Management of Severe & Complicated PE in the Real World (Options for Reperfusion, 2022)

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Definition

Reperfusion refers to an ADJUNCT to anticoagulation intended to restore pulmonary vascular patency.

Risk Category	Definition: Acute Pulmonary Embolism and…
High risk or massive; mortality 31.8–58.3% (8, 9)	Sustained hypotension, defined as systolic blood pressure < 90 mm Hg, or reduction of 40 mm Hg from baseline, for at least 15 min, or requiring pressors, and not due to any other cause Pulselessness Bradycardia of <40 beats/min with signs of shock
Intermediate risk or submassive, mortality 2.8–8.1% (10, 34)	Does not meet above criteria for high risk Evidence of right ventricle strain by any or all of the following:* Echocardiogram Computed tomographic scan Electrocardiogram Elevated troponins Elevated natriuretic peptides
Low risk, mortality 1.1% (55)	Does not meet above criteria for high risk or intermediate risk

*Definitions of right ventricular strain for each modality vary and are subject to interpretation.

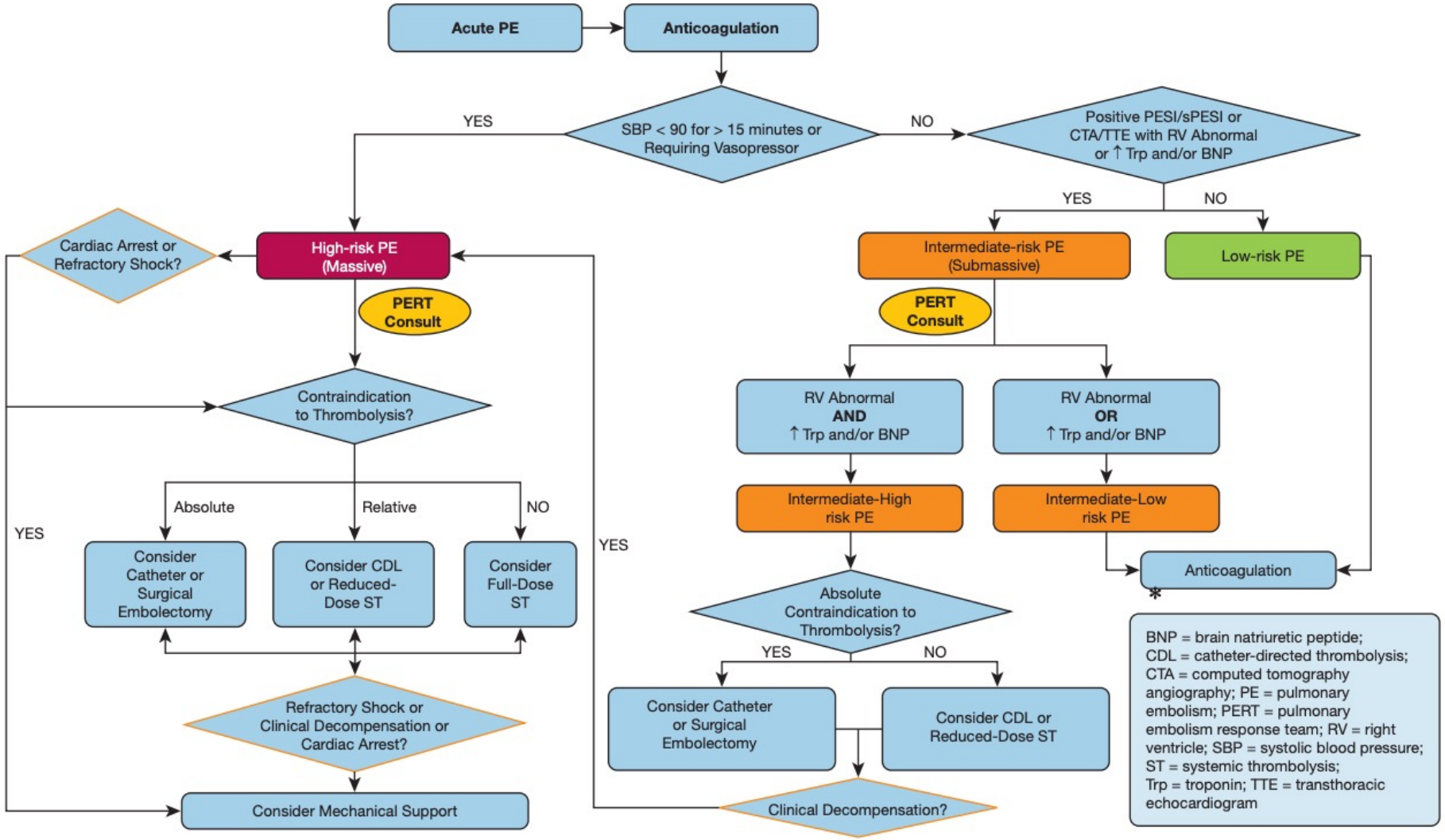
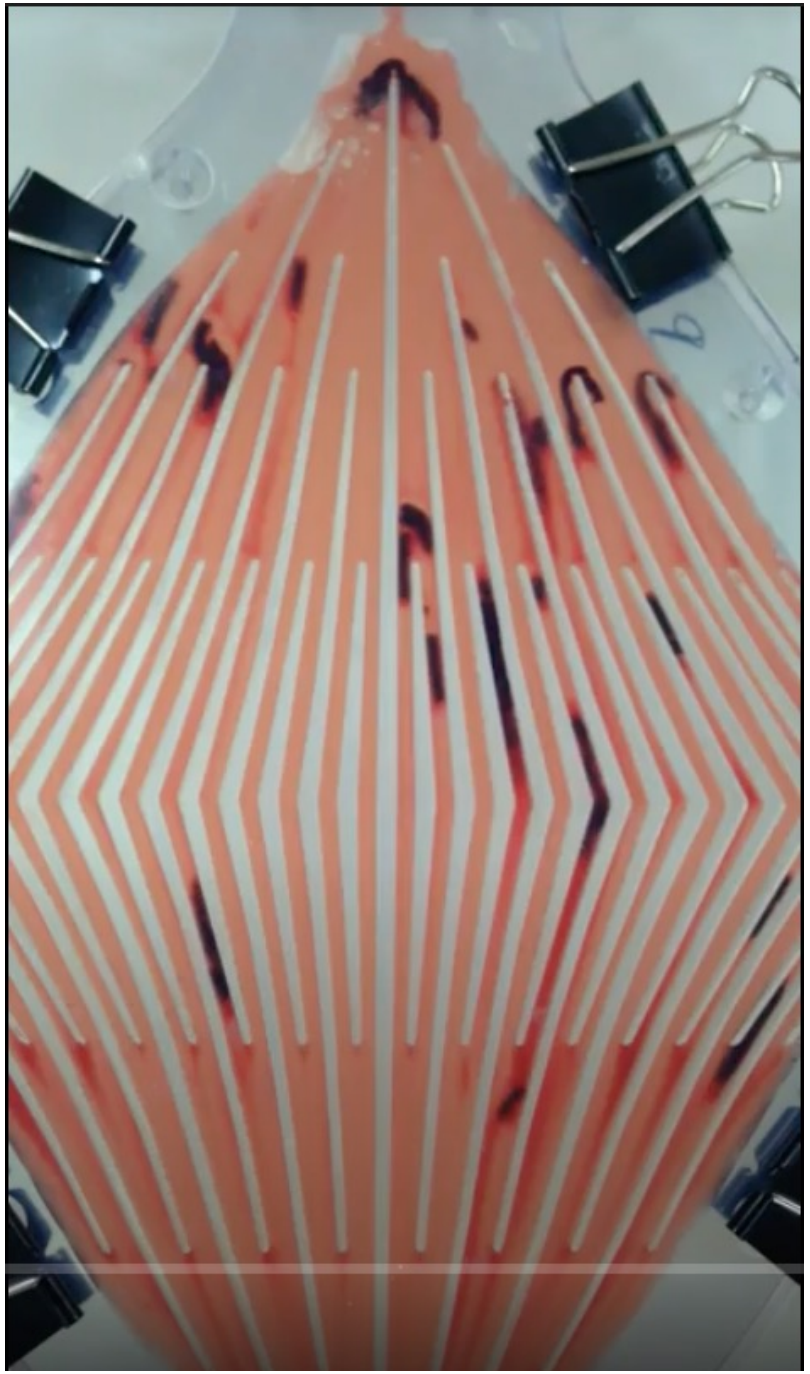


Figure 1 – *Acute pulmonary embolism treatment algorithm. Adapted from "Diagnosis, Treatment, and Follow-Up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium," by Rivera-Lebron BN.* Clin and Appl Thrombosis Hemost. *2019;25:1-16. Copyright 2019 by SAGE. Reprinted with permission.*

Options for reperfusion

1. Systemic fibrinolytics
   - Alteplase cleared by FDA, 100 mg over two hours
   - Tenecteplase by tiered dose
   - Other agents include urokinase and streptokinase infused over hours
2. Catheter-based methods
   - Catheter directed thrombolysis (CDT)
     - Bland catheters
     - Ultrasonic catheters (Ekos®)
   - Suction catheters
     - Inari Flowtriever®, Clotreiver
     - Penumbra Indigo®
3. Surgical thrombectomy



Does reperfusion work?

Table 1. Summary of randomized trials comparing catheter-measured pulmonary arterial pressures (PAPs) between patients treated with systemic fibrinolysis+heparin (Lytic) and heparin alone (Placebo)

Author	Year	Lytic Agent	N Lytic	N Placebo	Timing	Fibrinolytic Treatment (mmHg)		Placebo (mmHg)	
						Mean PAP (Pre)	Mean PAP (Post)	Mean PAP (Pre)	Mean PAP (Post)
Tibbut(1)	1974	SK	11	12	72h	30.8	18.5	34.3	29.6
PIOPED(2)	1990	TPA	9	4	1.5h	28	25	33	33
Konstantinides(3)	1998	TPA	27	13	12h	34	22	29	27
NHLBI(4)	1973	UK	82	78	24h	26.2	20	26.1	25
Dalla-Volta(5)	1992	TPA	20	16	2h	30.2	21.4	22.3	24.8
Mean (mm Hg)						Pre: 29.8	Post: 21.4	Pre: 28.9	Post: 27.9
SD						3.0	2.4	4.9	3.5

Alteplase specifically

Bleeding rates for full dose alteplase or heparin in placebo-controlled randomized trials						
Reference	Alteplase+heparin			Placebo+heparin		
	N	ICH	xPRBC	N	ICH	xPRBC
(2)	9	0	1	4	0	0
(5)	20	1	2	16	0	0
(10)	33	0	3	25	0	3
(12)	46	0	3	55	1	0
(13)	118	0	0	138	0	5
(14)	37	0	2	35	0	1
Total	263	1	11	273	1	9
		0.30%	4.0%		0.30%	3.2%
ICH-intracranial hemorrhage; xPRBC-patients requiring packed red blood cell transfusion						

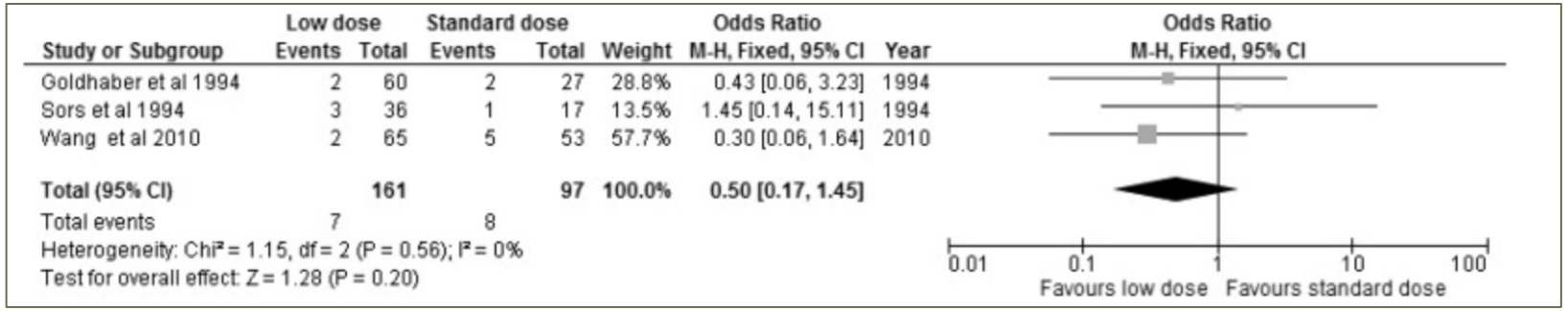
Systemic fibrinolytics-–efficacy and harm

1. Fourteen systematic reviews and meta-analyses since PEITHO, all reporting the same data2. Pooling of different types of fibrinolysis
3. Dosing and timing of heparin generally poorly described
4. Consistent findings(6):

Outcome	N reporting	Findings	N with statistical benefit
All cause mortality	12	All found benefit	3
PE mortality	3	All found benefit	2
Recurrent VTE	10	All found benefit	5
Clinical deterioration	3	All found benefit	3
Major bleeding	11	9 found INCREASE, 2 found DECREASE	5
Intracranial bleeding	3	All found INCREASE	2

Systemic fibrinolytics—”half dose”

- Two systematic reviews have pooled data from “half dose” trials (7,8).
  - Zhang et al found lower rate of major bleeding (odds ratio = 0.33, 95% CI 0.12-0.91) but Wang et al found no reduction

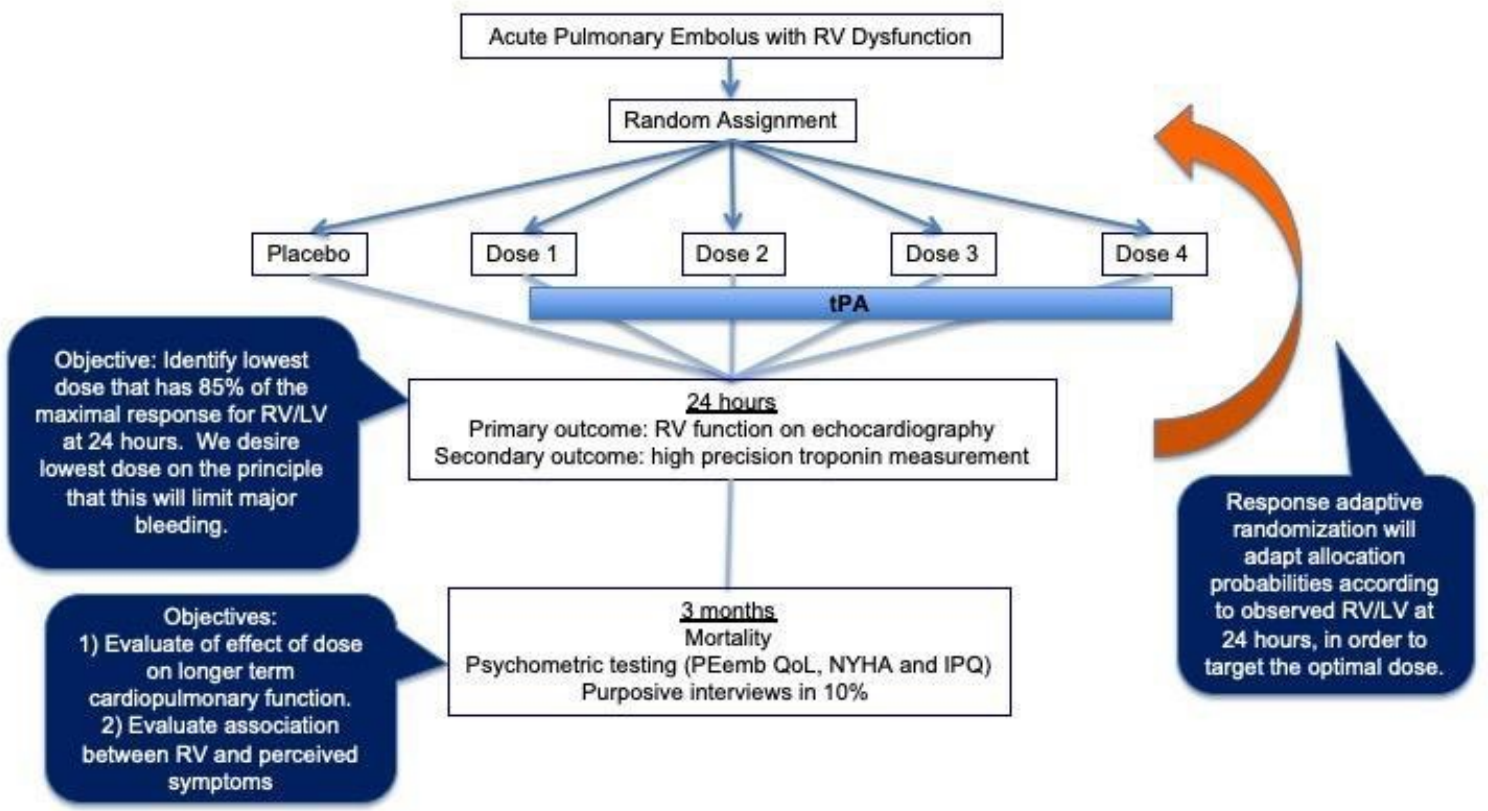


Study or Subgroup	Low dose Events	Total	Standard dose Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Goldhaber et al 1994	2	60	2	27	28.8%	0.43 [0.06, 3.23]	1994
Sors et al 1994	3	36	1	17	13.5%	1.45 [0.14, 15.11]	1994
Wang et al 2010	2	65	5	53	57.7%	0.30 [0.06, 1.64]	2010
Total (95% CI)		**161**		**97**	**100.0%**	**0.50 [0.17, 1.45]**	
Total events	7		8				

Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)

  - Data from a national billing database found half-dose associated with INCREASED rescue treatment and NO decrease in bleeding (9).

Pulmonary Embolism Reperfusion Fibrinolytic Efficacy Clinical Trial (PERFECT) trial*



*Submitted 2/22

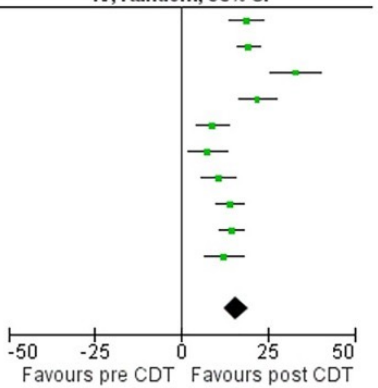
Catheter Directed Thrombolysis

- With exception of one small RCT, all data are before-after(16-18)
- Major Intracranial bleed rate 0.5% (16-18)
- German national study found 1.2% rate ICH(19)
- Upcoming studies (HI PEITHO and PE-TRACT) will compare CDT with placebo

Pulmonary artery systolic pressure

Study or Subgroup	Baseline Systolic PAP Mean	SD	Total	Systolic PAP after CDT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bagla et al.	49.8	13.8	45	31.1	9.9	45	10.0%	18.70 [13.74, 23.66]
Current Cohort	57.8	15.1	137	38.4	11.8	137	11.2%	19.40 [16.19, 22.61]
Dumantepe et al.	67	14	22	34	11	22	8.1%	33.00 [25.56, 40.44]
Engelberger et al.	62	16	52	40	11	52	9.8%	22.00 [16.72, 27.28]
Kennedy et al.	47	15	60	38	12	60	10.1%	9.00 [4.14, 13.86]
Lyang et al.	50.1	16	69	42.6	17.9	69	9.5%	7.50 [1.84, 13.16]
Mccabe et al.	51.4	15.5	53	40.7	10.8	53	9.9%	10.70 [5.61, 15.79]
PERFECT	51.2	14.1	100	37.2	15.8	100	10.6%	14.00 [9.85, 18.15]
SEATTLE	51.4	16	150	36.9	14.9	150	11.1%	14.50 [11.00, 18.00]
ULTIMA	52	11.5	30	39.7	10.3	30	9.6%	12.30 [6.78, 17.82]
Total (95% CI)			**718**			**718**	**100.0%**	**15.85 [12.20, 19.51]**

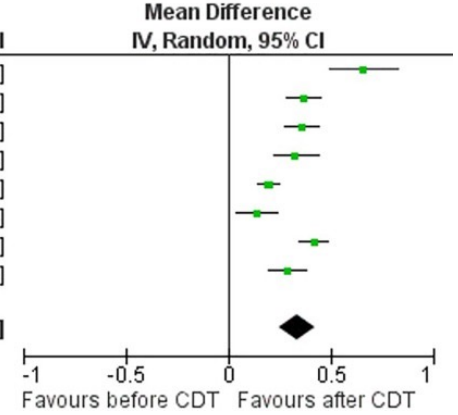
Heterogeneity: $Tau^2 = 28.29$; $Chi^2 = 54.37$, df = 9 ($P < 0.00001$); $I^2 = 83\%$
Test for overall effect: $Z = 8.50$ ($P < 0.00001$)



Right ventricular/left ventricular ratio

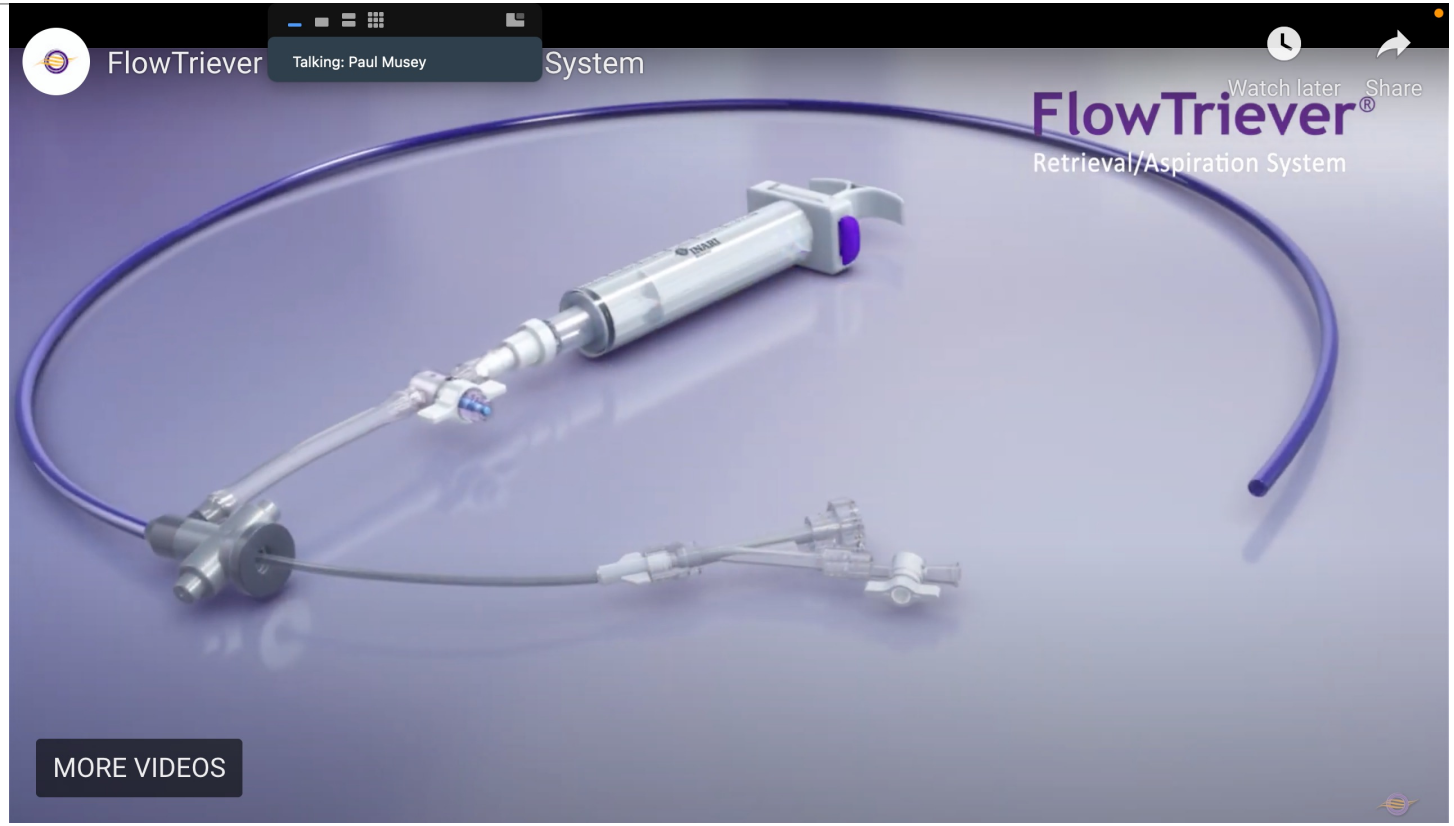
Study or Subgroup	Before CDT Mean	SD	Total	After CDT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bagla et al.	1.59	0.54	45	0.93	0.17	45	9.7%	0.66 [0.49, 0.83]
Dumantepe et al.	1.29	0.17	22	0.92	0.11	22	12.9%	0.37 [0.29, 0.45]
Engelberger et al.	1.42	0.21	52	1.06	0.23	52	12.9%	0.36 [0.28, 0.44]
Engelhardt et al.	1.33	0.24	24	1	0.13	24	12.0%	0.33 [0.22, 0.44]
Lyang et al.	1.1	0.2	69	0.9	0.1	69	14.0%	0.20 [0.15, 0.25]
Mccabe et al.	1.12	0.3	53	0.98	0.2	53	12.5%	0.14 [0.04, 0.24]
SEATTLE	1.55	0.39	150	1.13	0.2	150	13.4%	0.42 [0.35, 0.49]
ULTIMA	1.28	0.19	30	0.99	0.17	30	12.7%	0.29 [0.20, 0.38]
Total (95% CI)			**445**			**445**	**100.0%**	**0.34 [0.25, 0.42]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 58.52$, df = 7 ($P < 0.00001$); $I^2 = 88\%$
Test for overall effect: $Z = 7.51$ ($P < 0.00001$)



Suction catheters (FlowTriever® and Indigo®)

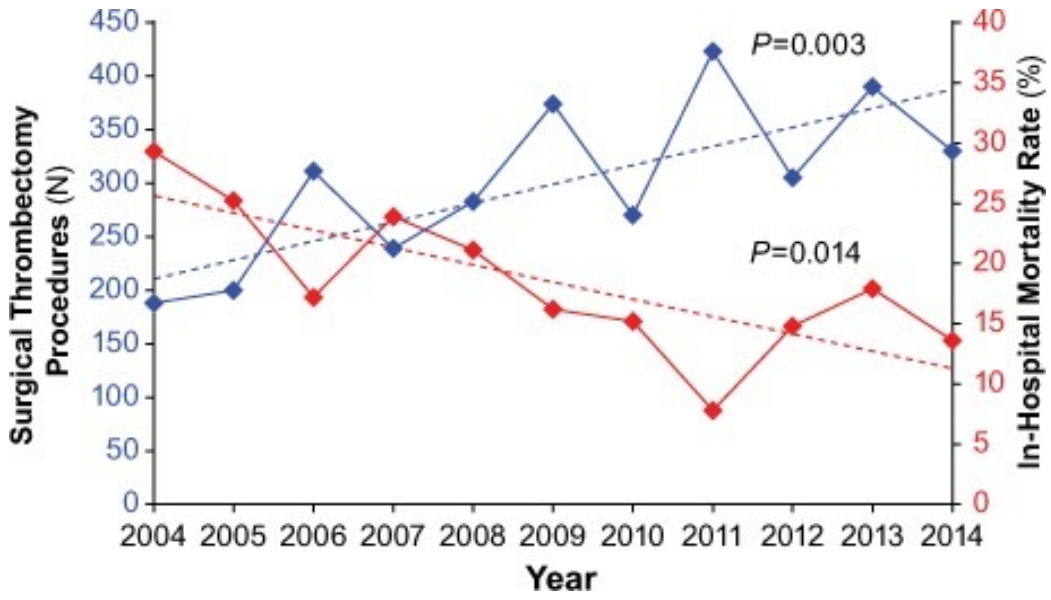
- 20-24 F hose
- No sheath, no fibrinolytics
- Similar before-after PAPs as with catheter directed thrombolysis (20-22)
- Vascular puncture, ventricular dysrhythmia and major hemorrhage occur in 3-5% (20-22)
- No controlled data showing superiority over anticoagulation alone



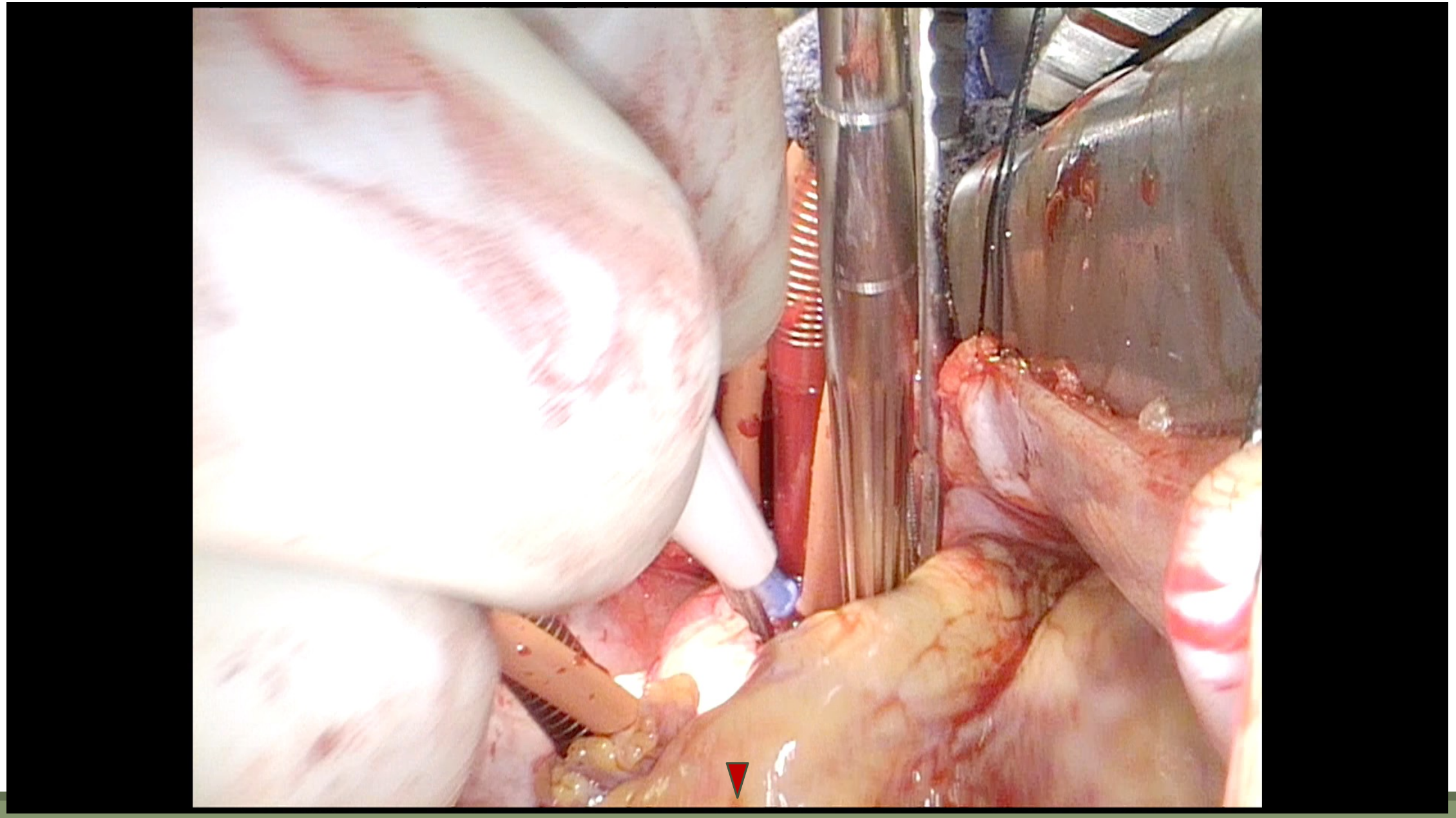
Pros (+) and cons (-) of Tenecteplase versus catheter directed therapy					
Method	Effectiveness	Availability	Safety	Patient/provider preference	Adoption/scalability
Catheter directed lysis	+ Registry evidence and one RCT(15) showing PAPs decrease at 24 hours; ability to keep going if 24 hr PAP still high - Low grade evidence of superiority over placebo (**only one small RCT**); Little effect on distal clots	+ Current default at many PERT teams - Requires intra- or **interfacility transfer** to a cath/IR suite. Requires expertise lacking 24/7 at most hospitals	+ Lower total dose lytics - Sheath in place >24 hours, associated bleeding risk; greater fibrinogen depletion; risk of cardiac/PA puncture	+Multidisciplinary care; lower dose lytics; more personalized - Psychological effects of the cath/IR experience	+ Used by PERT teams already at large hospitals - Superiority over placebo supported only by one small RCT; may be supplanted by suction catheters; requirement for specialty care
Bolus dose Tenecteplase	+ **Multiple RCTs show superiority over placebo**; more complete distal lysis; faster effect than CDT - The "zero flow boundary" hypothesis: the enzyme may not reach wedged-in clots	+ **Available at bedside** for rapid, bolus infusion; allows simplicity of LMWH -Not all EDs have tenecteplase at present	+ No indwelling sheath or risk of heart/PA puncture; minimal drop in fibrinogen[50] - **Increased major bleed risk at full dose**	+ Patient perception of less invasive and less intimidating than the CDT experience	+ Likely to become the stocked fibrinolytic of choice in EDs around the US (see 1.4 for rationale) - Increased risk of bleeding

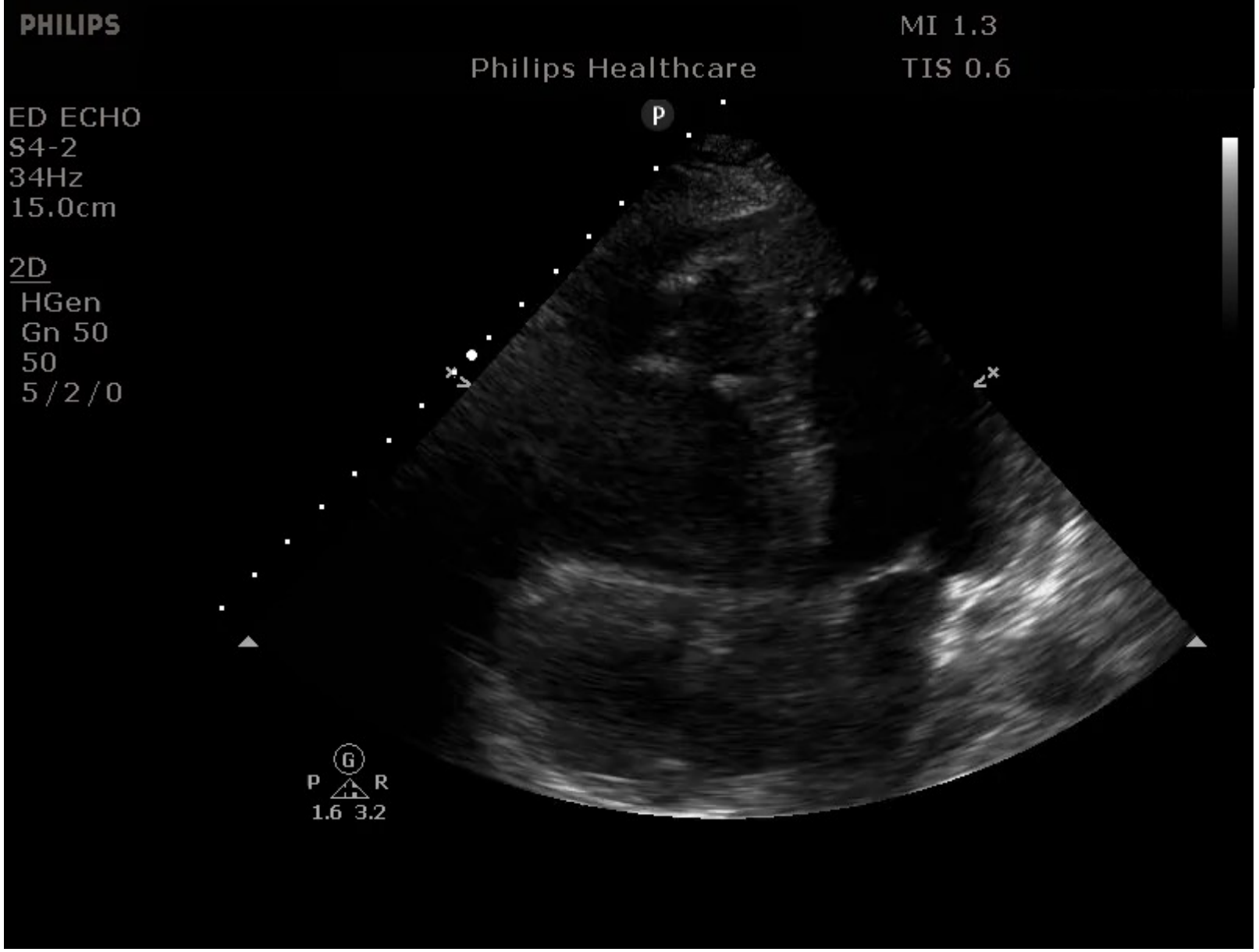
Surgical thrombectomy

- Mechanical solution to a mechanical problem (”Trendelenburg” operation*)
- Generally reserved for proximal clot, hypotension or clot in transit
- Evidence is case series or national databases(23)
- Do not confuse with chronic thromboembolic pulmonary hypertension



*Trendelenburg F. Ueber die operative Behandlung der Embolie der Lungenarterie. Arch Klin Chir 1908;86(3):686–700

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Philips Healthcare
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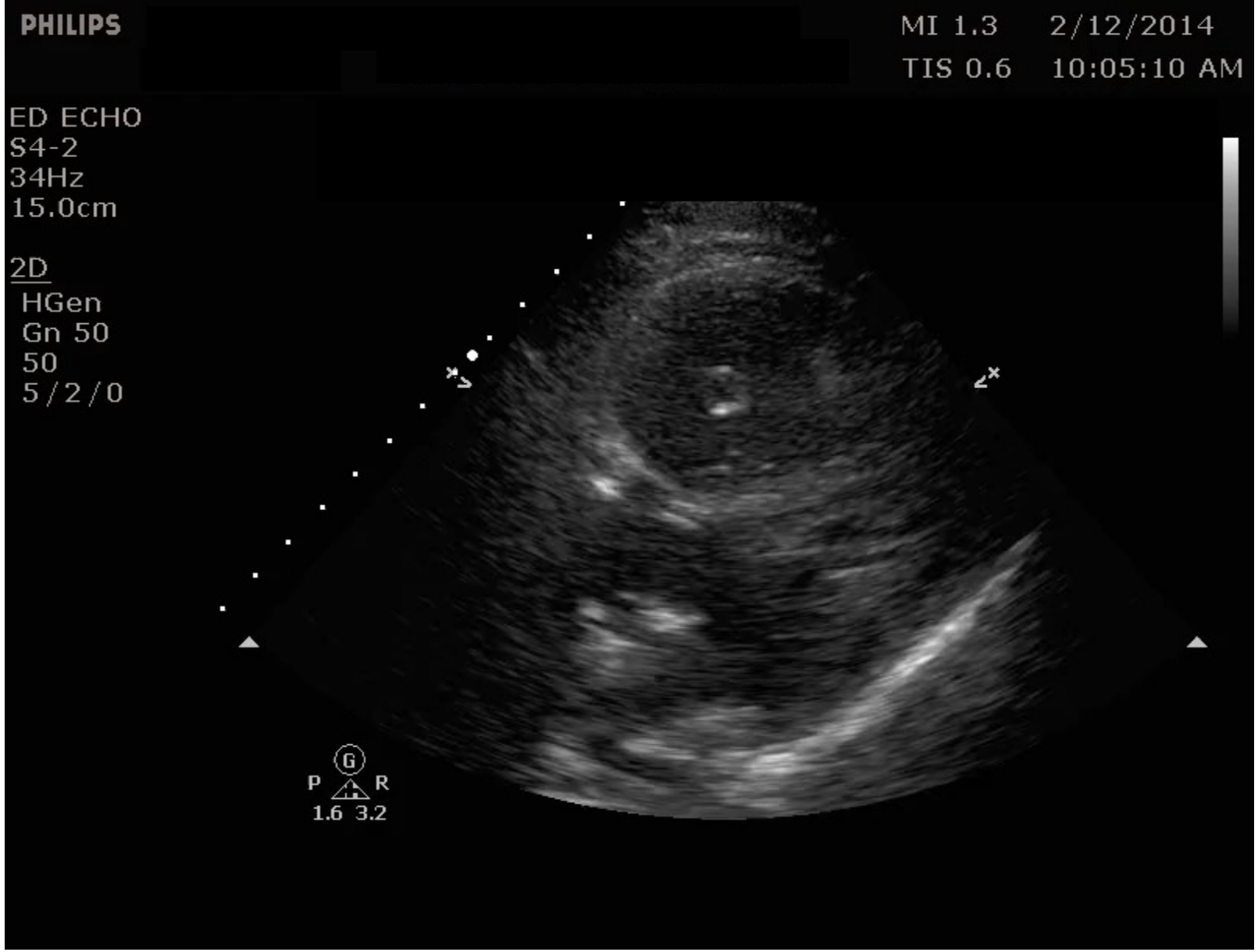
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Clot in transit: do more than anticoagulate

Heparin alone probably wrong

Table 3 Reperfusion Therapy as Determinant of Outcome in 325 Patients Who Had Acute Symptomatic Pulmonary Embolism and Right Heart Thrombi

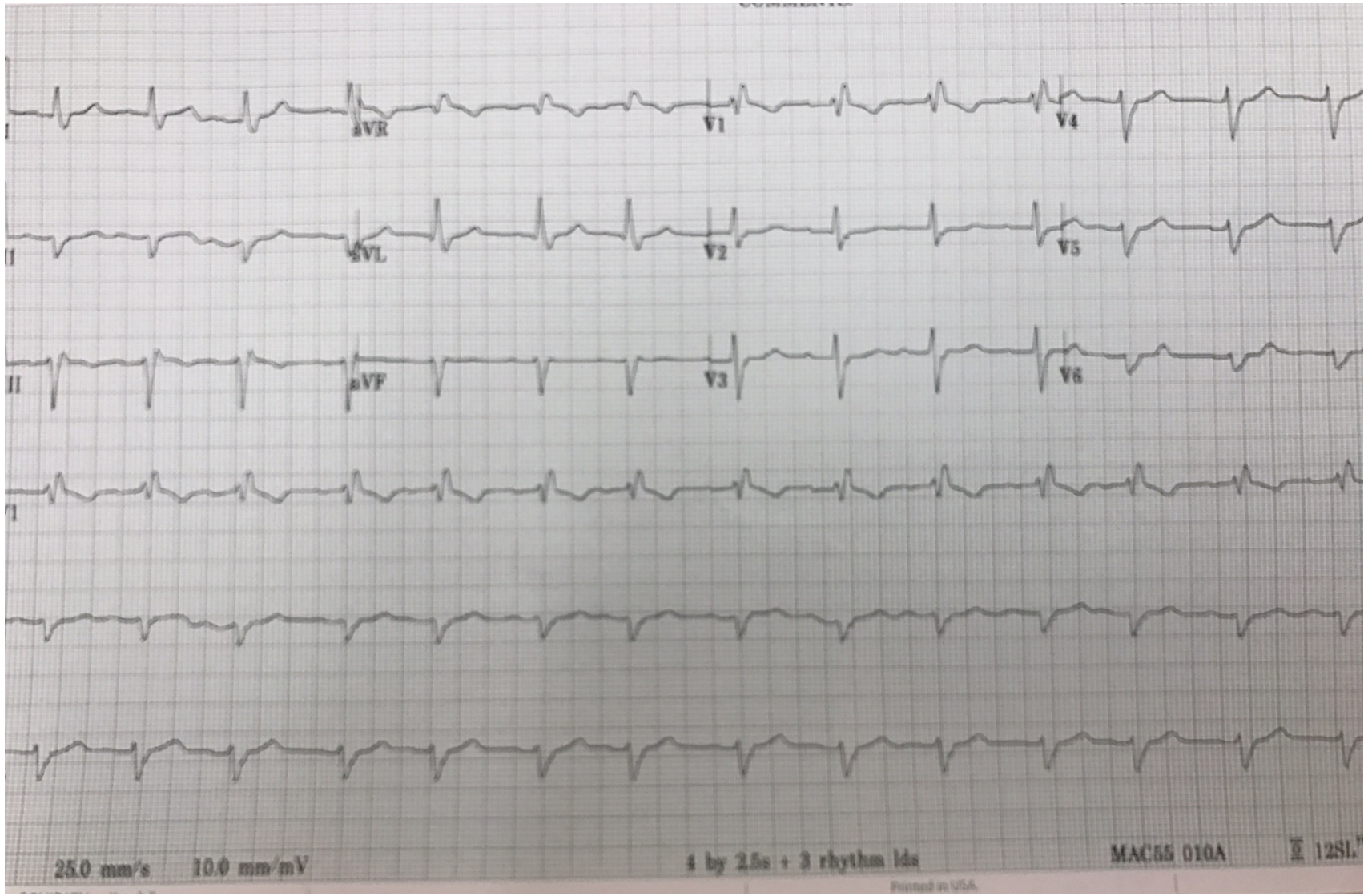
Event	Unadjusted OR (95% CI)	*P* Value	Adjusted OR* (95% CI)	*P* Value
All-cause mortality	0.58 (0.19-1.74)	.33	0.34 (0.10-1.11)	.08
PE-related mortality	0.77 (0.21-2.76)	.69	0.48 (0.12-1.92)	.30
Recurrent venous thromboembolism	7.67 (1.37-42.77)	.02	8.20 (1.35-49.61)	.02
Major bleeding	0.90 (0.24-3.30)	.88	0.70 (0.17-2.80)	.62

CI = confidence interval; OR = odds ratio; PE = pulmonary embolism.
*Multivariate adjustment for the simplified Pulmonary Embolism Severity Index[18] and recent bleeding.

Empiric treatment

“62 y/o male, became hypotensive and hypoxic after metatarsal surgery when they deflated his pneumatic tourniquet after over three hours ischemic time. I requested that they bolus 70/kg of heparin. Arrived here approximately 8:20 PM. Hypotensive 67/45, intubated. He is paralyzed and unresponsive.”

BP 75/57 HR 83, intubated O2Sat 98% FiO2 1.0


aVR
V1
V4
aVL
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V5
aVF
V3
V6
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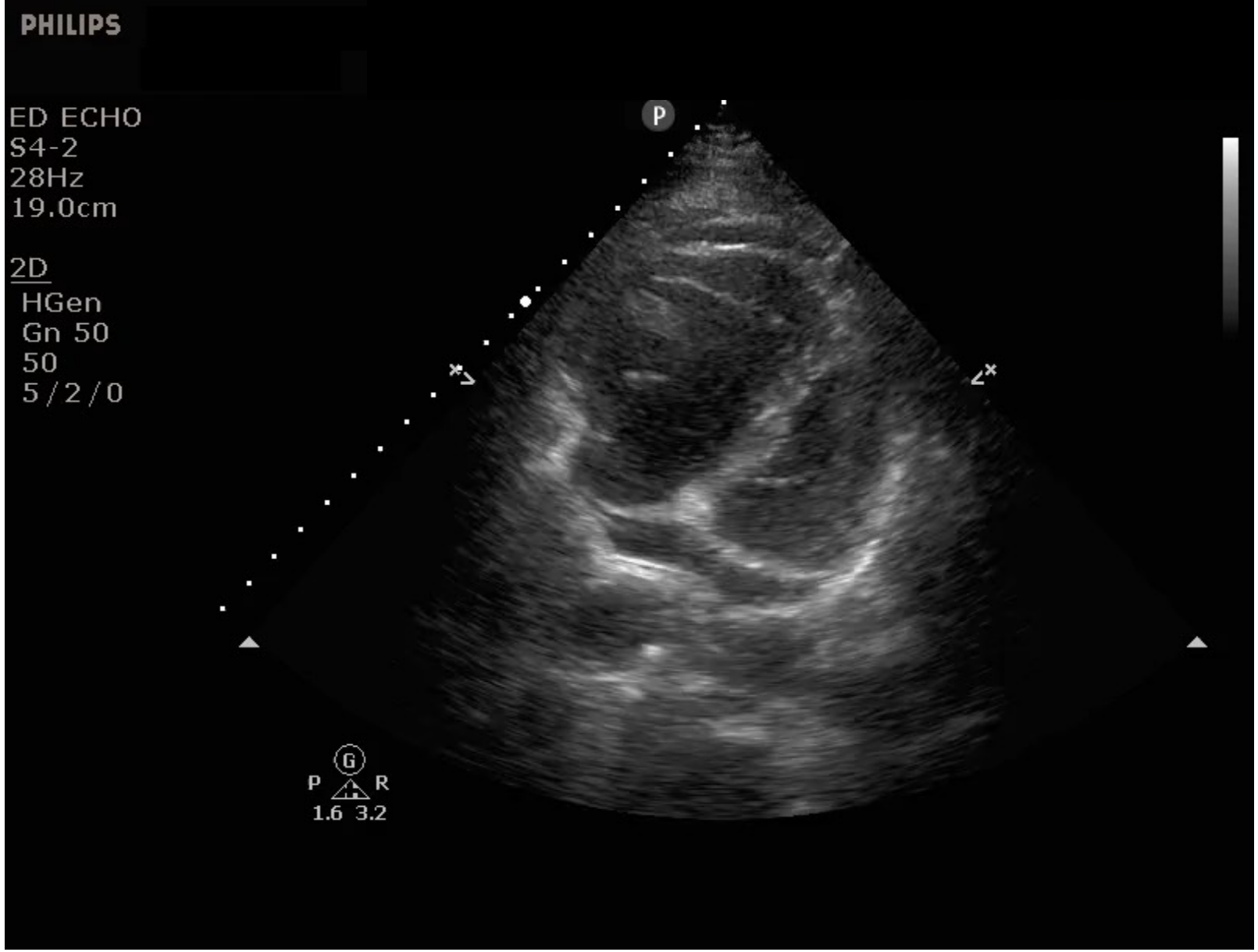
10.0 mm/mV
4 by 2.5s + 3 rhythm lds
MAC55 010A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ED ECHO
S4-2
28Hz
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2D
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1.6 3.2

Pregnancy with massive PE

29-year-old female presents as medical alert for syncope

911 was called after witnessed syncopal episode by mother and father, on EMS arrival patient was sitting in the bathroom and had another witnessed syncopal episode. Found to be hypoxic and tachycardic, upon awakening was complaining of chest pain and back pain. Patient is approximately 14 weeks pregnant

HR 120 bpm, RR 35, BP 143/96

Treating massive PE in pregnancy

Case report level of evidence; one systematic review

Fibrinolysis (n=61 antenatally):

- Maternal Survival 96%; Fetal survival 81.5%
- Maternal bleeding 18%

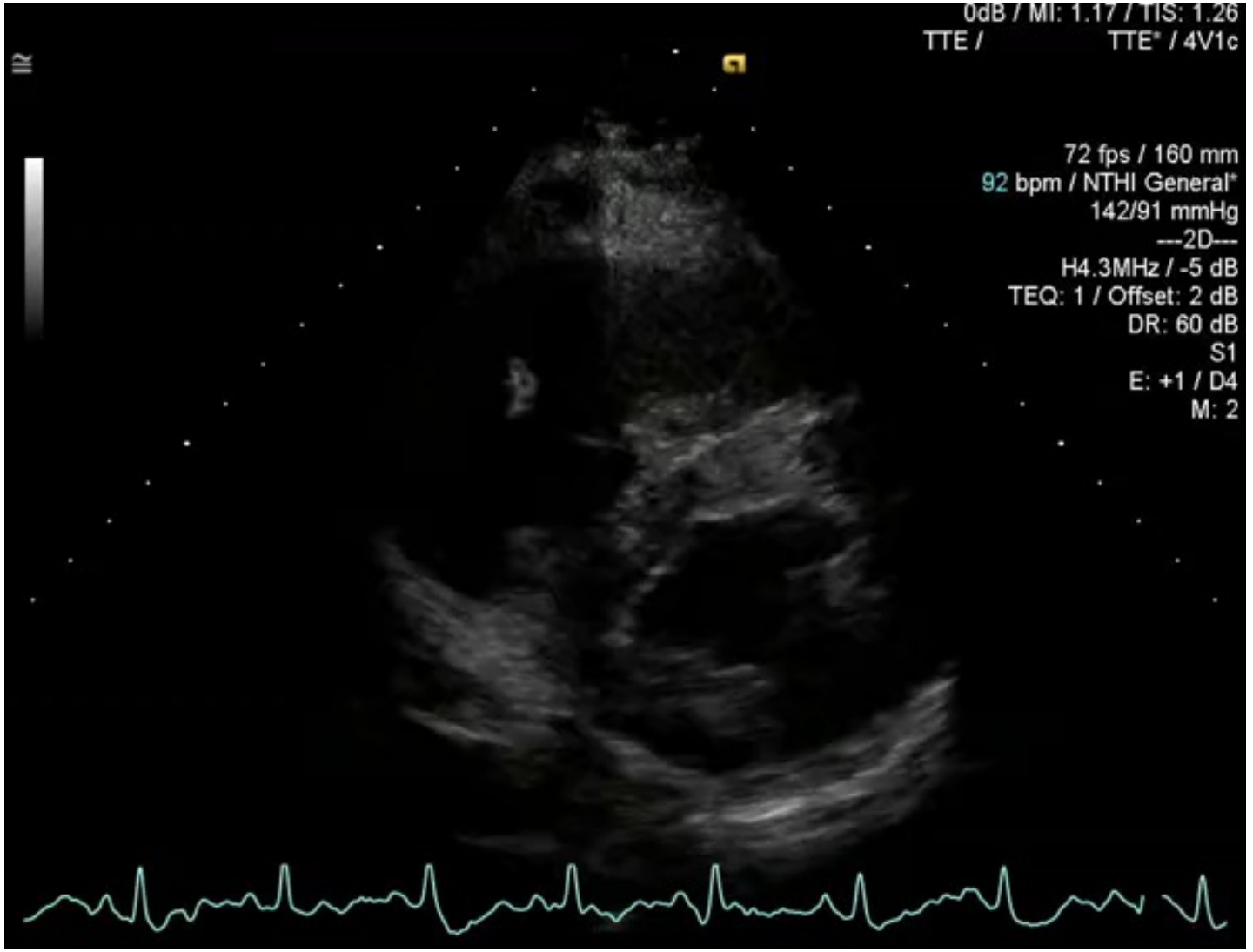
Surgical thrombectomy (n=21 antenatal)

- Maternal survival 84%; fetal survival 57%
- Maternal bleeding 20%

Martillotti G, et al. J Thromb Haemost. 2017.

Empiric lysis at bedside

- Near arrest situations
- Bedside echo has LR(+) of approximately 3.0 (24,25)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TTE /
TTE* / 4V1c
72 fps / 160 mm
92 bpm / NTHI General*
142/91 mmHg
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TEQ: 1 / Offset: 2 dB
DR: 60 dB
S1
E: +1 / D4
M: 2

Empiric lysis at bedside

- Near arrest situations
- Bedside echo has LR(+) of approximately 3.0 (24,25)
- Witnessed arrest + age <65 + PEA as first rhythm has predictive value + of 50% for PE (26)
- EKG with acute pulmonary hypertension LR(+) about 3.0 (27)

Pulmonary hypertension on ECG

- Daniel score *(Shopp JD, et al. Acad Emerg Med 2015; 22:1127-1137)*

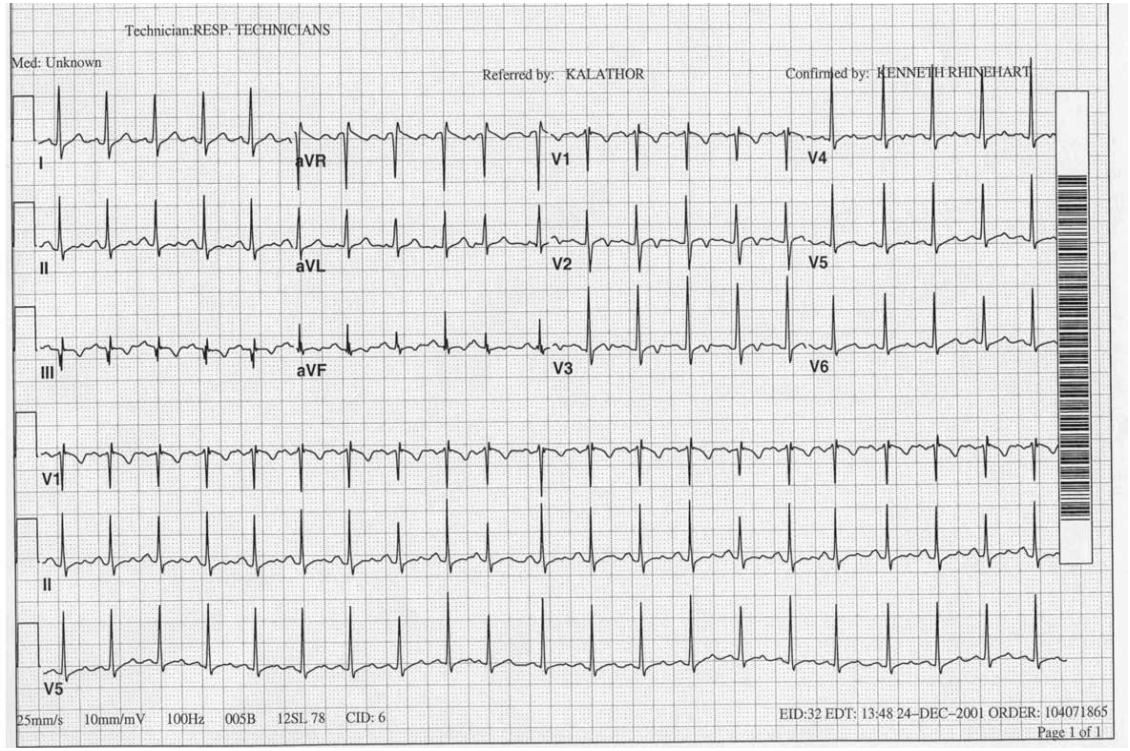

Table 5
ORs for the ECG Components for the Risk of Hemodynamic Collapse or Death

ECG Finding	OR (95% CI)
HR > 100 beats/min	4.46 (1.68–11.84)
S1	1.76 (1.09–2.85)
Q3	0.98 (0.5–1.93)
T3	1.68 (0.44–6.52)
S1Q3T3	2.06 (1.23–3.45)
RBBB	
Unspecified	1.89 (1.27–2.81)
Incomplete	1.05 (0.46–2.42)
Complete	2.67 (1.81–3.95)
iT wave	
V1–V4	1.69 (0.83–3.43)
V1	2.63 (1.47–4.73)
V2	6.94 (2.41–19.96)
V3	7.07 (1.13–44.22)
STEaVR	5.24 (3.98–6.91)
Atrial fibrillation	1.75 (1.15–2.66)

Afib = atrial fibrillation; ECG = electrocardiography; HR = heart rate; PE = pulmonary embolism; RBBB = right bundle branch block, STE = ST elevation.

Empiric lysis at bedside

- Near arrest situations
- Bedside echo has LR(+) of approximately 3.0 (24,25)
- Witnessed arrest + age <65 + PEA as first rhythm has predictive value + of 50% for PE (26)
- EKG with acute pulmonary hypertension LR(+) about 3.0 (27)
- Lower extremity venous ultrasound might confirm a donor site
- Please give heparin!
- Bolus lysis not associated with increased bleed rate

Treating PE with active bleeding

- Suction catheters
- Caval interruption
- Consider inhaled nitric oxide or epoprostenol

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Inhaled nitric oxide to treat intermediate risk pulmonary embolism: A multicenter randomized controlled trial

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Table 2
The primary outcome.

Measurement	Definitions	NO		Placebo		P value
		n/38*	%	n/38*	%	
Primary outcome	Normal right ventricular function on echocardiography and normal troponin T**	9	24%	5	13%	0.375
Components of primary outcome	Right ventricular diastolic diameter < 43 mm	31	82%	27	71%	
	Tricuspid annular plane systolic excursion > 16 mm	29	76%	28	74%	
	Right ventricular index of myocardial performance normal	22	58%	22	58%	
	Right ventricular fractional area of contraction > 33%	23	61%	21	55%	
	Plasma troponin T concentration < 14 pg/mL	14	37%	11	29%	

Summary

- Multiple options exist for reperfusion after pulmonary embolism. Only full-dose systemic fibrinolysis has been demonstrated superior to placebo in more than one randomized controlled trial.

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