

Predictors of Major Hemorrhage Following Fibrinolysis for Acute Pulmonary Embolism

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Objectives

- Review the epidemiology and pathophysiology of pulmonary embolism (PE)
- Identify the role of fibrinolytic therapy in PE
- Review literature regarding major hemorrhage following fibrinolysis
- Review Landefeld bleeding severity index
- Discuss the results of the study “Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism” and its implications on clinical practice

Background

- Pulmonary embolism is a common, potentially life threatening cardiopulmonary illness
- International Cooperative Pulmonary Embolism Registry of 2454 patients determined the 3-month mortality rate for PE to be 17.4%
- This mortality rate is much higher than that reported in clinical trials (exclusion criteria)

Background

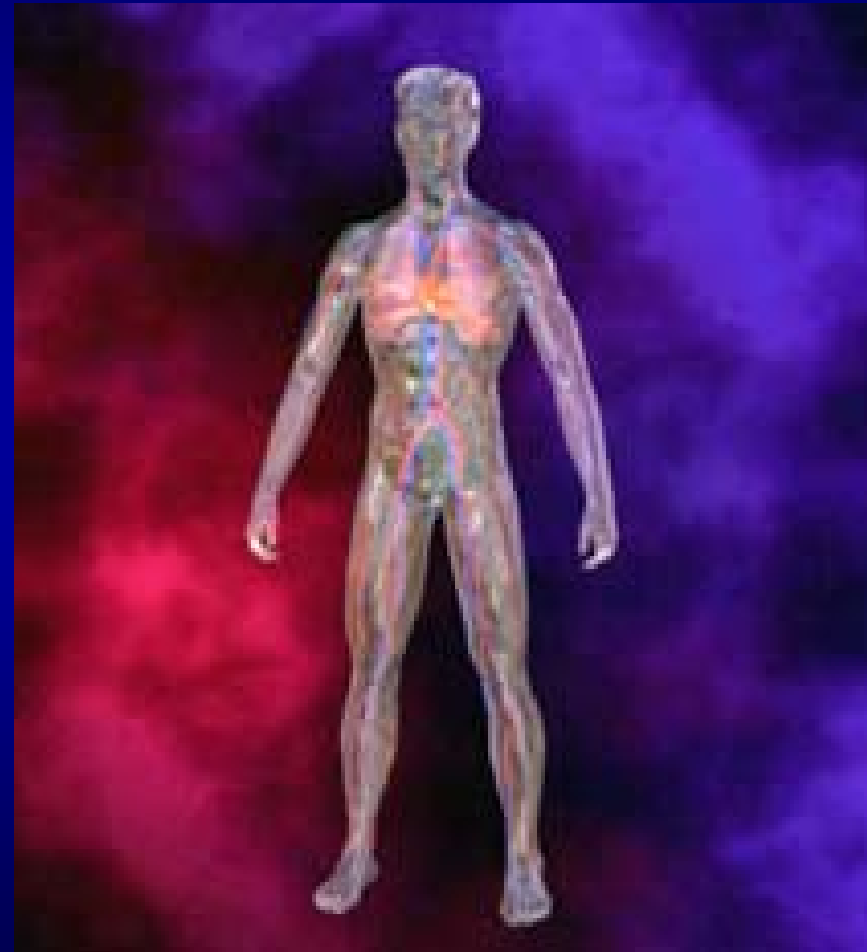
- Pulmonary embolism attracted the attention of the general public in October of 2000
- A 28 year old bride- to-be and fitness fanatic died suddenly following a 20 hour flight from Australia to the UK
- How can a young otherwise healthy individual die so suddenly from a blood clot?



Emma Christoffersen

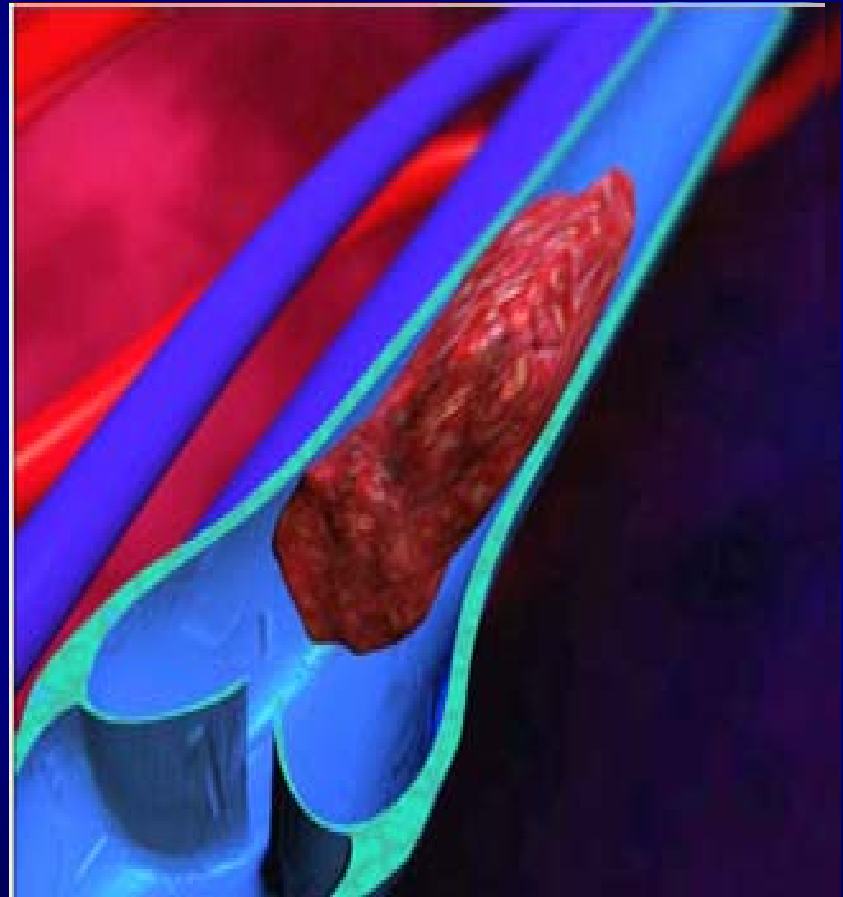
Pathophysiology

- Our circulatory system carries blood throughout our body via veins and arteries
- The venous system is designed to return used blood to the heart and lungs



Pathophysiology

- Occasionally a blood clot or thrombi will form in a vein
- Once formed, additional fibrin and red blood cells will deposit on the clot causing it to grow



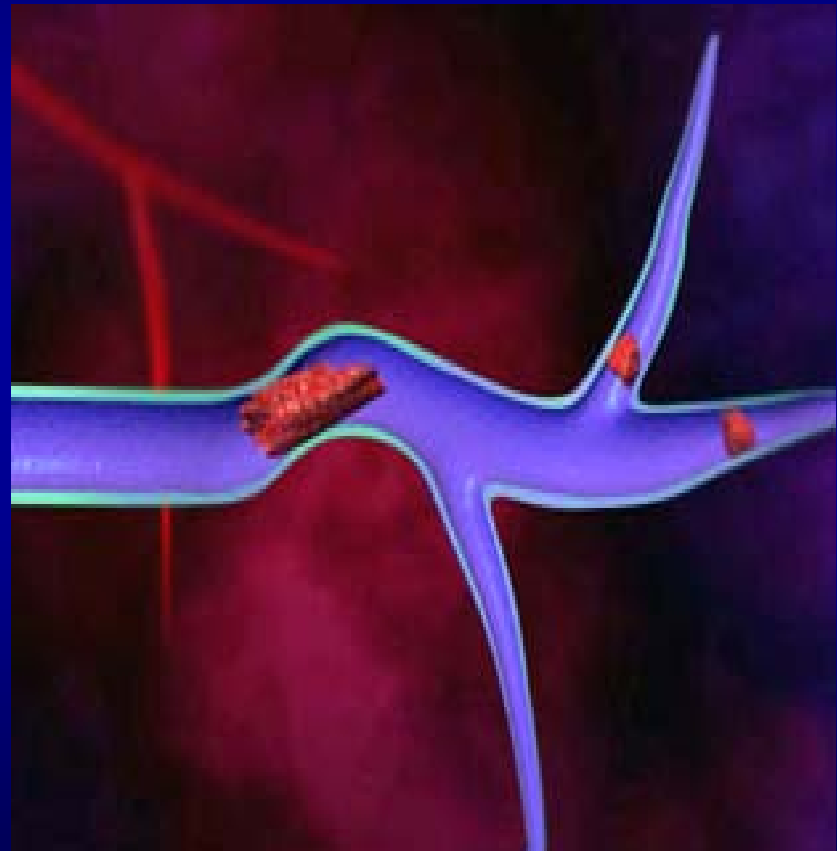
Pathophysiology

- In addition to obstructing blood flow in the vein, there is significant threat that a part of the thrombus may break off and travel through the blood



Pathophysiology

- These thrombi may eventually become lodged in the vessels of the lungs
- The thrombi are now called a pulmonary embolism



Pathophysiology

- Depending on the size and location of the pulmonary embolism it can result in:
 - Right ventricular dysfunction
 - Left ventricular dysfunction
 - Decrease cardiac output and pressure
 - Sudden death



Treatment Options for Massive PE

- Fibrinolysis
 - Urokinase
 - Streptokinase
 - Alteplase
- Surgical Embolectomy
- Catheter Thrombectomy

Mechanism of Fibrinolysis in PE

- Fibrinolytics convert plasminogen to plasmin
- Plasmin – proteolytic enzyme that is formed from plasminogen which breaks down fibrin and promotes clot lysis
- Also cause systemic plasminogen activation
- Produce a hypocoagulable state

Use of Fibrinolytic in PE

- An overview of 5 randomized controlled trials that included patients with massive PE, fibrinolytic therapy reduced the risk of recurrent PE by 55%
- Fibrinolytic therapy is a recommended treatment option in patients with massive PE
- Fibrinolytic therapy is associated with increased risk of hemorrhage

Risk of Hemorrhage

- Meta-analysis of 11 randomized controlled trials showed PE treated with fibrinolysis was associated with twofold increase in the risk for major bleeding
- International Cooperative Pulmonary Embolism Registry showed 21.7% of patients treated with fibrinolysis had major bleeding complication and 3% suffered ICH
- 132 thrombolized patients from a tertiary care hospital in Paris, 25% suffered major bleeding

Wan S et al. Circulation 2004;110:744-749

Goldhaber S et al. Lancet 1999;353:1386-1389

Meyer G et al. Am J Med 1998;105:472-477

Risk of Hemorrhage

- These studies provide data on bleeding rates associated with fibrinolytic therapy
- Risk factors predisposing patients to bleeding events have not been precisely defined
- We designed a study to evaluate the frequency and predictors of hemorrhage in patients receiving fibrinolytic therapy for pulmonary embolism

Methods

- Retrospective review 1996 - 2004
- 104 consecutive patients diagnosed with PE
- Received alteplase 100 mg over 2 hours
- Evaluated medical records:
 - Demographics, comorbidities, medications, laboratory findings, and hospital course following the administration of alteplase
- Bleeding identified according to Landefeld bleeding index
- Multivariate logistic regression analysis identified independent predictors of major bleeding

Landefeld Bleeding Index

Major Bleeding

- Fatal
- Life threatening
 - MI
 - Stroke
 - surgical or angiographic intervention to stop bleeding
- Potentially life threatening
 - Systolic hypotension
 - Critical anemia
 - re-operation

Landefeld Bleeding Index

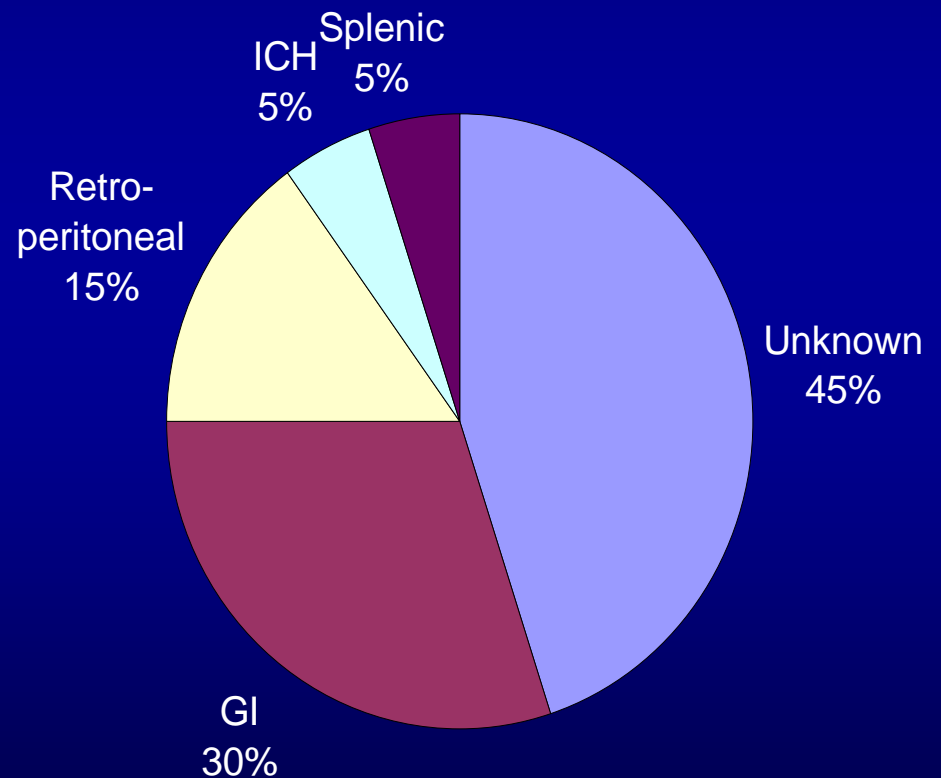
Minor Bleeding

- Overt bleeding from an internal site
 - Gastrointestinal, hemoptysis, gross hematuria
- Moderate or severe blood loss that occurred without internal bleeding
 - Transfusion of 2.0 or more units and either:
 - 1.0 unit/week rate of blood loss
 - 20% Hct drop
 - Discharge Hct less than 30% and 1.0 unit/week rate of blood loss and Hct drop of at least 20%

Major Bleeding Sites

- 20 patients (19.2%) experienced major hemorrhage
- All 6 in-hospital deaths occurred in patients with major bleeding
 - Bleeding was clinical cause of death in only 1 patient
- 21 patients experienced minor bleeding (20.2%)

Major Hemorrhage Sites



Description of Major Bleeding Events

Major Bleeding (n=20)	n (%)
Fatal	1 (5%)
Severe Blood loss >3 units	7 (35%)
Hypotension*	7 (35%)
Critical Anemia [†]	14 (70%)
Re-operation	1 (5%)

* >20 % decrease in systolic systemic pressure to <90 mm Hg

[†] 20% decrease in hematocrit to <20%

Description of Minor Bleeding Events

Minor Bleeding (n=21)	n (%)
Gross Hematuria	17 (81%)
SC or Muscular Hematoma	10 (48%)
Veinpuncture	9 (43%)
Gastrointestinal	2 (10%)
Hemoptysis	2 (10%)
Retroperitoneal	1 (5%)
Blood loss that occurred w/o internal bleeding site	2 (10%)

Independent Predictors

	Major Bleeding	No/Minor Bleeding	<i>p</i> -Value
Hemodynamic instability	35%	1%	<0.001
Current cancer	40%	7%	<0.001
Renal dysfunction	35%	10%	0.004
DM	30%	11%	0.03
Elevated INR	1.4 (1.0-2.4)	1.1 (0.9-3.3)	0.016

[†]defined as systolic arterial pressure <90 mmHg or the administration of pressors for systolic arterial hypotension

Comorbidities

	Major bleeding (n = 20)	No / Minor bleeding (n = 84)	<i>p</i> - value
Cancer	8 (40)	6 (7)	<0.001
Hypertension	10 (50)	27 (32)	0.13
Coronary Artery Disease	1 (5)	8 (10)	0.51
Diabetes Mellitus	6 (30)	9 (11)	0.03
Chronic Lung Disease	2 (10)	6 (7)	0.67
Congestive heart failure	3 (15)	7 (8)	0.36
Creatinine >1.5 mg/dL	7 (35)	8 (10)	0.004
Surgery within 2 weeks	2 (10)	14 (17)	0.46
Prior History of DVT or PE	4 (20)	13 (16)	0.62
History of stroke	1 (5)	2 (2)	0.53

Medications Prior to Thrombolysis

	Major bleeding (n = 20)	No/Minor bleeding (n = 84)	<i>p</i> -value
LMWH within 24 hours	1 (5)	4 (5)	0.96
Warfarin within 1 week	1 (5)	3 (4)	0.76
Salicylates within 5 days	4 (20)	10 (12)	0.46
NSAIDs within 5 days	2 (10)	7 (8)	0.67

Multivariate Analysis for Predictors of Landefeld Major Bleeding

	Adjusted Odds Ratio	95% Confidence Interval	<i>p</i> -value
Current Cancer	16	3.2-80	0.004
Hemodynamic Instability*	115	9.4-1,411	<0.001
DM	9.6	1.7-54	0.010
Elevated INR [†]	5.8	1.5-22	0.012

* Defined as systolic arterial pressure < 90 mm HG or the administration of pressors for systolic hypotension

[†] entered as a continuous variable

Study Caveats

- Small sample size
- Retrospective data
- Data obtained from one site
- Evaluation using single bleeding index
 - TIMI
 - GUSTO
- “Real life” reflection of clinical practice

Conclusions

- Bleeding occurs frequently with fibrinolytic therapy
- Awareness of bleeding risk factors can enhance patient safety
- Cancer, hemodynamic compromise, DM, and increased INR may independently predict major bleeding complications
- Patients at high risk for major bleeding may be better candidates for surgical embolectomy or percutaneous catheter thrombectomy

Thank you for your attention!

