

## Bleeding, Clotting and Finding the Balance: Implications for the CRNA

Aaron Ostrowski, CRNA, MSN

University of Pittsburgh Nurse Anesthesia Program

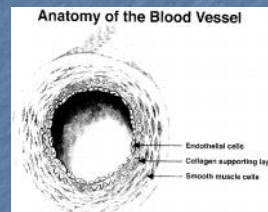
## The Big Picture

- Insult to vessel, big or small
  - Trauma (shearing) or surgery (sharp)
- Clot forms: Hemostasis
  - Two major clotting factors: What are they?
    - Thrombin (IIa) and Fibrin (1a)
- Clot dissolves: Fibrinolysis
  - One major player: What is it?
    - Plasmin

## Role Players

- Platelets: major contributors
- Other clotting factors:
  - Intrinsic and Extrinsic pathways, classically
  - Now conceptualized as components of a coordinated, cell-based process
- Let's look into this...

## The Normal State of Things



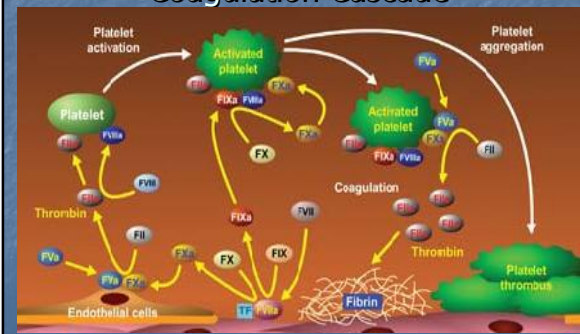
- Endothelial cells control vascular tone<sup>1</sup>
  - Nitric oxide: vasodilator and antiplatelet agent
  - Endothelin: vasoconstrictor
- Active endogenous anticoagulants are circulating<sup>4</sup>

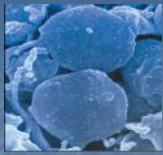
## Vascular Spasm

- Reflex
  - Immediately active
    - lasts 20 to 30 minutes
  - Diminished by sharp edged wounds
  - Small vessels from 30 to 50 microns
- When spasm isn't enough...

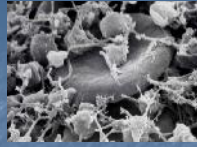


## Platelet Plug and the Coagulation Cascade

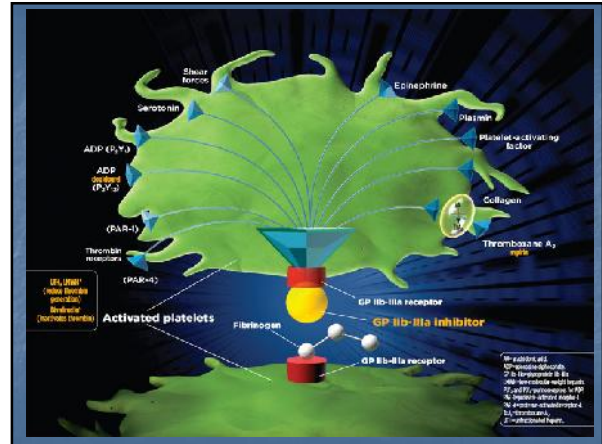




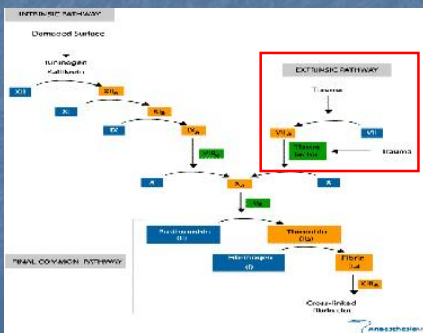
## Platelets



- Vessel wall damage exposes collagen under the endothelium
  - Tissue Factor (III) is exposed with this damage, changes shape, and sensitizes platelets<sup>4</sup>
- A sensitized platelet morphs from a smooth, rounded shape into an irregular, tentacled coagulation factory.



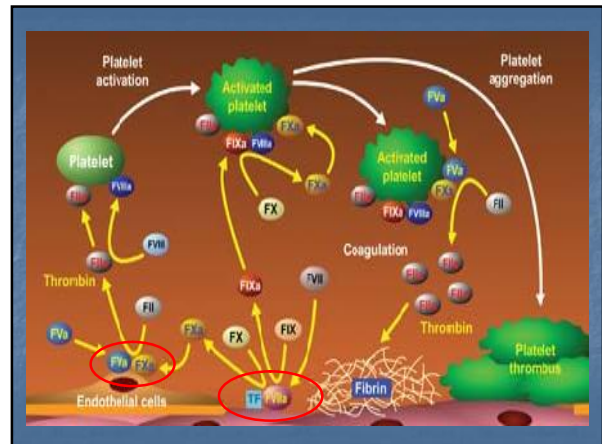
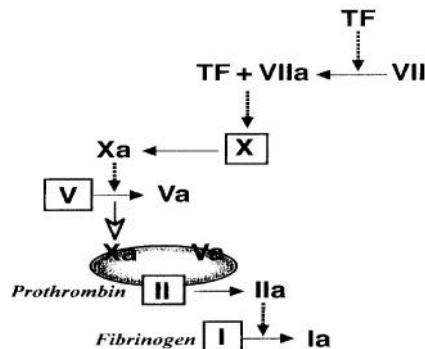
## The Classical View



## Extrinsic Pathway

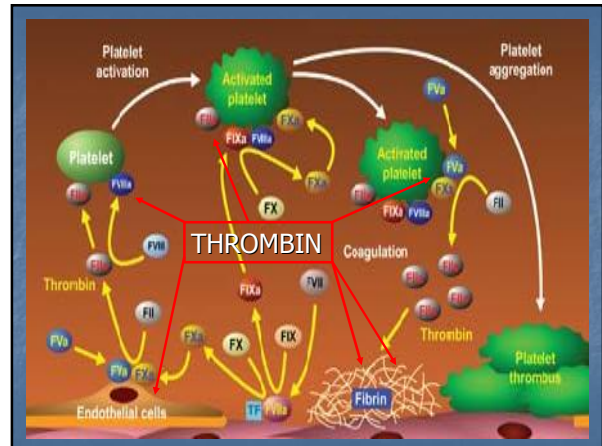
- Also called the Tissue Factor Pathway
- Circulating FVII contacts the exposed Tissue Factor (III) from the damaged endothelium
- FVIIa activates FX, known as "tenase"
  - FX then combines with FV
  - FXa + FVa = Mom & Pop thrombin production, aka "prothrombinase"<sup>2</sup>
    - Soon to be bought out by a Big Box platelet producer

## The Classical Extrinsic Pathway

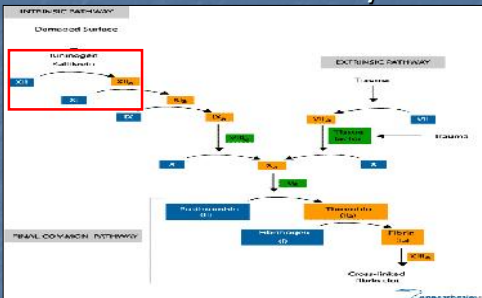


## Roles of Thrombin

- Transform fibrinogen to fibrin
- Liberate vWF from FVIII
- Activates platelets at the site of injury
  - A potent positive feedback cycle
- Activates FV and FX for thrombin burst
- Activates Factor XI of Intrinsic Pathway
- Activates FXIII for clot stabilization<sup>4</sup>



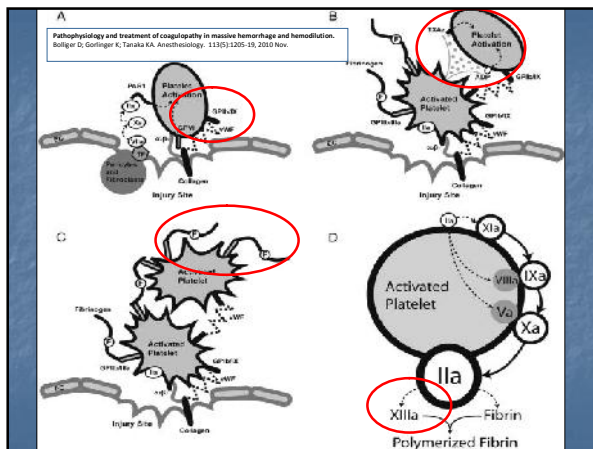
## Intrinsic Pathway



- In vivo, not relevant to the initiation of a clot

## Updated Concept: Initiation, Acceleration, Control, and Lyses<sup>1</sup>

- Initiation: Endothelial damage followed by platelet plug formation
- Acceleration: Coag factor and further cellular activation
- Control: Feedback mechanisms activated
- Lyses: Clot breakdown and initiation of healing



## Initiation and Acceleration

- Damage occurs to endothelium
- Tissue Factor released, attracts Factor VII
  - vWF released, bridges collagen and platelets via the GPIb receptor
  - Attracts other platelets, exposes GPIIb-IIIa receptor, other recruited platelets are interconnected bridges of soluble fibrin
- Platelets release their contents
  - Greater than 90 procoagulant substances



## Late Coagulopathy

- More familiar version associated with dilution
- Massive bleeding
  - One blood volume in less than 24 hrs.
  - Loss of half of blood volume in three hours
- Blood product administration is hazardous
  - Increased mortality
  - Major adverse cardiac and noncardiac outcomes<sup>6</sup>

## Task Force for Advanced Bleeding Care in Trauma<sup>7</sup>

- Convened in 2005 to 2006
- A group of European professional societies
- Critical survey of published literature with consensus agreement among the societies
- Formulated recommendations based on their findings...

## Targeted Blood Pressure (2C)

- SBP of 80 to 100 mm Hg
  - Until major bleeding stopped in patients without brain injury
  - MAP of 80 mmHg recommended in TBI
- Increased blood pressure associated with increased hydrostatic pressure<sup>7</sup>

## Fluid Management (2C)

- Suggest crystalloids initially
- Colloids within prescribed limits
  - Studies are equivocal but suggest limits of 30 cc/kg
- 3% Saline better than NS in increased ICP

## Management of Bleeding, and Coagulation (1C)

- Target Hgb 7 to 9 g/dl
  - Rheological effect of RBC's may marginalize the platelets in the vessel
- FFP for coags > 1.5 times control
  - Dosed 10 to 15 cc/kg
  - Problems include overload, ABO, TRALI
- Platelets to maintain platelet count > 50K
  - A 4 to 8 pool or one apheresis pack

## Packed Red Blood Cells

- Preserved in CPDA or "Additive Solution"
  - CPDA: Hct 70-75%, TV 275 ml, 35 day shelf life
  - Additive: Hct 60%, TV 350 ml, less citrate, 42 day shelf life, 75% fewer microaggregates
- One unit raises hgb 1g/dl and hct 3%
- With known ABO and Rh alone in naïve pt.
  - 99.8% likelihood of a compatible transfusion<sup>11</sup>

## Fresh Frozen Plasma

- One unit is the plasma from one donated unit of whole blood
  - contains preservative: CPDA or AS
  - Frozen quickly to preserve FV and FVIII
  - Must be ABO compatible, Rh not a factor
- Dosing is 10 to 15 cc/kg, usually 4 units to replenish clotting factors adequately<sup>11</sup>
  - 1 unit of FFP increases most factors ~2.5%

## Platelets

- Dose is 1 unit/10 kg of body weight
  - Generally a 6 pool of platelets
- Raises the platelet count 5 to 10 K/mcl
- Four hour expiration
- ABO compatibility not as critical
  - Very few RBC's and about 60 cc's of plasma in platelet pools<sup>11</sup>

## Cryoprecipitate

- A precipitate that remains when FFP is thawed slowly at 4° C.
  - One unit cryo is the yield from one unit of FFP
  - No ABO compatibility issues
- Concentrated source of FVIII, vWF, FXIII, fibronectin and fibrinogen<sup>11</sup>
- Hypofibrinogenemia is less than 100 mg/dl
  - 6 pack of cryo raises fibrinogen by 45 mg/dl

## Transfusion Ratios

- Low ratio is FFP to PRBC less than 1:4
- Medium ratio is FFP to PRBC 1:4 to 1:2
- High ratio is greater than 1 unit of FFP for every 2 units of PRBC
  - Has shown decreased rates of complication in massive transfusions after combat injuries
- FFP to PRBC to Platelet of 1:1:1 with minimal crystalloid resuscitation

## Transfusion Practices

- Transfusion with all components of whole blood in preserved form does not produce a whole blood equivalent
  - 1FFP+1PRBC+1PLT = Hct of 29%
  - Total volume of 660cc, platelets of 88K, and coagulation activity 65% of whole blood
- Whole blood Hct is 38 to 50%, Plts 150 to 400K, and 100% of coag factors<sup>3</sup>

## Tranexamic Acid:

the solution to fibrinolysis

- Studies on surgical patients have used wide ranges of dosing
  - Loading doses: 2.5 to 100 mg/kg
  - Infusion doses: 0.25 to 4 mg/kg/hr
- No benefit between high and low dosing
  - Bolus of 10 mg/kg and infusion of 1 mg/kg/hr provides sufficient plasma levels for antifibrinolysis<sup>8</sup>

## CRASH-2

- Randomized over 20,000 trauma patients
  - 274 hospitals in 40 countries
  - First patient enrolled in May, 2005
- Bolused with TA 1 gm over 10 mins and infused with TA 1 gm over 8 hours.
- TA reduces the risk of death from hemorrhage
  - No apparent increase in fatal or nonfatal vascular occlusive events
  - All-cause mortality was significantly reduced with tranexamic acid<sup>9</sup>

### References:

1. Soliman DE, Broadman LM. Coagulation Defects. *Anesthesiology Clin.* 24 (2006) 549-578
2. Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *Anesthesiology.* 113(5):1205-19, Nov 2010.
3. Shler, KC, Napolitano, LM. Complications of Massive Transfusion. *Chest.* 137(1), January, 2010.
4. Stoelting, RK, 5<sup>th</sup> Edition, *Basics Principles of Anesthetic Practice*, 2010
5. McCunn, M, Gordon, EKB, Scott, TH. Anesthetic Concerns in Trauma Victims Requiring Operative Intervention: The Patient Too Sick to Anesthetize. *Anesthesiology Clin.* 28 (2010) 97-116.
6. Ganter, MT, Spahn, DR. Active, Personalized, and Balanced Coagulation Management Saves Lives in Patients with Massive Bleeding. *Anesthesiology.* 113(5):1016-1018. November, 2010.
7. Spahn, DR, Cerny, V, et.al. Management of Bleeding Following Major Trauma: A European Guideline. *Critical Care*, 2007.
8. CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet Online*, June 15, 2010.
9. Van Dredena, P, Ie Rousseau, R, Savourec, A, Lenormand, B, Fontaine, S, and Vasseb, M. Plasma thrombomodulin activity, tissue factor activity and high levels of circulating procoagulant phospholipid as prognostic factors for acute myocardial infarction. *Blood Coagulation and Fibrinolysis* 2009, 20:635-641
10. Philbert, YV et.al. High Transfusion Ratios Are Not Associated With Increased Complication Rates in Patients With Severe Extremity Injuries. *J Trauma.* 2010;69: 564-568
11. Barash, PG, Cullen, BF, Stoelting, RK, 5<sup>th</sup> edition. *Clinical Anesthesia*. Ch. 10 Hemotherapy and Hemostasis. 2006