Challenges in Perioperative Hemostasis: Managing Coagulopathy in Elective and Urgent Cardiac Surgery

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Physiology of Hemostasis

- Response to traumatic or surgical injury
- Complex interaction between vascular wall, platelets, coagulation factors, and fibrinolysis
- Clotting is a complicated process
  - Platelet-mediated primary hemostasis, explosive thrombin generation
    - Conversion of fibrinogen to fibrin
    - Stable fibrin and platelet network or clot produced

Overview of Hemostasis

Coagulation Cascade

- Thrombin
  - APC
  - TAFI
  - TAFI
  - FXIIIA
  - Clot stabilizing factor

Fibrinolytic Cascade

- Plasminogen
  - Plasmin

Fibrinogen

- Fibrin
- Fibrin degradation products (FDPs)

Adapted from Nesheim M. Chest. 2003;124:33S-39S.

FDPs = fibrin degradation products.
Maintaining Hemostasis

- Hemostatic control depends on balance between procoagulant and anticoagulant factors\(^1\)
  - Coagulation
  - Fibrinolysis
- Disorders in balance may result in severe bleeding or thrombotic complications\(^1\)
- Hemostatic agents must maintain balance without causing adverse thrombotic effects of drug toxicity
- Challenge is to maintain patient physiology between balance of bleeding and clotting\(^2\)

Preoperative Management of Elective Cardiac Patients

- Patient evaluation
  - Medical history
    - Bleeding from minor procedures
    - Easy bruising
    - Problems with previous surgeries
    - Family members having had difficult surgeries
- Patient medications
  - Platelet inhibitors, including ASA, clopidogrel, ticlopidine, disopyramide, vitamin E supplements
  - Anticoagulants, including vitamin K antagonists
  - For thienopyridines, such as clopidogrel, ACC/AHA and STS/SCA guidelines recommend 5- to 7-day drug holiday prior to surgery, if possible\(^1,2\)
  - For reversal of anticoagulants in emergent setting, can use vitamin K, FFP, PCC, or rFVIIa\(^3\)

Evaluation of Hemostasis

- Platelet count
- Platelet function
  - PFA-100®
  - TEG®
  - ROTEM®
- PT/INR
- aPTT
- Fibrinogen level

- Antiplatelet drug effects may only be detected by aggregometry; history may be more valuable
  - Clopidogrel: reduced ADP aggregation
  - Aspirin: reduced AA aggregation
  - Eptifibatide (IIb/IIIa): reduced ADP, AA and collagen
# Lab Values and Bleeding

## Association of Bleeding After CABG With Lab Values

<table>
<thead>
<tr>
<th>TEG MA</th>
<th>PLT</th>
<th>PT</th>
<th>Fibrinogen</th>
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<tbody>
<tr>
<td>R</td>
<td>-.57</td>
<td>-.44</td>
<td>.43</td>
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<tr>
<td>P value</td>
<td>.003</td>
<td>.02</td>
<td>.02</td>
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## Association of Lab Values With TEG MA Parameter

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Fibrinogen</th>
<th>PT</th>
<th>APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>.72</td>
<td>.65</td>
<td>-.46</td>
</tr>
<tr>
<td>P value</td>
<td>(&lt;.001)</td>
<td>(&lt;.001)</td>
<td>(.01)</td>
</tr>
</tbody>
</table>

The MA is a measure of clot strength.

Three Components of Hemostasis

- Fibrinogen
- FII (prothrombin)
- FXa
- FV
- FIIa (α-thrombin)

Platelet plug at site of injury

Primary Hemostasis

vWF/collagen on subendothelium
Treatment of Coagulopathy: Blood Products

- Prophylactic transfusion not warranted; follow algorithms
- Define/identify coagulopathic bleeding first
- Platelet transfusion
  - If <50 x10⁹/l
    - Consider if 50-100x10⁹/l
    - Consider if history of antiplatelet drugs
    - Consider if known platelet dysfunction
- Plasma transfusion
  - INR >2.0
  - PTT ratio >1.5
- Cryoprecipitate transfusion
  - If fibrinogen 80-100 mg/dl
  - Rarely indicated if >150 mg/dl

Treatment of Refractory Coagulopathy: Off-Label Use of Factor Concentrates

- Recombinant activated factor VII (rFVIIa)
  - FDA-approved for congenital FVII deficiency, hemophilia
  - ACCP guidelines: for urgent coumadin reversal\(^1\)
  - ↓ bleeding, ↑ thrombotic events\(^2\)
- Prothrombin complex concentrates (II, VII, IX, X, PC, PS)
  - ACCP guidelines: for urgent coumadin reversal\(^1\)
  - Some association with thrombosis
    - Primarily aPCC (FEIBA)\(^3,4\)
- Purified/plasma-derived factor VIII/vWF complex
  - Rarely described outside obstetric hemorrhage
- Purified/plasma-derived fibrinogen
  - FDA-approved for congenital afibrinogenemia
  - Low thrombogenicity in venous stasis animal models\(^5\)

Restoration of Hemostasis

- **Restoration of primary hemostasis**
  - DDAVP to increase vWF multimers
  - Platelet transfusion
    - Thrombocytopenia
    - Platelet dysfunction

- **Restoration of thrombin generation**
  - Coagulation factor replacement

- **Restoration of stable fibrin clot formation**
  - Antifibrinolytic drugs
  - Fibrinogen replacement
  - FXIII replacement
Restoration of Primary Hemostasis

- Platelet transfusion
- DDAVP infusion
  - Augments primary hemostasis
- Each apheresis unit or “6 pack” concentrate dose contains
  - $\geq 3 \times 10^{11}$ platelets in $\approx 250$ mL plasma
- Assuming $4 \times 10^{11}$ platelets and a BSA of 2m2:
  - $25 (+/-17) \times 10^9$/L typical response
- Reduced increment seen with:
  - Men/higher body surface area
  - DIC
  - Sepsis
  - Bleeding
  - ABO incompatible

BSA=body surface area; DIC=disseminated intravascular coagulation.

• Restoration of primary hemostasis
  ▪ DDAVP to increase vWF multimers
  ▪ Platelet transfusion
    ▪ Thrombocytopenia
    ▪ Platelet dysfunction

• Restoration of thrombin generation
  ▪ Confirm full heparin reversal (protamine)
  ▪ Coagulation factor replacement

• Restoration of stable fibrin clot formation
  ▪ Antifibrinolytic drugs
  ▪ Fibrinogen replacement
  ▪ FXIII replacement
Dosing of plasma (70-kg patient):
- 1 unit (250 mL) increases factor levels by ≈2.5%
- 4 units (1000 mL) increases levels by ≈10%
  - Less for FV, FVIII, vWF
- PT or PTT ratio >1.5 or INR >1.6 factor levels <30%

What factor level is sufficient for hemostasis during surgery? In hemophilia, rFVIIa activity depends on FII\(^1\) and FX\(^2\) levels

Restoration of Thrombin Generation

- **FFP provides procoagulant factors**
  - Pro- and anticoagulant factors at normal levels
- **Thawed plasma**
  - FV $\approx 65\%$
  - FVIII/vWF $\approx 40\%$ normal (lower for Group O)
- **PCCs replenish II (prothrombin), VII, IX and X, PC, PS**
- **Varying factor levels depending on product rFVIIa drives production of IXa and Xa**

**Activation and propagation of coagulation**
Restoration of Hemostasis

- **Restoration of primary hemostasis**
  - DDAVP to increase vWF multimers
  - Platelet transfusion
    - Thrombocytopenia
    - Platelet dysfunction

- **Restoration of thrombin generation**
  - Coagulation factor replacement

- **Restoration of stable fibrin clot formation**
  - Antifibrinolytic drugs
  - FXIII replacement (in plasma)
  - Fibrinogen replacement
Treatment of Coagulopathy: Fibrinogen

- Optimal level of plasma fibrinogen necessary to maintain perioperative hemostasis not fully understood\(^1\)
- Boosting fibrinogen level (mean 3.6 g/L) can reduce transfusion of allogeneic blood products\(^1\)
- Most transfusion algorithms do not treat levels unless they are <100-150 mg/dL\(^2\)
- Higher than normal levels may be effective\(^1\)

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Treatment of Coagulopathy:
Fibrinogen (cont)

- **Plasma**
  - Normal levels of fibrinogen
- **Increasing concentration difficult with plasma**
  - 10-15 mL/kg increases fibrinogen by 40 mg/dL
  - 30 mL/kg increases fibrinogen by 100 mg/dL
  - Risk of volume overload
- **Cryoprecipitate content (adult dose = 10 units or 100 mL)**
  - Fibrinogen (1.5-3 g)
  - FXIII (400-600 U)
  - FVIII/vWF (800-1000 U)
  - Albumin, fibronectin, IgG, IgM (less than FFP)
- **One dose (10 units) of cryoprecipitate increases fibrinogen ≈60 mg/dL**
## Advantage of Factor Concentrates

<table>
<thead>
<tr>
<th>4 units FFP</th>
<th>Adult dose “10 pack” CRYO</th>
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<tbody>
<tr>
<td>3g</td>
<td>3.5 g</td>
</tr>
<tr>
<td>in 1000 mL</td>
<td>in 100 mL</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>150 mg/dL FIB</td>
<td>CV = 5000 mL</td>
</tr>
<tr>
<td>Total 7.5 g FIB</td>
<td>Total 10.5 g FIB</td>
</tr>
<tr>
<td>CV = 6000 mL</td>
<td>CV = 5000 mL</td>
</tr>
<tr>
<td>175 mg/dL FIB</td>
<td>215 mg/dL FIB</td>
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</tbody>
</table>
Drawbacks of Transfusable Factors

- TRALI risk (plasma > cryoprecipitate)
- Infection risk (10 donors for cryoprecipitate, 4 for plasma)
- Allergic reactions (plasma > cryoprecipitate)
- Volume overload/TACO (plasma)
- Purified/plasma-derived or recombinant factors
  - Possible alternative or adjunct to blood products
  - Not currently FDA-approved for acquired deficiencies
  - Use for refractory bleeding currently off-label
  - Preliminary studies have been performed
  - Studies to support FDA approval pending
Presentation highlights:

- Explain the essential aspects of hemostasis, from primary hemostasis through thrombin generation, and cleavage of fibrinogen to formation of a stable fibrin clot
- Evaluate the clinical utility of coagulation lab assays as markers for excessive perioperative bleeding and targeting hemostatic therapy
- Discuss current and emerging therapeutic options for restoring perioperative hemostasis in cardiac surgery patients
Challenges in Perioperative Hemostasis: Managing Coagulopathy in Elective and Urgent Cardiac Surgery

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Cardiac surgery induces abnormalities of primary and secondary hemostasis resulting from:

- Blood contact with nonendothelial surfaces of the extracorporeal circuit
- Release of TF (tissue factor) after surgical trauma
- Reinfusion of TF and activated coagulation factors
- Shear forces generated by cardiotomy suction
- Activation of the inflammatory system, generation of circulating thrombin
- Activation of platelets

Perioperative Impairment of Hemostasis

Bleeding following cardiac surgery is often multifactorial

- Inhibition of hemostasis or platelets
  - Hypothermia
  - Mechanical or inflammatory injury
  - Heparin or protamine
  - Preoperative drug therapies
- Extrinsic pathway activation
  - Tissue or vascular injury
  - Reperfusion of ischemic tissues
  - Local thrombin generation
- Dilutional coagulopathy

Predictors of Postoperative Bleeding in Cardiac Surgery

- Advanced age
- Small body size or preoperative anemia (low RBC volume)
- Antiplatelet, antithrombotic drugs
- Prolonged operation
  - CPB time – high correlation with surgery type
- Low preoperative fibrinogen level
- Emergency surgery
- Other comorbidities
  - CHF
  - COPD
  - Hypertension
  - PVD
  - Renal failure

RBC=red blood cell; CPB=cardiopulmonary bypass; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; PVD=peripheral vascular disease.

Frequently Encountered Complications of Cardiac Surgery

Hemostatic imbalance often occurs after prolonged cardiopulmonary bypass

- Platelet dysfunction\(^1\)
- Depletion of coagulation factors\(^1,2\)
  - Hemodilution
  - Cell saver
  - Fibrinolysis
- Hypothermia\(^1\)
- Residual anticoagulants\(^1\)

Major bleeding and hemorrhage a major challenge after surgery

- Prevalence 5%-7%\(^1\)
  - Surgical reexploration for bleeding occurs after 2%-6% of CABG procedures\(^2\)
  - More likely in urgent or emergency setting\(^3\)
  - Significant multivariate predictor of increased morbidity and mortality\(^3\)
- Associated with prolonged LOS\(^4\)
- Increased cost after surgery\(^4\)

Patient Case: Harold C.

**History:** 72-year-old white man undergoing urgent aortic valve replacement for aortic stenosis and LIMA to LAD with cardiopulmonary bypass; prior myocardial infarction (MI); heart failure; history of hypertension

- No prior history of excessive bleeding
- Family history of coronary artery disease (father had fatal MI at age 58)
- Current medications:
  - Lisinopril 40 mg/d
  - Clopidogrel 75 mg/d
  - Aspirin 81 mg/d
Harold C.: Preoperative Status

- Vital signs
  - BP 110/75 mm Hg
  - HR 72 BPM
- Echocardiogram findings:
  - Pulmonary artery pressure 45/26 mm Hg
  - Pulmonary artery occlusion pressure (wedge) 15 mm Hg
  - Decompensation of left ventricle
    - Ejection fraction 30%
- Preoperative labs: HCT 42%; Hb 14 g/dL; PLT 210K; PT 13 sec; aPTT 37.5 sec; fibrinogen 90 mg/dL
• After intubation 1 g tranexamic acid given over 30 min
• Heparin administered at loading dose of 300 IU/kg of body weight
• Additional heparin doses given during CPB
• Careful sternotomy and dissection
  ▪ Left internal mammery artery (IMA) taken down
  ▪ Aortic cannulation
• AVR with porcine tissue valve
• LIMA to LAD bypass graft
Aortic clamp time: 72 min
CPB time: 108 min
Following weaning from CPB, persistent and diffuse bleeding observed
Surgeon determines that this is coagulopathic bleeding after careful survey of operative field
Intraoperative labs: HCT 25%; Hb 7 g/dL; PLT 103K; PT 30 sec; aPTT 50 sec; fibrinogen 70 mg/dL
Transfusion of allogeneic blood products
- FFP
- Platelet concentrate
- Cryoprecipitate
Treatment of acquired von Willebrand disease
- Cryoprecipitate
- DDAVP
Strategies for Reversing Perioperative Bleeding

Multifaceted approach

- Correction of hypothermia and acidosis
- Resuscitation with crystalloids or colloids
- Infusion of RBCs, FFP, platelets, and cryoprecipitate
- Antifibrinolytic therapy

- Transfuse patients on CPB with Hb $\leq 6$ g/dL

- Transfusion justified when Hb $\leq 7$ g/dL in patients older than 65 years and patients with chronic CVD or respiratory disease

- Benefit unclear for stable patients with Hb between 7 and 10 g/dL

- Transfusion recommended for patients with acute blood loss $>1500$ mL or $>30\%$ of blood volume

- Evidence of rapid blood loss without immediate control warrants transfusion

STS/SCA=Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists.
Benefits and Risks of Blood Transfusion

Benefits:
- Blood volume replacement
- Transport of O₂ and CO₂
- Coagulation factors

Risks:
- TACO
- TRALI
- Disease transmission (especially platelets)
- TRIM
- Transfusion errors

Evidence: Not enough data about benefits

TACO=transfusion-associated circulatory overload; TRALI=transfusion-related acute lung injury; TRIM=transfusion-related immunomodulation.

Harold C.: Assessing Intraoperative Developments
Harold C.: Additional Complications

- Active bleeding continues
- Second round of intraoperative labs reveals the following:
  - HCT 30%; Hb 10 g/dL; PLT 110K; PT 20 sec; aPTT 45 sec
  - Fibrinogen level drops to 65 mg/dL
  - Fibrin split products indicate intravascular consumption
Harold C.: Surgical Decisions

Harold C. has received two “rounds” of blood products, including cryoprecipitate, FFP, and platelets.

He has required 10 units of RBCs and continues to have major hemorrhage without an identifiable surgical source. The patient is becoming difficult to ventilate, and is becoming hypoxic despite an FiO2 of 1.0.

The surgeon determines that it is not safe to close, and that the degree of bleeding is life threatening and not amenable to conventional therapy.

What would be your next step at this juncture?
• Administration of additional blood products, including cryoprecipitate and platelets?
• Close and autotransfuse shed mediastinal blood?
• Administration of rVIIa?1,2
• Prothrombin complex concentrates (II, VII, IX, X, PC, PS)?1,3,4,5
• Fibrinogen replacement therapy?6-8

Postoperative Status of Harold C.

- Resolution of intraoperative bleeding complications
- Lab values postop day 3
  - HCT 31%
  - Hb 10 g/dL
  - PLT 220K
  - PT 16 sec
  - aPTT 36 sec
  - Fibrinogen 200 mg/dL
- Transesophageal echocardiography on postop day 3 is unremarkable
- Aspirin started at 81 mg/d
This patient’s case has demonstrated the following:

- Cardiopulmonary bypass is often a cause of hemostatic imbalance
- It is essential to normalize clotting factor levels and platelet function, and to inhibit fibrinolysis to achieve hemostasis
- Controlling perioperative bleeding necessitates the employment of a multifactorial approach
- Massive uncontrollable coagulopathic bleeding occurs with currently approved therapies and may not respond to normal measures
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