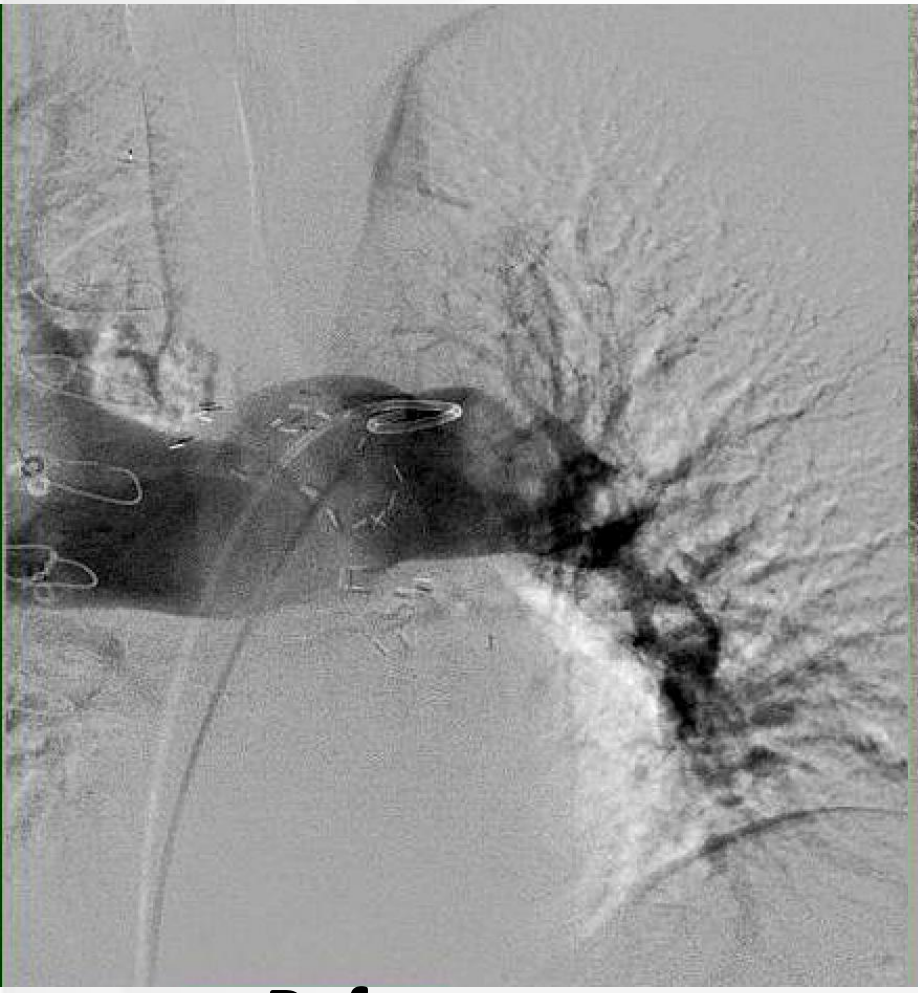
Case Presentation



Before

After

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Case Presentation

Treatment of PE-CDT

- PERFECT registry
  - Global prospective registry of CDT
  - >100 massive and submassive PE patients
  - > 80% clinical success rate
  - No major bleeds
  - Significant reductions in pulmonary arterial pressure.

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Chest 2015;148(3):667–673.

Treatment of MASSIVE PE

- Stay Calm
  - Resist Intubation
- Upfront Stabilization Principles
- +/-Mechanical Circulatory Support
- Options for Definitive Therapy
  - Lytics
  - Surgery
  - CDT
    - Maceration of clot
    - Embolectomy
    - Lytic Infusion
  - AC alone

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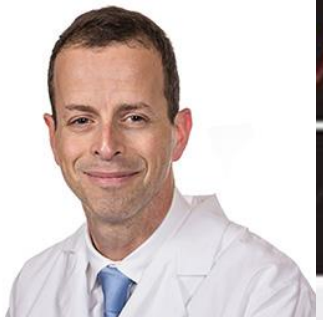
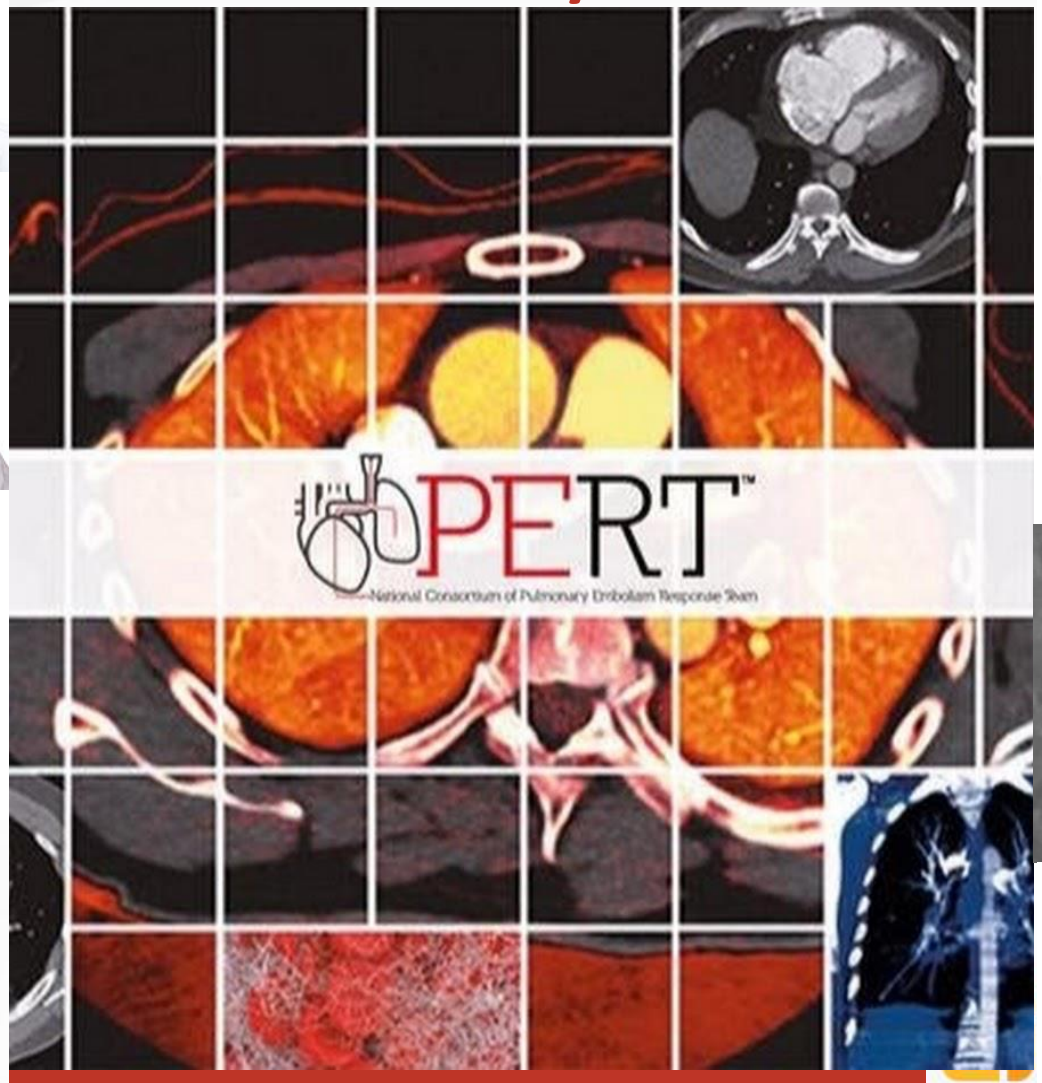
Thank you!





Georgia Lung Associates
Pulmonary & Critical Care Medicine

Thank you

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