2019 MID-ATLANTIC
CONFERENCE

9th ANNUAL CURRENT CONCEPTS IN

VASCULAR THERAPIES

2019

Hilton Virginia Beach Oceanfront
Virginia Beach, Virginia

MAY 2-4

2019 MID-ATLANTIC
CONFERENCE

9th ANNUAL CURRENT CONCEPTS IN
VASCULAR THERAPIES

2019

Submassive Pulmonary Embolism: Anticoagulation is the Treatment of Choice

John Ligush, Jr. M.D.

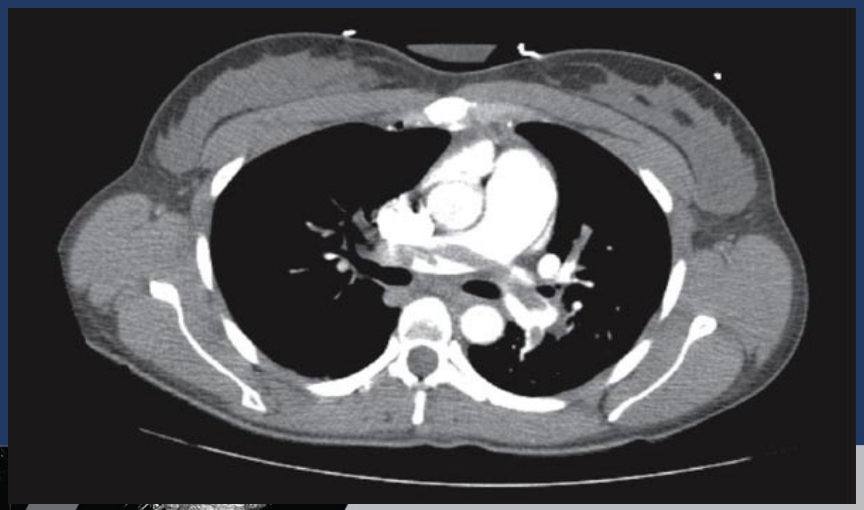
Sentara Martha Jefferson Hospital

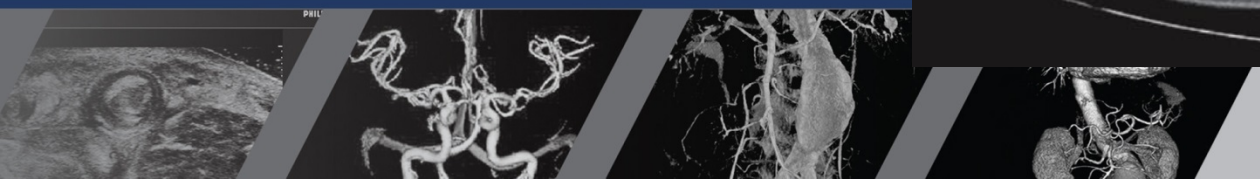
Scientific Evidence

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% f/u
2C	“Outcomes” research
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal - “first principles”
6	Dr. Dexter does it this way

Pulmonary Embolism

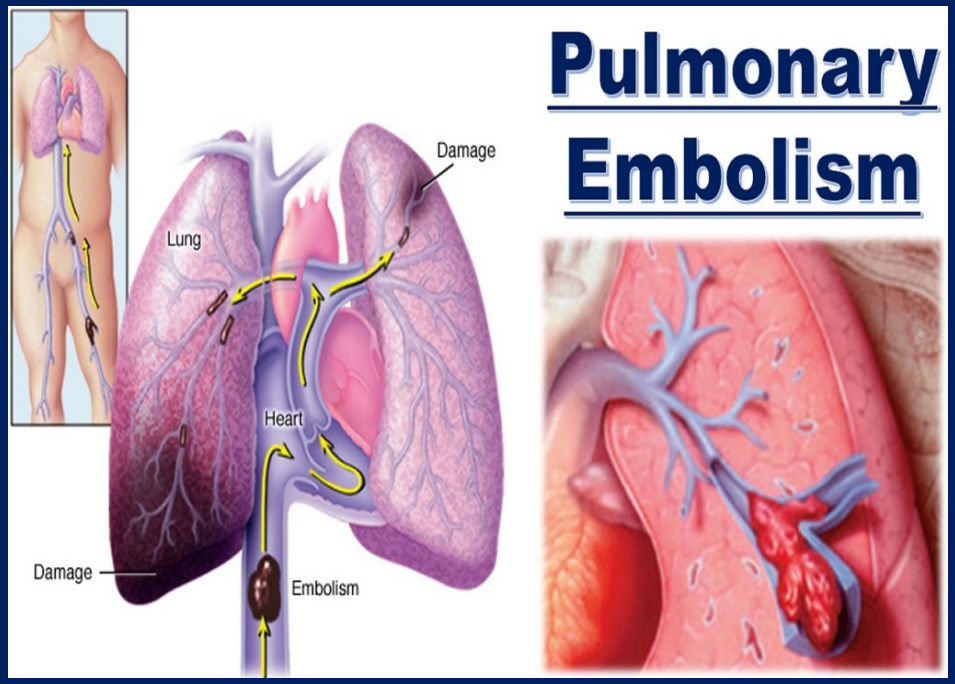
- Pulmonary embolism (PE)
  - Spectrum of “venous thromboembolism” (VTE)
  - VTE = PE + DVT
  - Defined by a thrombus that travels to the lung
    - Most commonly related to lower extremity DVT
      - Pelvic veins
      - Upper extremity veins
      - Unknown source





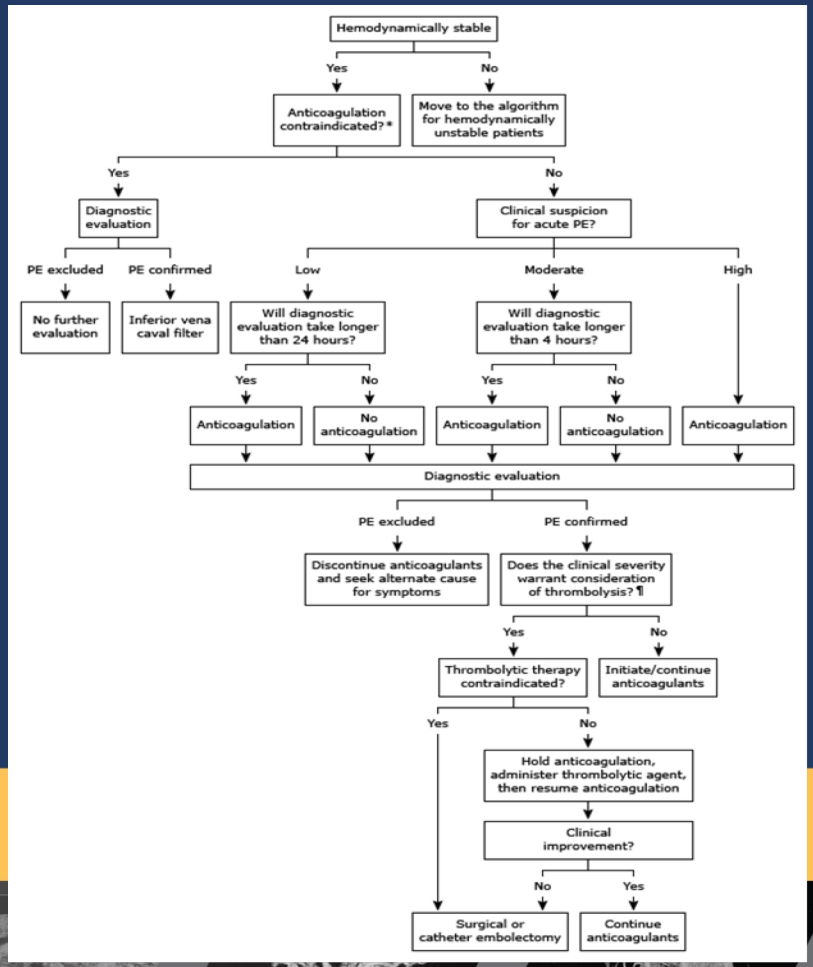
Pulmonary Embolism

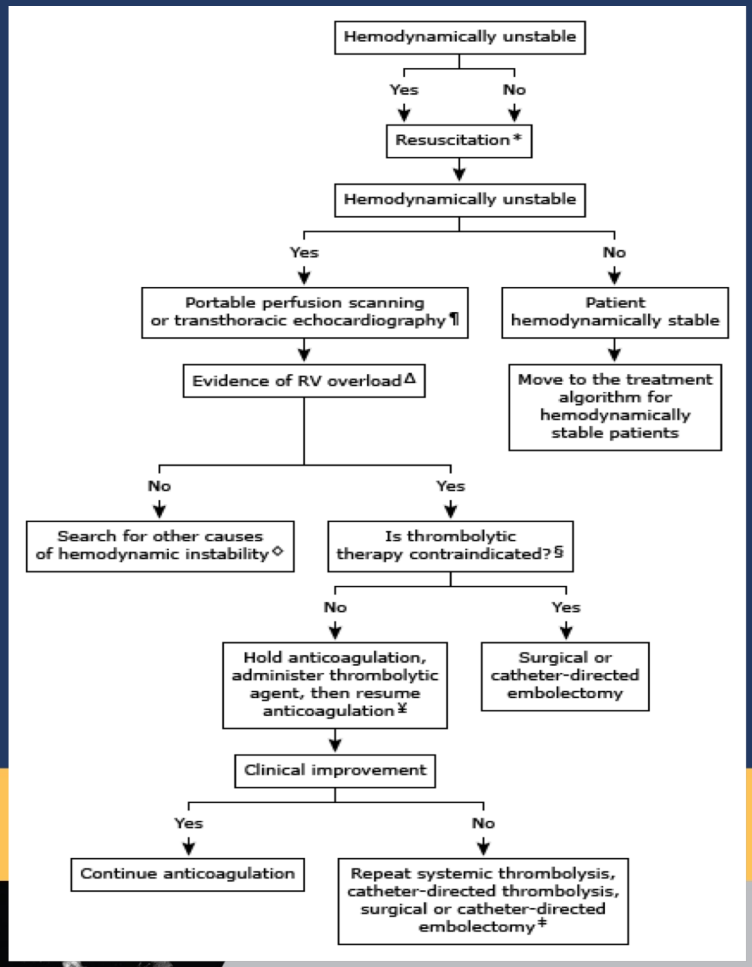
- Clinical significance
  - Respiratory compromise
    - Shunting/infaction
  - Cardiac compromise
    - Ventricular strain
  - Death
    - PE is a sometimes fatal disorder with a highly variable clinical presentation. Overall mortality is low, but relates to clinical presentation – “massive” vs “submassive”.
    - It is critical that therapy be administered in a timely fashion so recurrent thromboembolism and death can be prevented.



Pulmonary Embolism

- Therapy based on clinical picture





Pulmonary Embolism

- Standard Therapy - Unfractionated heparin to achieve anticoagulation
  - Nomograms are available based on patient weight (eg, initial bolus, 80 units/kg; followed by 18 units/kg/hour)
  - Other nomograms with non-weight-based initial dosing have also been published. The ACCP Guidelines use initial bolus of 5000 units followed by an infusion of 1300 units per hour (32,000 units/24 hours); others use an initial bolus of 5000 units followed by 1680 units per hour (40,320 units/24 hours).
  - The advantages of dosing based on patient weight are especially important for individuals with a large VTE (eg, massive pulmonary embolism), whereas initial dosing with an upper limit (rather than weight-based dosing) may be more appropriate in individuals with a higher-than-average risk of bleeding.

Pulmonary Embolism

- Massive/HD Unstable/High Risk PE
  - Used interchangeably
  - Not size of the embolus
  - Life threatening
  - Rapid decision making
  - Must be distinguished from submassive PE because more likely to die from obstructive shock in the first two hours of presentation and may therefore benefit from more aggressive treatment.
- Definition from AHA
  - Sustained hypotension - systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to other causes (such as dysrhythmia, hypovolemia, sepsis, LV dysfunction, profound bradycardia, etc.).

Pulmonary Embolism

- Submassive (Hemodynamically Stable PE)
  - PE that does not meet the definition of massive PE
  - Mild or borderline hypotension that stabilizes in response to fluid therapy, or those who present with right ventricle dysfunction
  - Spectrum of severity within this population
  - Small, mildly symptomatic or asymptomatic PE (also known as "low-risk PE")

Submassive Pulmonary Embolism (SMPE)

- Dilemma
  - Normotensive patient
  - Confirmed pulmonary embolism
  - Right ventricular dilation
- Action
  - Publications have demonstrated that RV dysfunction is associated with adverse outcomes
  - Recurrent VTE/Chronic thromboembolic pulmonary hypertension (CTEPH)
  - Must “do something”
- Facts
  - There are no RCT (no 1A/B) comparing standard anticoagulation vs catheter-directed therapy (CBT)
  - CBT proponents extrapolate data/make arguments in favor of CBT from trials comparing anticoagulation alone vs systemic thrombolytic therapy (STT) (2A-C/3)

Submassive Pulmonary Embolism

- Facts about alternative therapies
  - The decision to administer SST/CBT would be easier if SMPE had a high mortality rate that was significantly reduced by these treatments.
  - In larger studies, in-hospital or 30-day mortality for SMPE treated without SST is typically between 1% and 5%
  - In the excellent, landmark RCT of SST versus heparin alone for SMPE (NEJM 2002), mortality was 3.4% in the SST group and 2.2% in the 'heparin-alone' group.
  - The argument is commonly made that some trials excluded elderly patients or patients with comorbidities, artificially reducing mortality rates. However, the large RIETE registry (>15,000) also suggested a 90-day mortality of around 3% in patients with SMPE.
  - The problem for advocates of SST/CBT for SMPE is that it may be technically impossible to demonstrate beneficial effects on mortality. This is because a RCT comparing SST/CBT and standard treatment would require prohibitively large numbers of patients to generate sufficient statistical power to detect a clinically meaningful difference in mortality.

Grifoni S, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000;101:2817–22

Konstantinides S, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1142–50

Laporte S, et al. Clinical predictors for fatal pulmonary embolism in 15520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008;117:1711–16.

Submassive Pulmonary Embolism

- Facts about alternative therapies
  - Faced with this problem, those who champion CBT for SMPE commonly argue first that RV dilatation (and particularly persistent RV dilatation) is associated with a poor prognosis in PE and second that CBT improves RV dynamics acutely (ULITMA, SEATTLE II, PERFECT)
  - Consequently, they suggest we should perform CBT on patients who have sufficient thrombus load to generate RV dilatation.
  - However, there is very little evidence in SMPE to support this contention. A crucial point is that RV dilatation is a dynamic process. A large study indicated that 93% of patients with SMPE, treated without SST, had normal RV systolic pressure (assessed by echocardiography) 6 months after diagnosis. The same study reported only two inpatient deaths among 200 patients with SMPE – 1%.

Kline JA, et al. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism. Chest 2009;136:1202–10.

Submassive Pulmonary Embolism

- Facts about alternative therapies
  - Reality
    - At the point of presentation, patients with SMPE are highly likely to survive if treated with heparin alone and the associated RV dilatation is likely to resolve spontaneously in the significant majority.
  - The nagging doubt, of course, surrounds the small proportion of patients who will have persistent RV dysfunction, particularly as this group seems vulnerable to recurrent VTE.
  - The decision for CBT would again be easier if, at the point of presentation, we had tools accurately identifying those patients in whom RV function will fail to improve.

Submassive Pulmonary Embolism

- Facts about alternative therapies
  - However, two problems arise
    - First, while biomarkers such as brain natriuretic peptide afford some additional information, they do not yet provide anywhere near the level of prognostic accuracy on which to base the decision to offer CBT.
    - Second, even if they did, we have no evidence to suggest that early CBT could outperform existing treatment options for these patients.
  - Extending this argument, CBT proponents focus attention on the two major concerns in patients with persistent RV dysfunction: the higher rate of recurrent VTE in patients with residual thrombus load and the potential for the development of chronic thromboembolic pulmonary hypertension (CTEPH).
    - However attractive it may be theoretically, we have no strong evidence to inform whether early CBT can reduce VTE recurrence — we know that longer-term anticoagulation does. Similarly, we have no evidence that early CBT reduces the risk of CTEPH.
  - Yet prolonged anticoagulation significantly improves outcomes for these important complications. So, instead of early CBT, why not repeat echocardiography at 3 months, prolong anticoagulation in those with persistent RV impairment, and assess carefully for evidence of CTEPH in the ensuing period? At least this approach would generate long-term data and perhaps guide future studies regarding the identification of a cohort that would benefit from CBT.

Submassive Pulmonary Embolism

- Facts about alternative therapies
  - The theoretical argument against this approach, proposed by CBT advocates, is based on the hypothesis that CBT improves hemodynamics acutely and that a normally functioning RV might lead to fewer complications downstream.

  - However, careful studies have shown that while CBT improves RV dilatation more than heparin alone in the first 12 h, the benefits are lost by 48 h. There is no evidence in SMPE to suggest that the early hemodynamic improvements translate into benefits in terms of survival, VTE recurrence, or development of CTEPH.

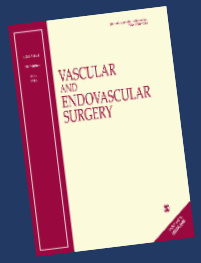
  - Where early CBT does seem to benefit patients with SMPE is in reducing the amount of supportive care (e.g., blood pressure support) required in the early stages of admission to hospital. However, again, at the point of presentation, we have no accurate way to predict which patients will require extra hemodynamic support, and whether the extra supportive care we give obviates any additional morbidity associated with CBT.

Submassive Pulmonary Embolism

- Multiple societal recommendations:
  - ACCP, AHA, ESC - SST/CDT only in patients in whom imminent cardiac decompensation is present.

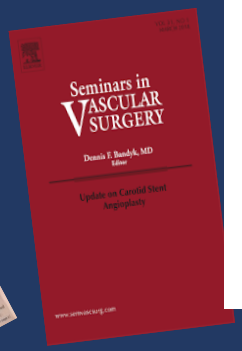
- Consensus panel future CBT trials should focus on:
  - Identifying impactful and feasible endpoints
  - Determining appropriate selection criteria
  - Maximizing enrollment
  - Collecting robust safety data

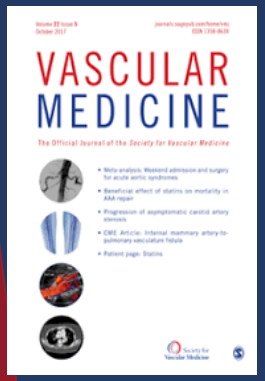
Sista AK, Goldhaber SZ, Vedantham S, Kline JA, Kuo WT, Kahn SR, et al. Research priorities in submassive pulmonary embolism: Proceedings from a multidisciplinary research consensus panel. J Vasc Interv Radiol 2016;27:787-94

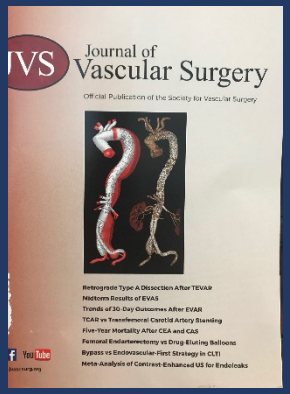


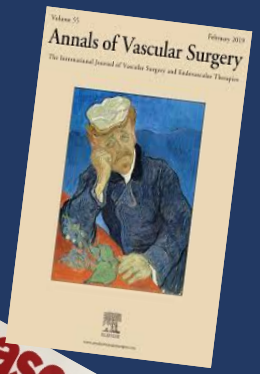
Evidence-based Medicine

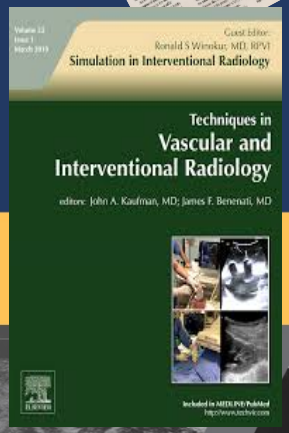
- Vascular community is being challenged to provide meaningful data regarding treatment.
- With regard to CBT specifically
  - Evidence level 2A/B/C

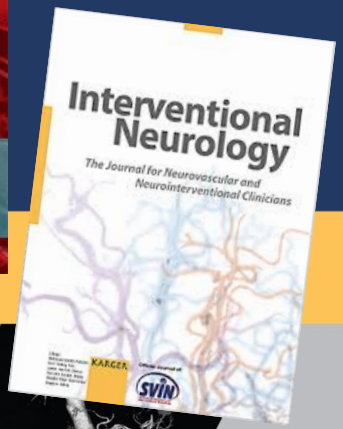


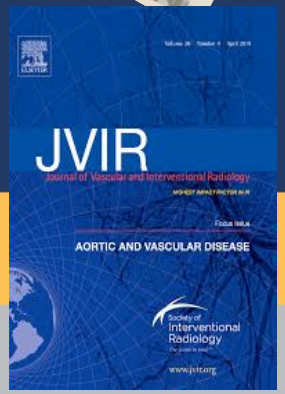








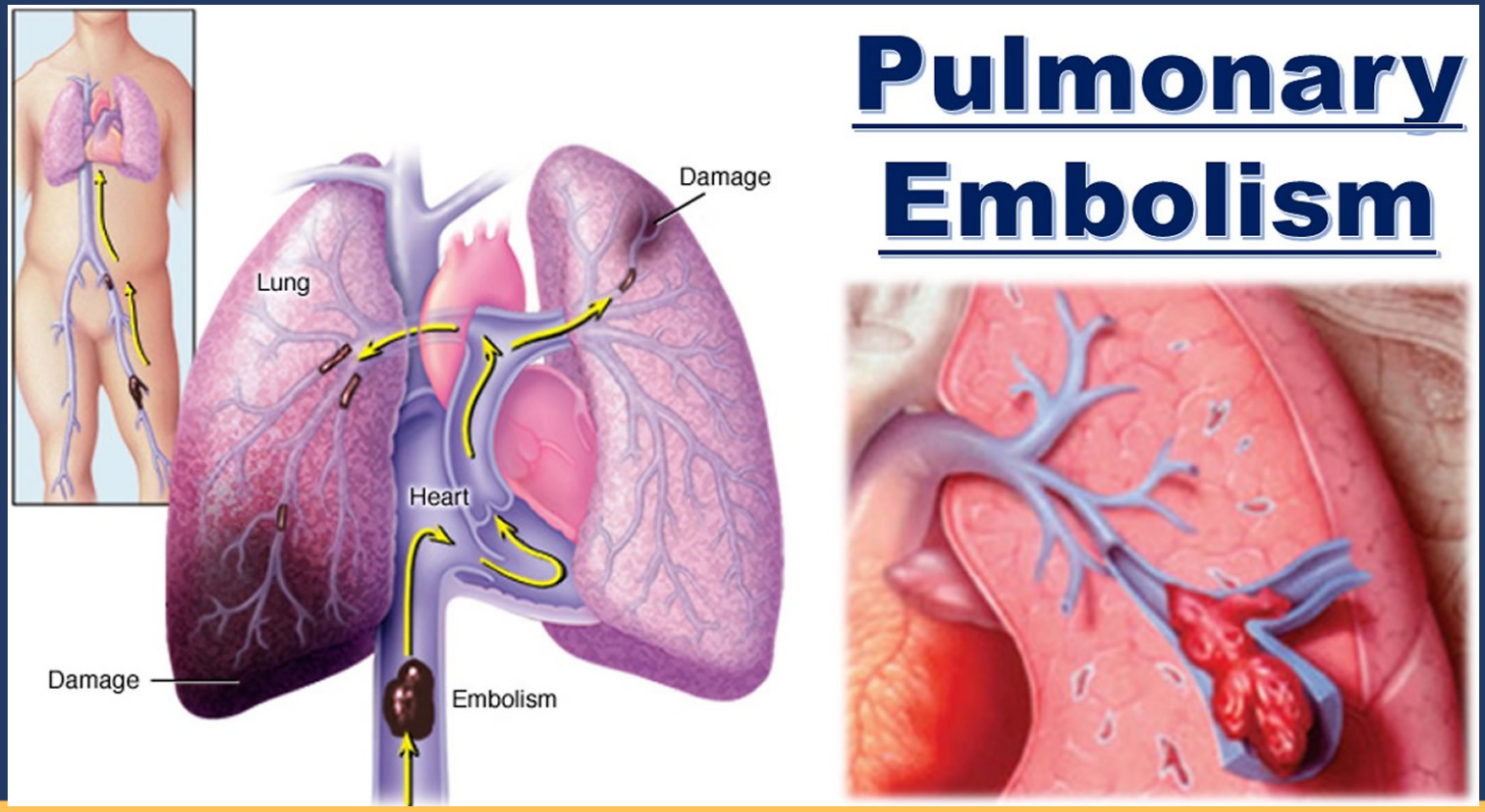




Submassive Pulmonary Embolism - Conclusion

- The management of submassive PE is in a current state of evolution
- CBT appears to allow rapid reduction in right heart strain with low rate of hemorrhagic complications.
- HOWEVER, additional prospective data are needed to further justify the use of CBT as a standard of care for submassive PE
  - Specifically with respect to demonstrating superior clinically relevant outcome metrics
- Future studies should focus of the safety of CBT and also define better prognostic tests to identify patients in whom CBT will be most beneficial.
- **UNTIL THEN** systemic anticoagulation will remain the treatment of choice and CBT should be reserved for the management of submassive PE patients requiring escalation of care beyond systemic anticoagulation.
- "Further investigative work is clearly necessary to help fine tune the role of CBT in PE".

Pulmonary Embolism



Pulmonary Embolism

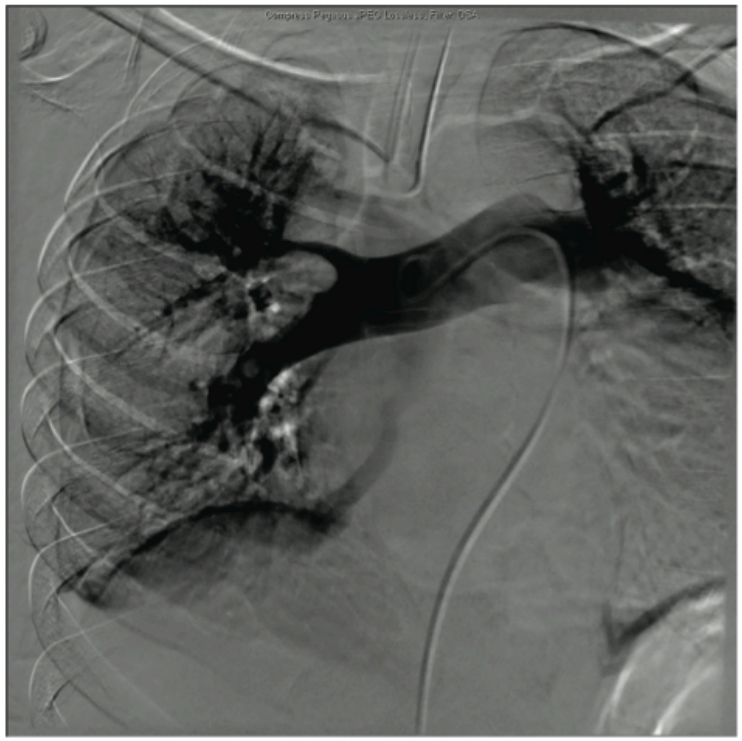


Figure 2. Angiogram showing right PE before treatment with the EkoSonic system.

Pulmonary Embolism