2024 SEOUL | May 31st - June 1st | Seoul Dragon City Hotel

아주대학교의료원
Ajou University Medical Center

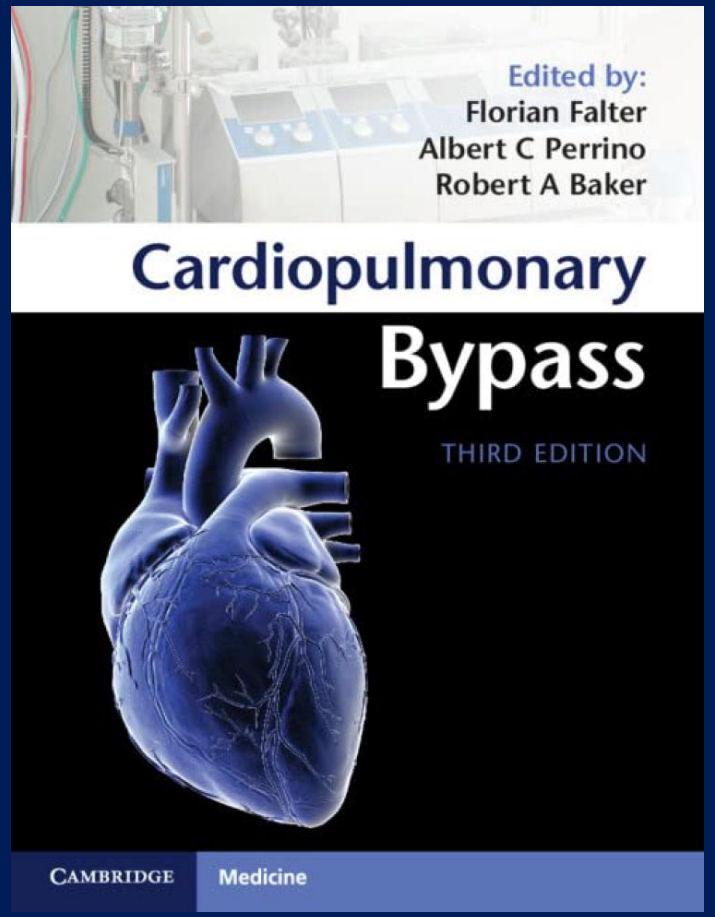
아주대학교의료원 30주년
AJOU UNIVERSITY MEDICAL CENTER
30th ANNIVERSARY

2024 대한심장혈관흉부외과학회 제 38차 춘계통합학술대회 체외순환사 아카데미 교육

Prevention of coagulopathy after CPB

아주대학교의료원
심장혈관 흉부외과 박수진

Reference



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Coagulopathy and Hematological Disorders Associated with Cardiopulmonary Bypass

Bruce D Spiess and Erik Ortmann

CAMBRIDGE Medicine

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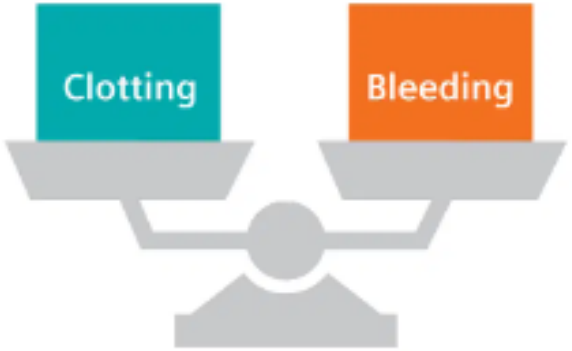
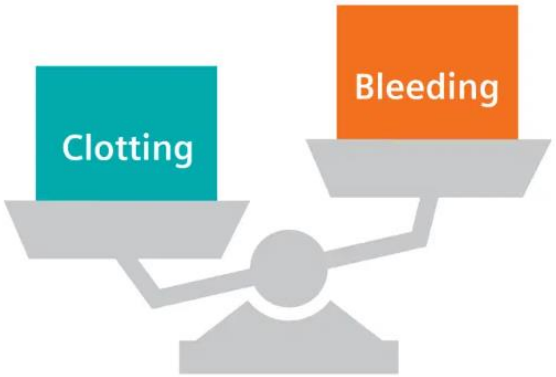
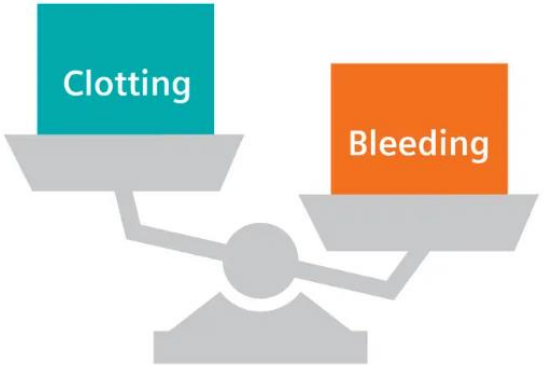
00 Coagulation system



Balanced coagulation system

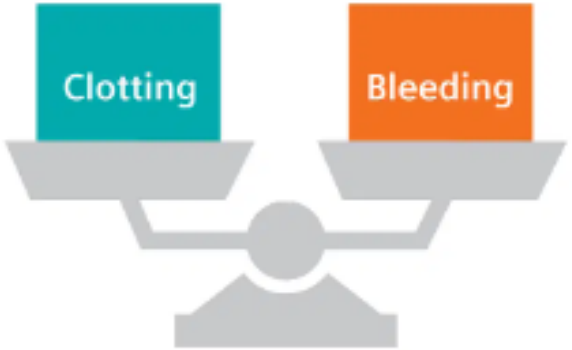


Risk of thrombosis



Risk of bleeding

00 Coagulation system



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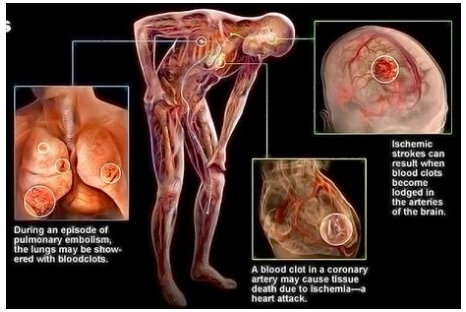

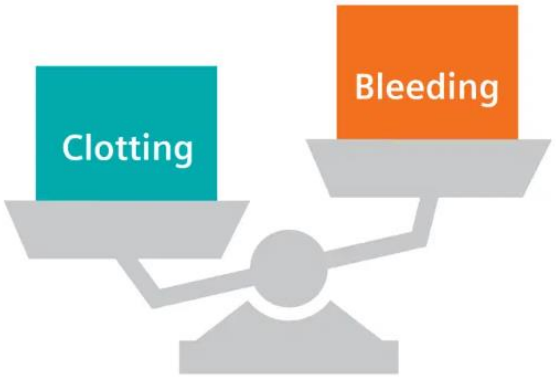

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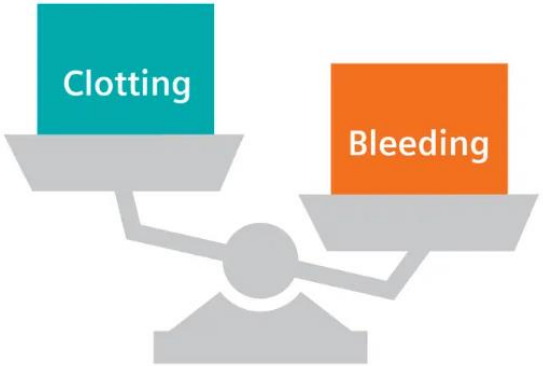
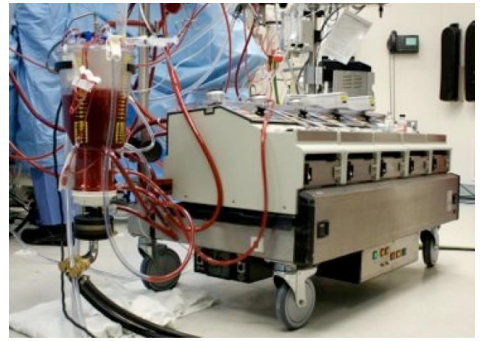


Risk of bleeding



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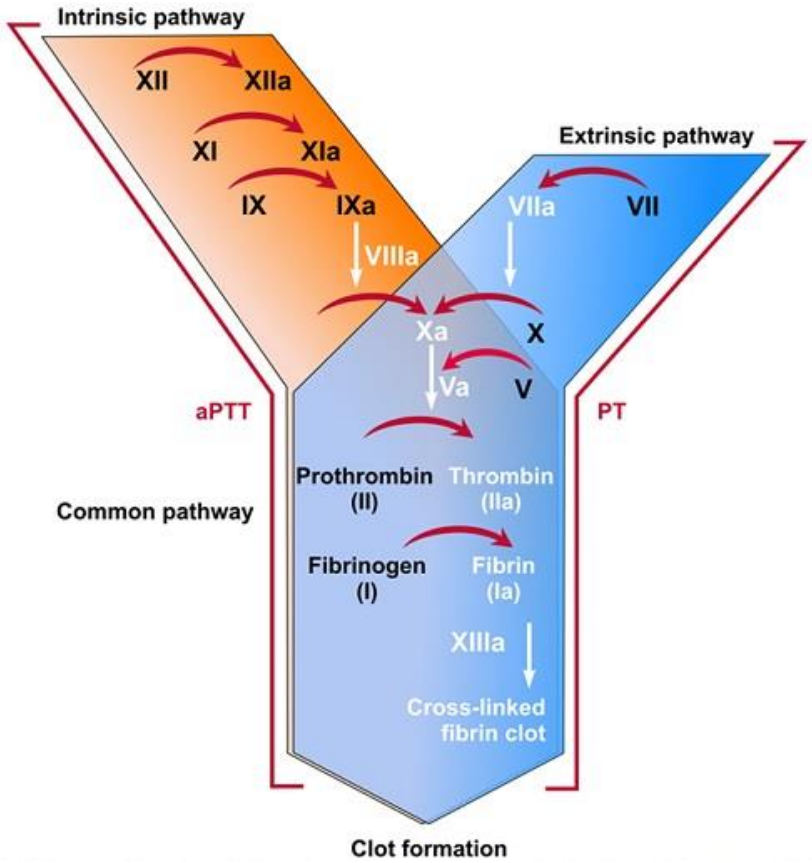
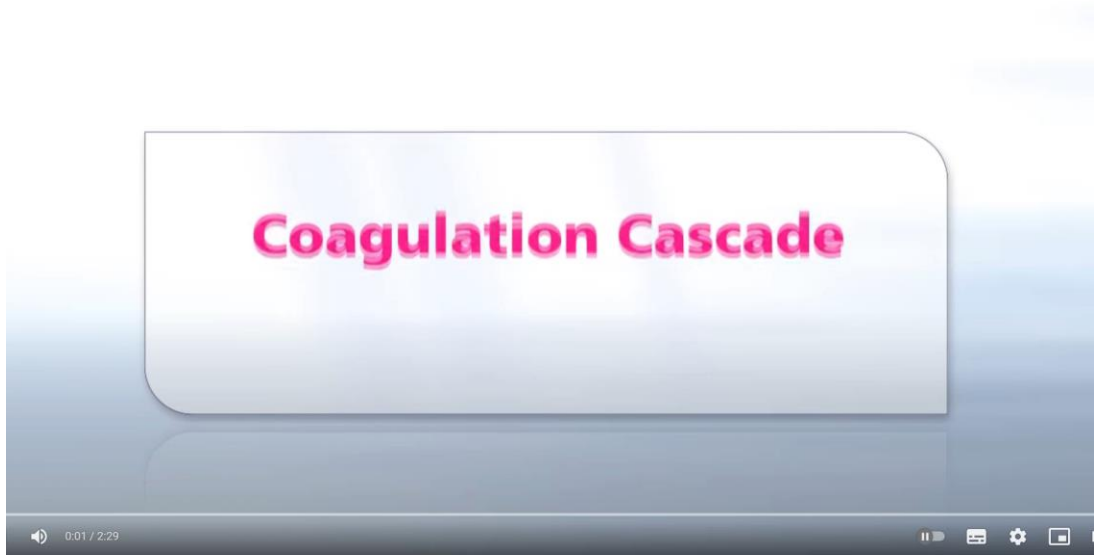
00 Activation of coagulation system





Thrombosis Adviser by Bayer AG. 2022 Oct.

01 Pathophysiology of Coagulopathy After CPB

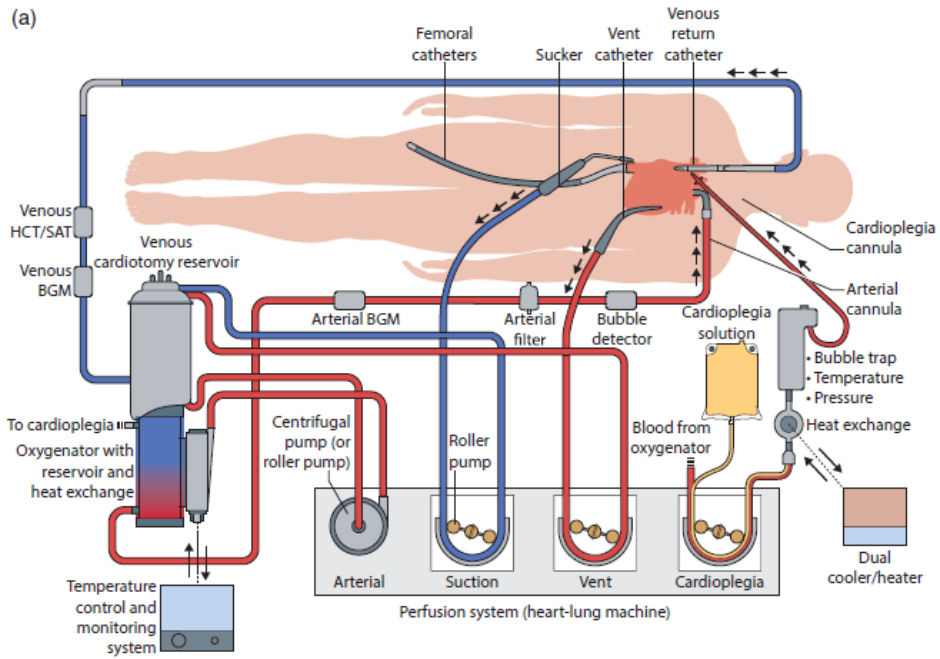
- The coagulation and inflammatory systems are so complex
- Restoration of homeostatic balance cannot be achieved by giving blood products alone

01 Pathophysiology of Coagulopathy After CPB

- *Hemodilution*
- *Contact with artificial surfaces → Activation of the coagulation system*
- *Platelet dysfunction, Fibrinolysis*
- *Effects of heparin and protamine*
- *Hypothermia, Hypocalcemia*
- *Ischemic reperfusion reaction → Tissue factor from the endothelium*

01 Pathophysiology of Coagulopathy After CPB

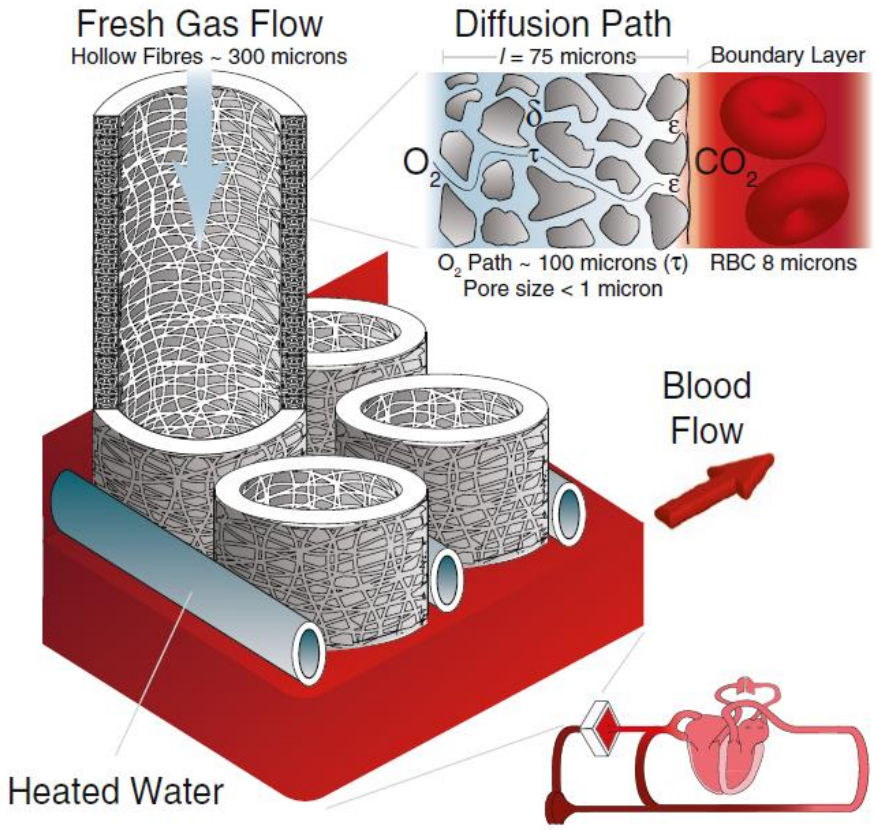
Hemodilution

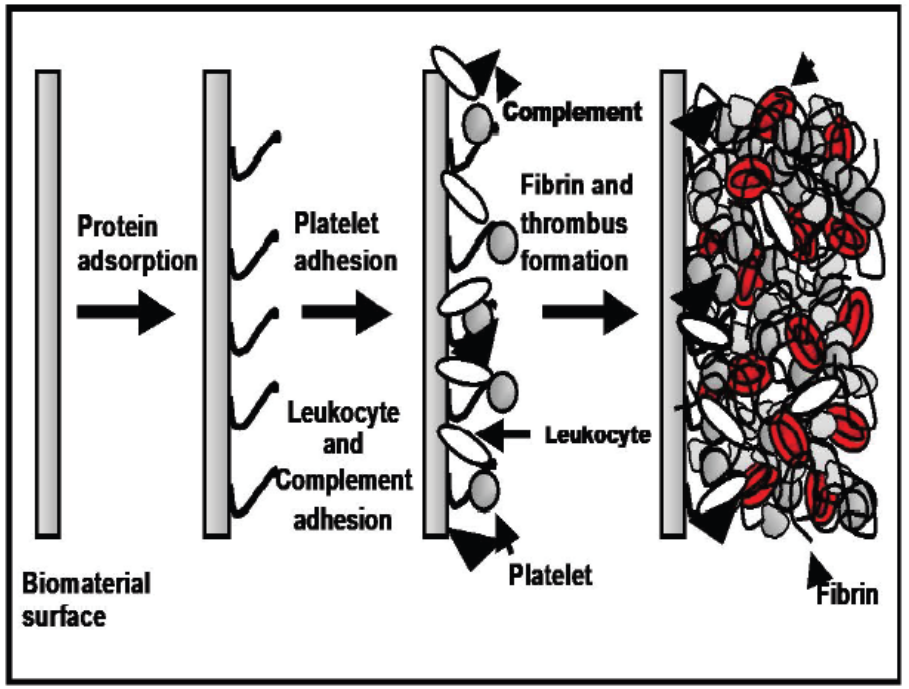


- Adult CPB circuit leads to ***20–30%*** hemodilution
- Loss of activity for isolated clotting factors → ***30–50%*** of normal activity
- Reduce hemodilution
  - by using smaller CPB circuits
  - by retrograde autologous priming

01 Pathophysiology of Coagulopathy After CPB

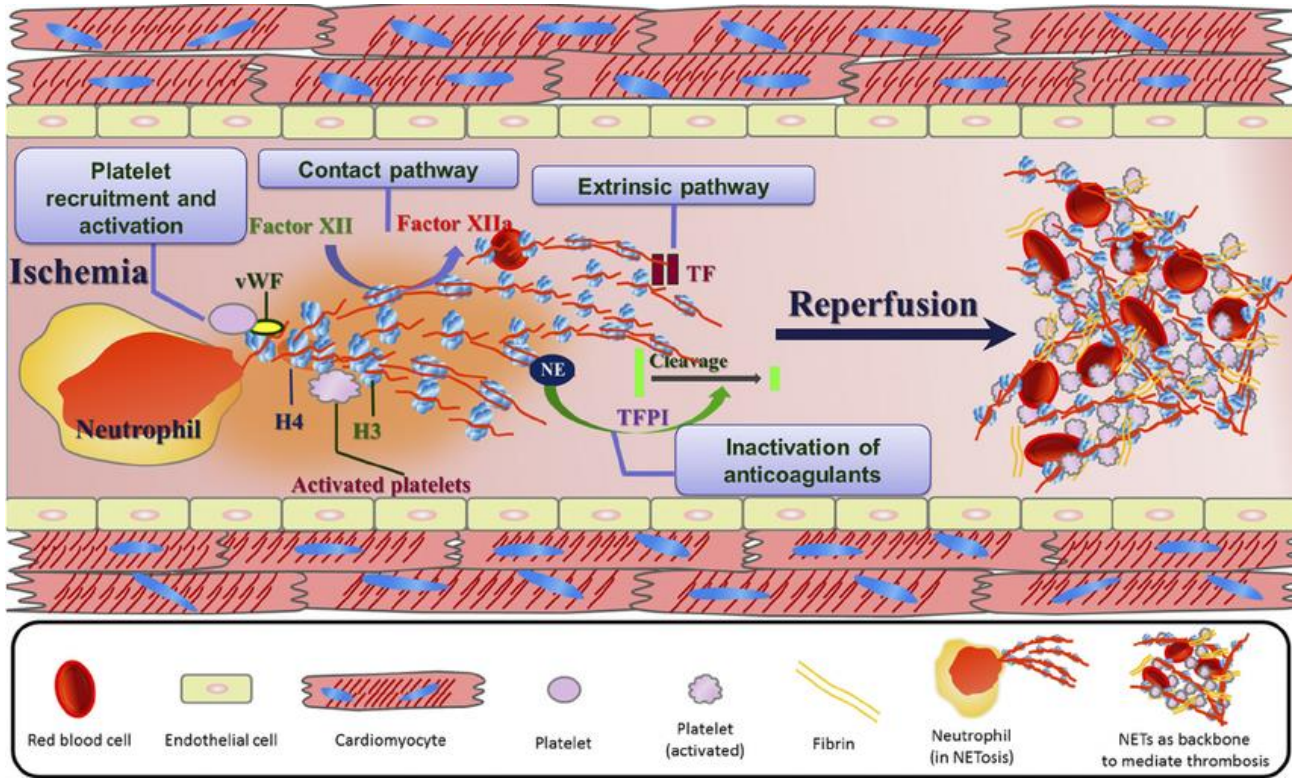
Contact with artificial surfaces





01 Pathophysiology of Coagulopathy After CPB

Arteriolar microemboli may lead to localized ischemia and reperfusion



+ cardiotomy sucker

Am J Physiol Heart Circ Physiol. 2015 Mar 1;308(5):H500-9.

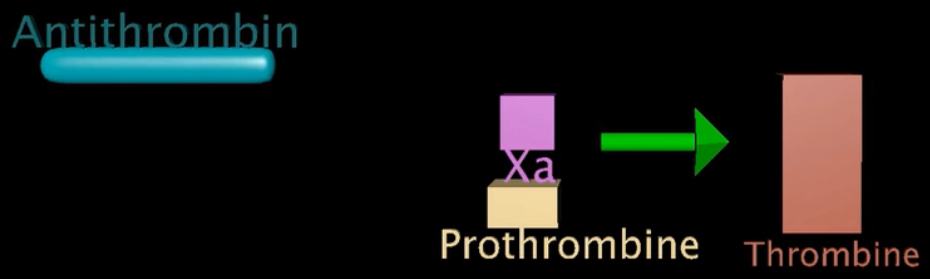
01 Pathophysiology of Coagulopathy After CPB

Platelet dysfunction

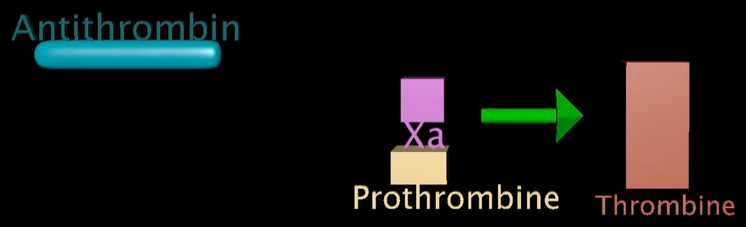
- Count decreases
  - Hemodilution and mechanical destruction
- Dysfunction
  - Hypothermia
  - Reversible with rewarming
- Platelet aggregation
  - Changes in morphology with increasing length of bypass

Function of Heparin

1. Faster antithrombin activity



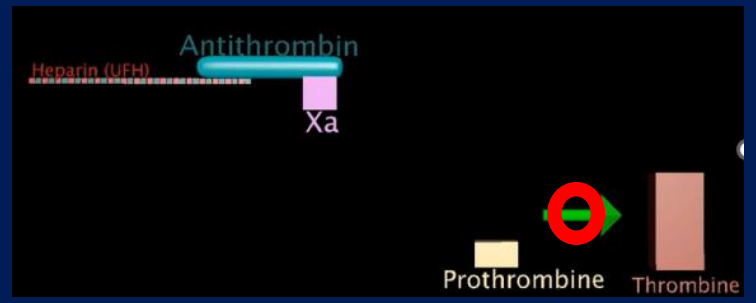
2. Enhance antithrombin's thrombin inactivation



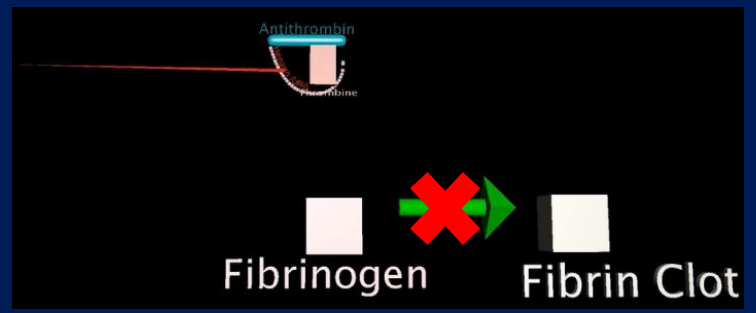
01 Pathophysiology of Coagulopathy After CPB

Effects of heparin and protamine

- Heparin do not “paralyze” the hemostatic system
  - Thrombin generation is ever present



  - Heparin combined with antithrombin blocks the formation of fibrin.



01 Pathophysiology of Coagulopathy After CPB

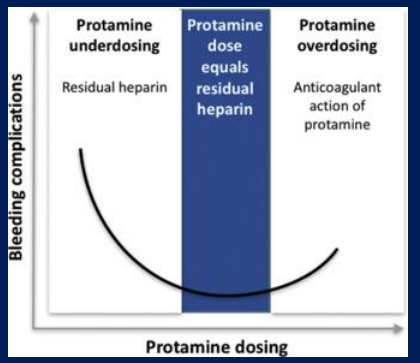
Effects of heparin and protamine

- Thrombin triggers fibrinolysis
  - Lead to the breakdown of clots
  - Fibrin degradation products (particularly D-dimers) further impair fibrin polymerization

01 Pathophysiology of Coagulopathy After CPB

Effects of heparin and protamine

- Residual heparin can cause bleeding after reversed with protamine
- Non-heparin-bound protamine has anticoagulant effects



Br J Anaesth. 2018 May;120(5):914-927

- Heparin rebound might occur by redistribution from tissue or cell surfaces even hours after initial reversal.

02 Role of Preoperative Medication in Coagulopathy

- Genetic Factors
- Anti-platelet Agents
- Vitamin K Antagonists
- Novel Oral Anticoagulants

02 Role of Preoperative Medication in Coagulopathy

Genetic factor

- ***Angina patient*** are more hypercoagulable than the general population
- ***Blood group O patients*** have more bleeding, transfusion and postoperative chest tube output than those with groups A, B or AB
- ***Anti-platelet (P2Y12) agents and aspirin*** have a significant proportion of non-responders

02 Role of Preoperative Medication in Coagulopathy

Anti-platelet agent

	Plasma half-life	Time to effect offset	Reversal agent available
Aspirin	15–30 minutes	7–10 days	no
Clopidogrel	8 hours	7–10 days	no
Prasugrel	7 hours	7–10 days	no
Ticagrelor	7 hours	5 days	yes (PB2452, in clinical stage trials)
Abciximab	10–15 minutes	12 hours	no
Eptifibatide	2.5 hours	2–4 hours	no
Tirofiban	2 hours	2.5 hours	no

- Pre-opeative dual anti-platelet agent
  - ***Meta-analysis*** including **54** studies
    - Risk of re-exploration for bleeding 2.5-fold
    - without decreasing myocardial infarction
  - ***Meta-analysis*** comprising of **30** studies
    - Mortality increased 47%
    - Bleeding and excessive use of allogeneic blood products.

02 Role of Preoperative Medication in Coagulopathy

Vitamin K antagonist (warfarin)

- No “safe” INR elevation for bleeding risk (correct the INR close to 1.0)
- Reverse warfarin
  - administer 4 factor prothrombin complex concentrate (4FPCC)

Reversal Agent	Type	Coagulation Factors
Profilnine SD, Bebulin	Unactivated PCC, 3-factor	II, IX, X
Kcentra	Unactivated PCC, 4-factor	II, VII, IX, X
FEIBA NF	Activated PCC, 4-factor	II, VII, IX, X

  - Superior to FFP in restoring a normal INR
    - Co-administer Vit. K hepatic synthesis of Vit. K dependent coagulation factors

02 Role of Preoperative Medication in Coagulopathy

Novel Oral anticoagulants

- Block the final common pathway

- Reverse NOAC (Rivaroxaban, Apixaban and dabigatran)
  - ***FFP*** (with huge volume to overcome the effects of these drugs)
  - Andexanet-α and idarucizumab
    - Fully reverse effect of NOAC
    - Very expensive
  - 4FPCC appears to at least partially reverse NOACs

03 Assessment of Coagulopathy

- Standard laboratory tests (SLT)

- Viscoelastic tests (VET)

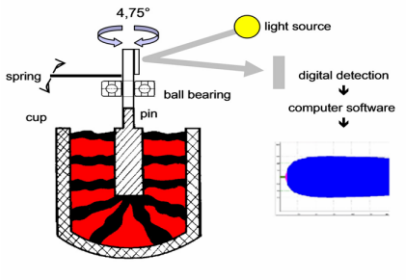
03 Assessment of Coagulopathy

Standard laboratory tests (SLT)

- Platelet count, fibrinogen levels, aPTT or PT
- Abnormal result cannot not differentiate between factor deficiency and residual heparin effect
- Too long (30–90min) to guide clinical decisions

03 Assessment of Coagulopathy

Viscoelastic tests (VET)



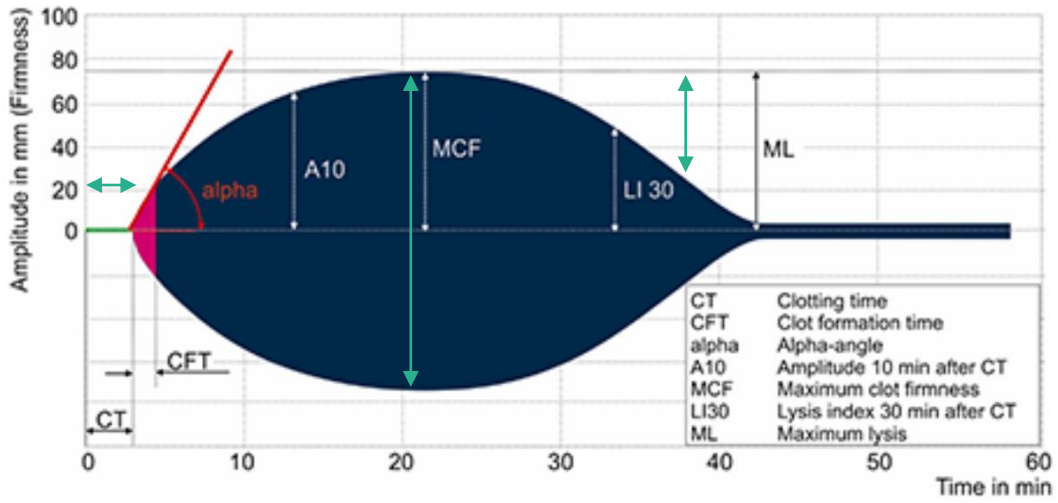
- ROTEM™, TEG™, ClotPro™, TEG6s™, Quantra™
- Result times of around 20 minutes

- Results
  - Clotting time (integrity of clotting factors),
  - Total clot firmness
  - Fibrinolysis (lysis index)

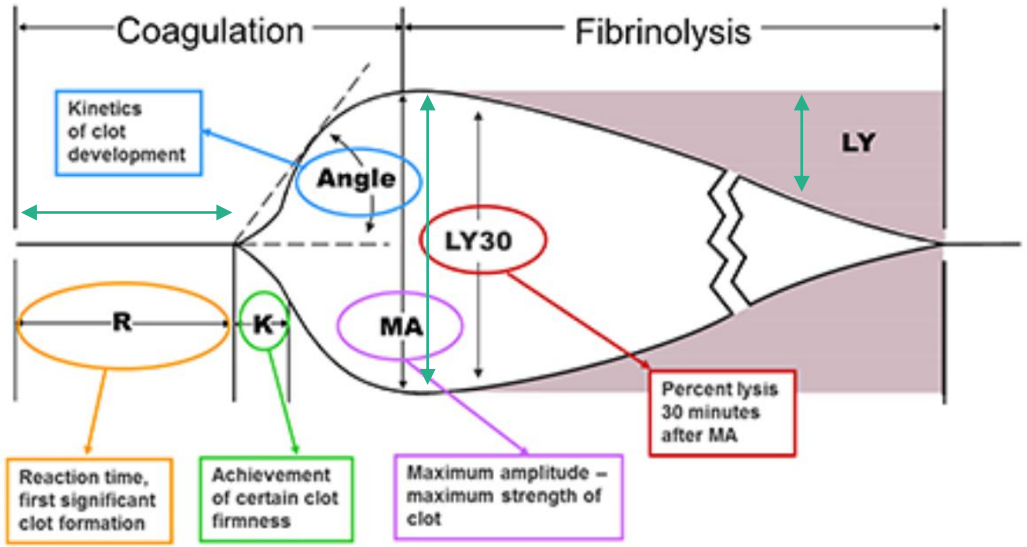
03 Assessment of Coagulopathy

Viscoelastic tests (VET)

ROTEM™



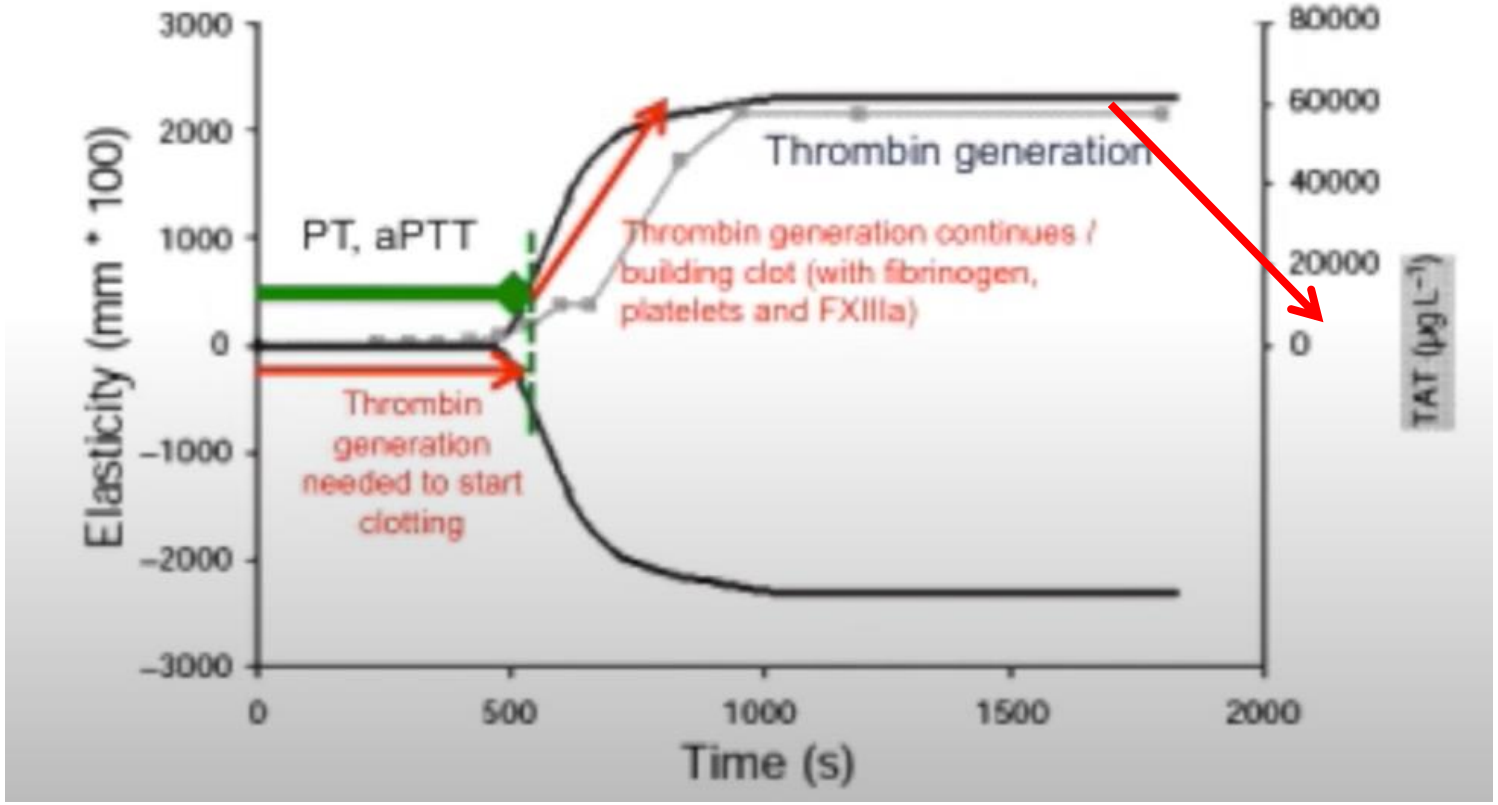
TEG™



Coagulation | Clot firmness | Fibrinolysis

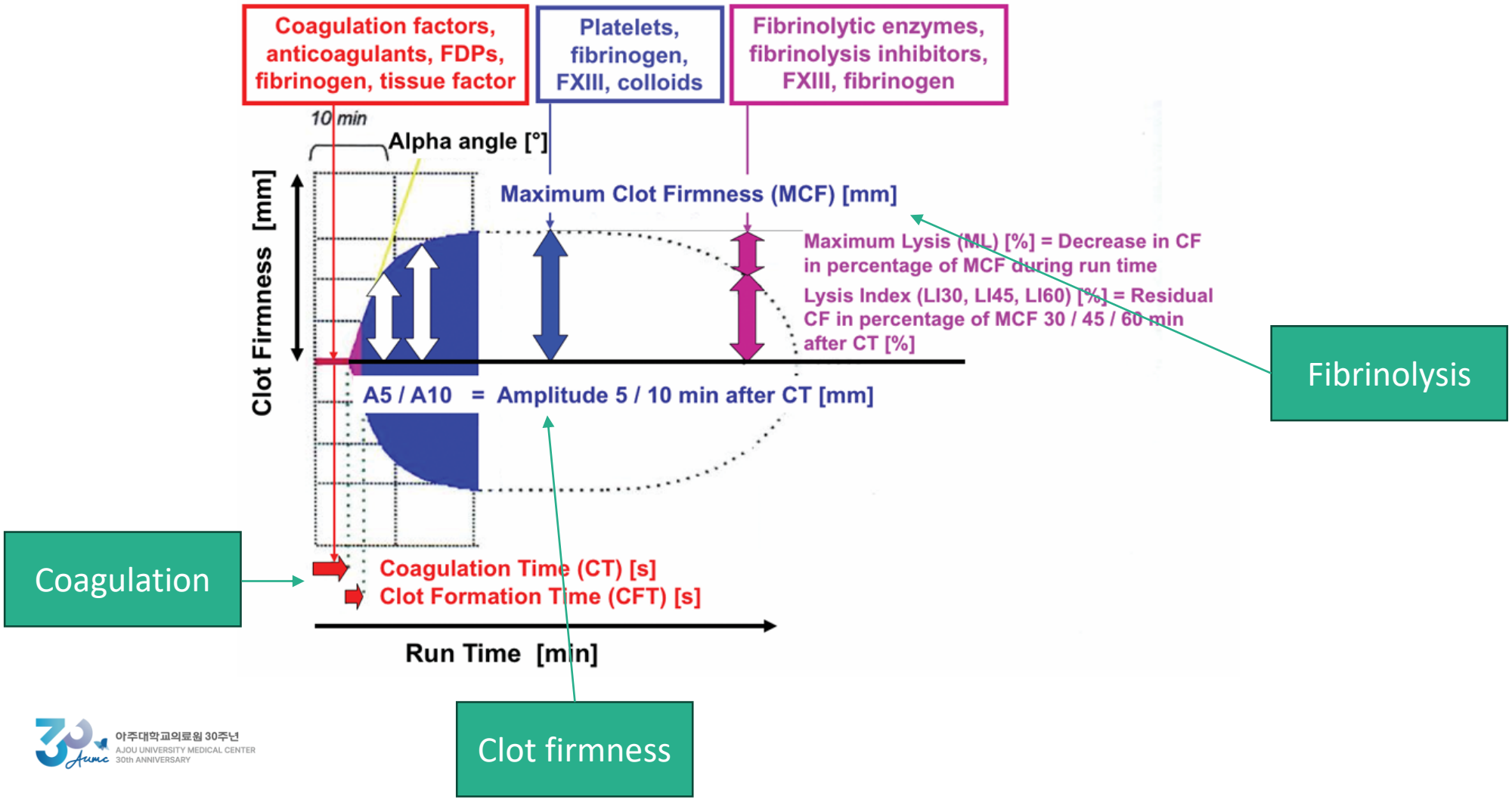
03 Assessment of Coagulopathy

Standard laboratory tests (SLT) vs Viscoelastic tests (VET)



03 Assessment of Coagulopathy

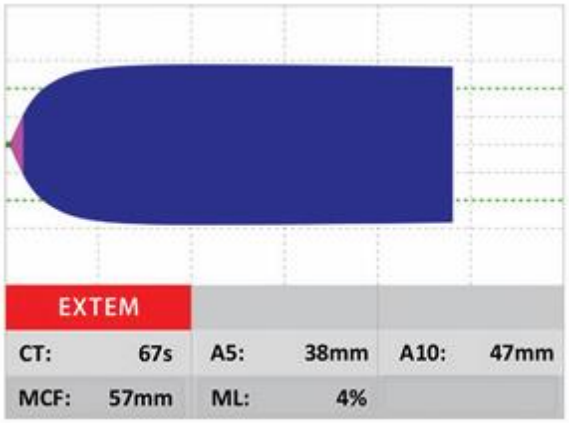
Viscoelastic tests (VET)



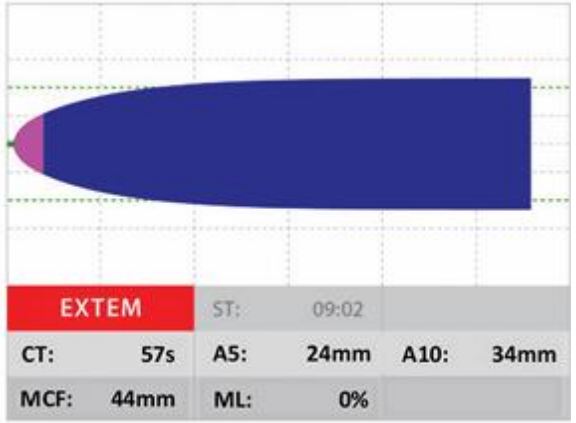
03 Assessment of Coagulopathy

Viscoelastic tests (VET)

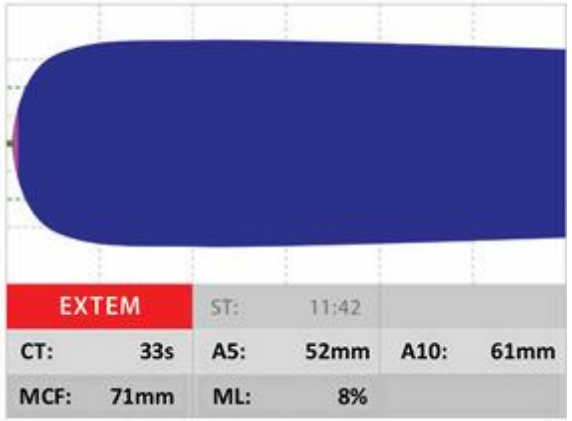
Firm & Stable



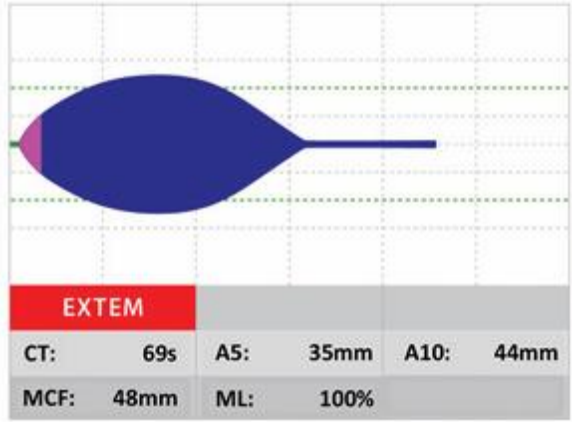
Relatively Weak



Hypercoagulative

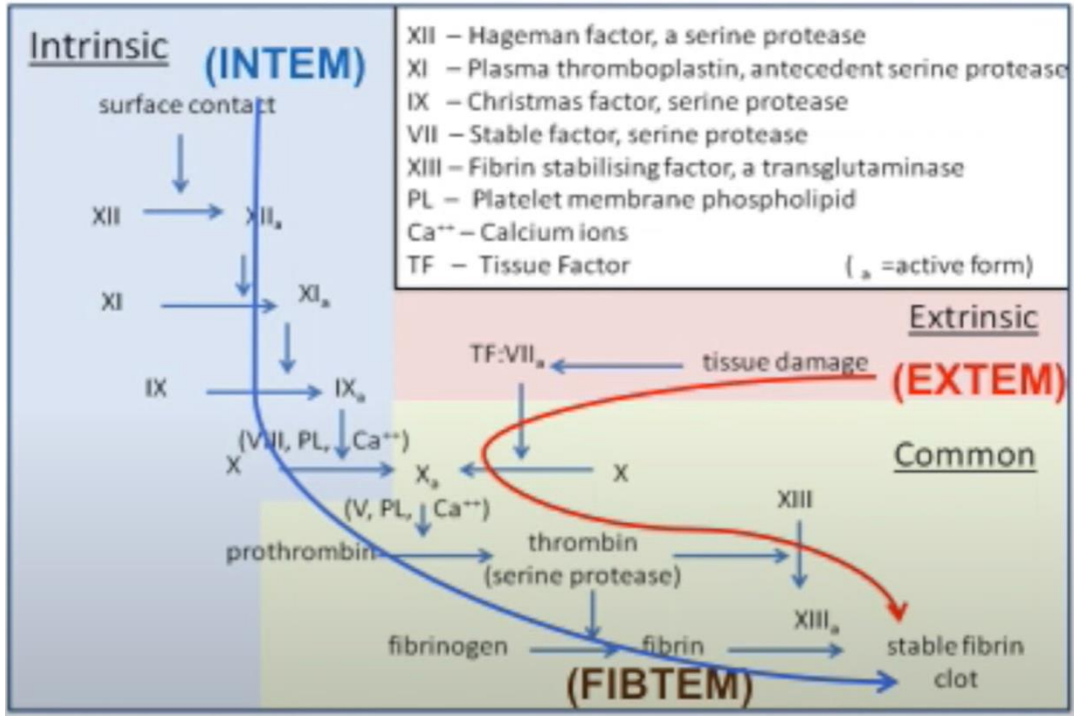


Unstable (early Lysis)



03 Assessment of Coagulopathy

Viscoelastic tests (VET)



ROTEM® Thromboelastometry - Assays

INTEM – Intrinsic activation (via Ellagic Acid)

HEPTEM – adding Heparinase removes heparin from sample

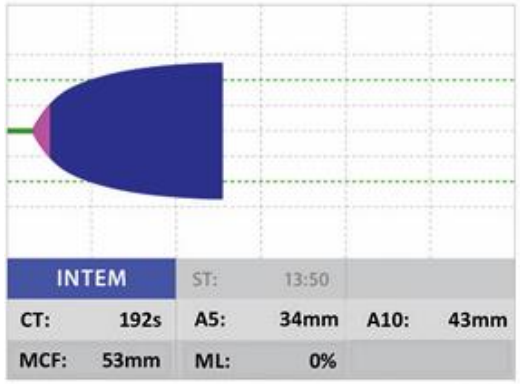
EXTEM – Extrinsic activation (via Tissue Factor)

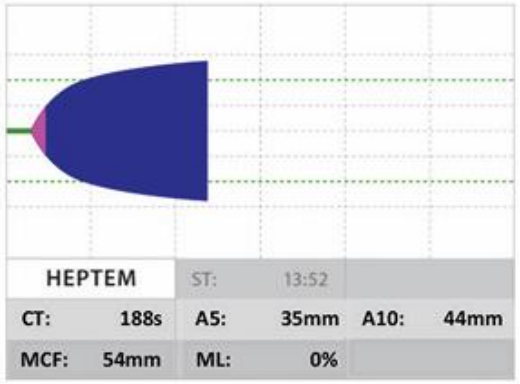
FIBTEM – adds Cytochalasin D to inhibit platelet contribution

APTEM – adds aprotinin to inhibit hyperfibrinolysis

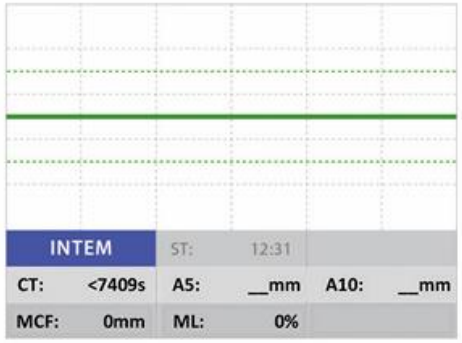
03 Assessment of Coagulopathy

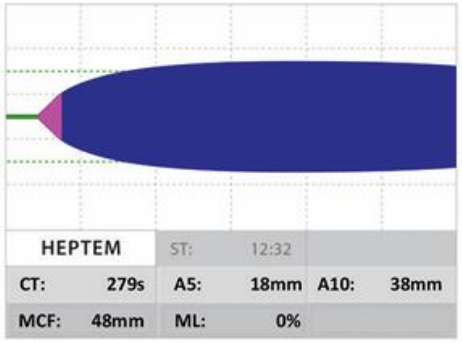
Viscoelastic tests (VET) (Examples)



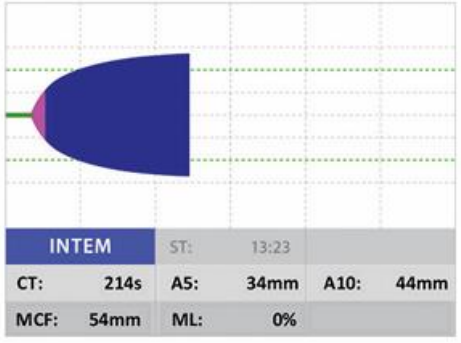


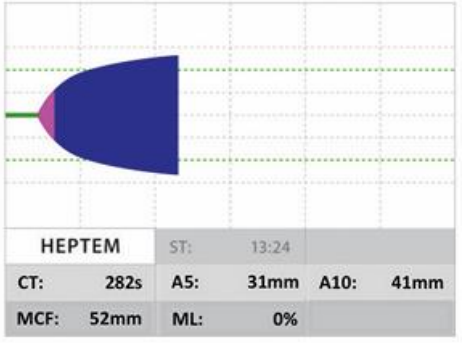
Heparin, high dose (e.g., during CPB):
INTEM flat-line (CT_{IN}>1200s)
<u>and</u>
CT_{HEP} < 280 s





Protamine overdose (after heparin-reversal):
CT_{HEP} prolonged (> 280 s)
<u>and</u> CT_{IN} /CT_{HEP}-ratio < 1.1;
disappears within 10-20 min after protamine administration





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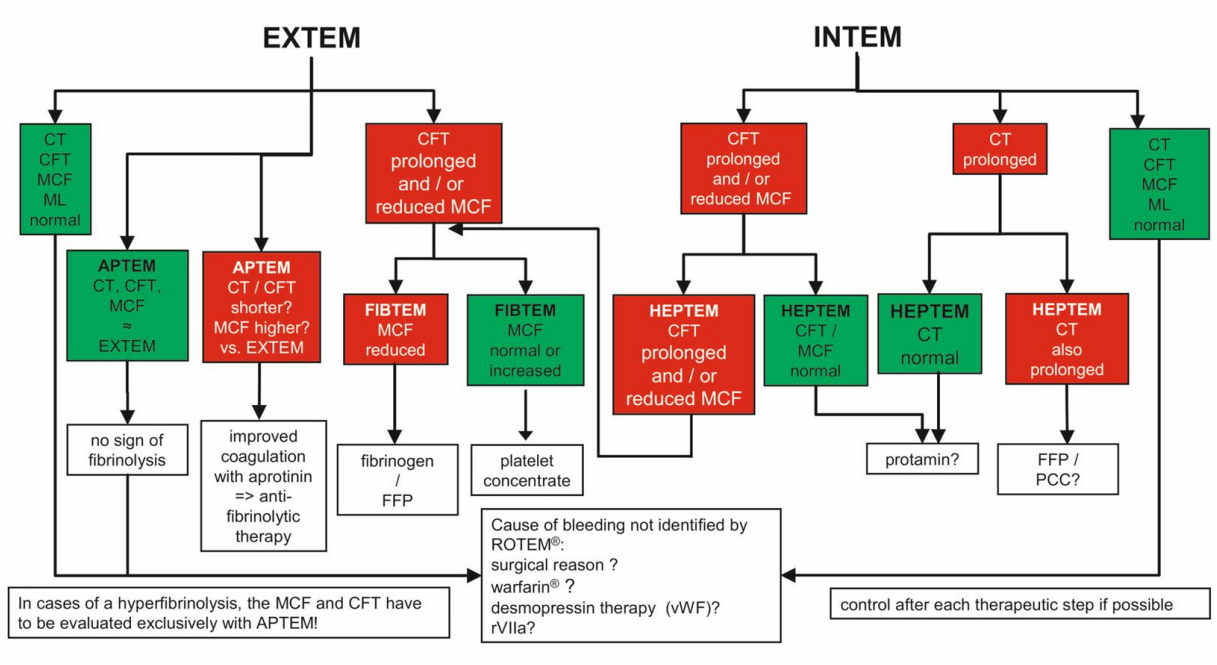
03 Assessment of Coagulopathy

Viscoelastic tests (VET)



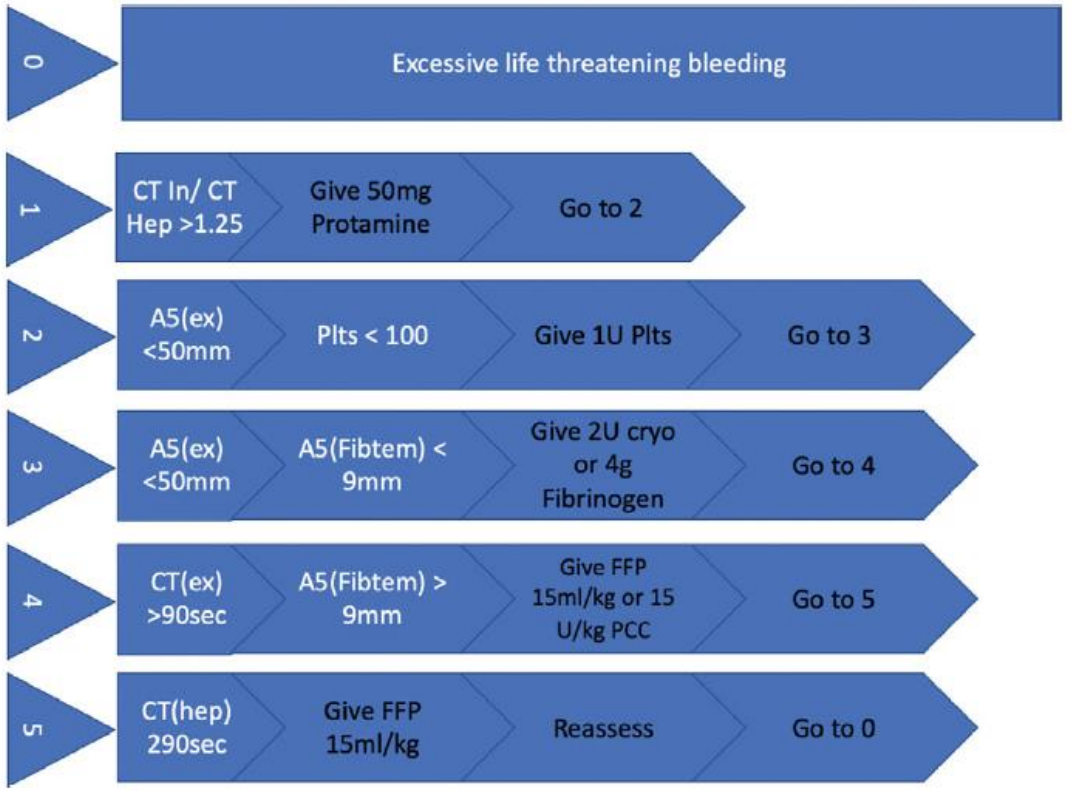


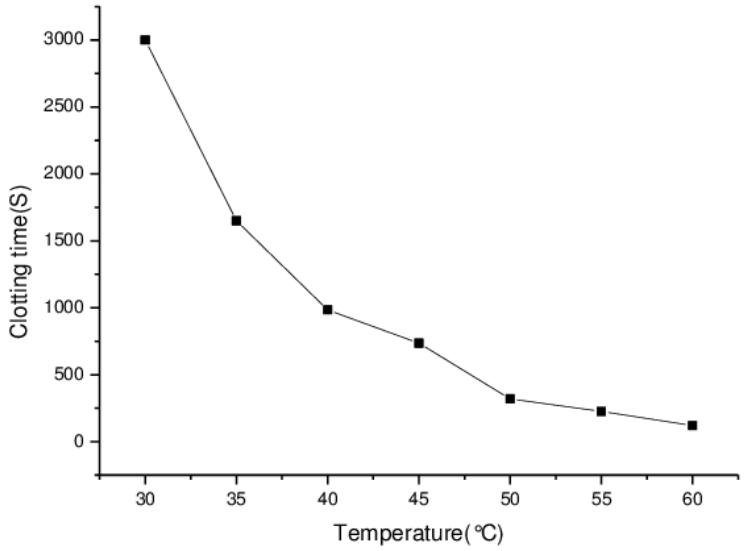
Figure 16.2 Typical ROTEM based algorithm for managing post-CPB bleeding with POC tests.

04 Therapeutic Interventions and Management of Bleeding Patients

- Temperature control
- Transfusion (Platelet, FFP and Cryoprecipitate)
- Factor concentrates
- 1-desamino-8-Darginine-vasopressin (DDAVP)
- Antifibrinolytic agents
- Avoid hemodilution

04 Therapeutic Interventions and Management of Bleeding Patients

Temperature



- Temperature control is of utmost importance as blood does not coagulate ***below 30–32 ℃.***
- Not the central core temperature but ***wound temperature.***

04 Therapeutic Interventions and Management of Bleeding Patients

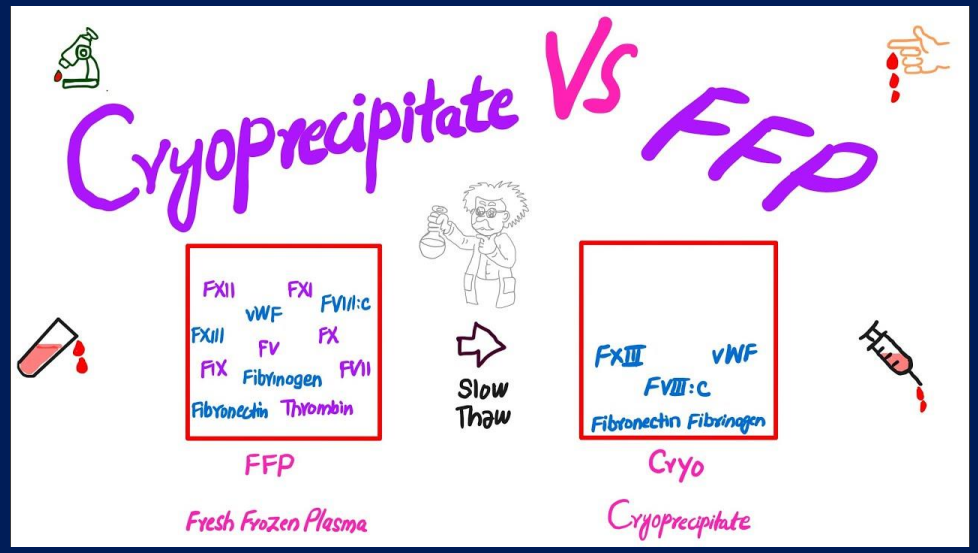
Platelet

- Most affected coagulation system affected by CPB
- ***Platelet count*** currently provides the best guidance for transfusion.
- Lower than 50.000 and 100.000.

- Large proportion of packed platelets are dysfunctional, dying or apoptotic and can act as ***prothrombotic microparticles***.
- Large concentrations of cytokines and can be a major risk for septic /bacterial transfusions (1/2000)

04 Therapeutic Interventions and Management of Bleeding Patients

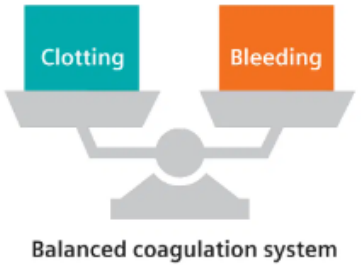
FFP and cryoprecipitate

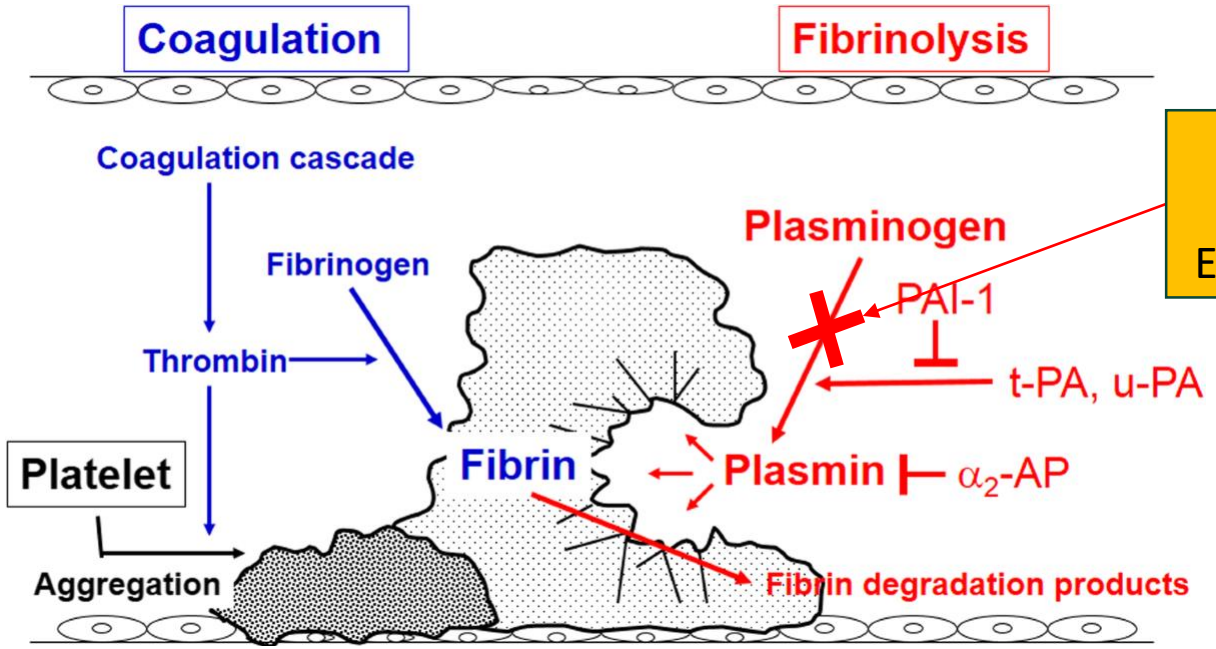


- ***FFP*** contains all the protein coagulants found in circulating plasma at normal levels
- FFP has been processed at 1–6°C to produce ***cryoprecipitate***
- At least ***15 ml/kg*** of FFP (ex.60kgx15 = 900ml) are necessary to achieve a meaningful rise of coagulation factors

04 Therapeutic Interventions and Management of Bleeding Patients

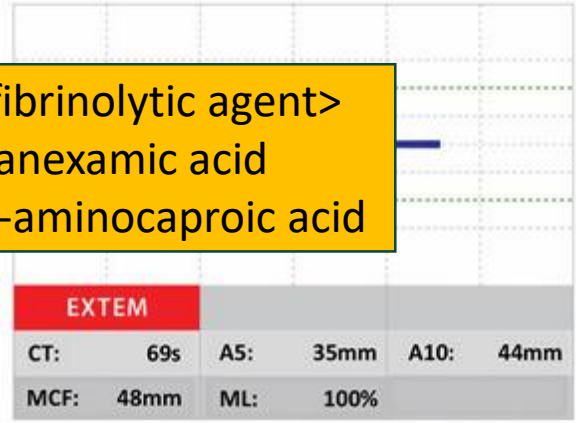
Antifibrinolytic Agents





Unstable
(early Lysis)

<Antifibrinolytic agent>
Tranexamic acid
Epsilon-aminocaproic acid



04 Therapeutic Interventions and Management of Bleeding Patients

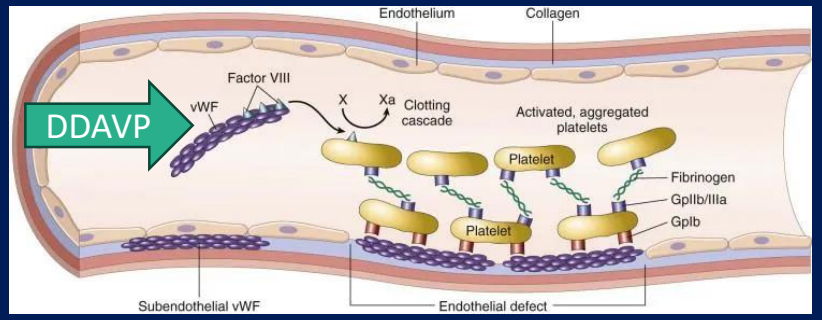
Antifibrinolytic Agents

- Blocking antifibrinolytic activity has been shown to ***reduce postoperative blood loss*** in cardiac surgical patients.
- The ***prophylactic administration of antifibrinolytic agents*** has become a standard practice and is recommended in current guidelines.
- ***High doses of TXA*** have been linked to an increased incidence of ***seizures***.
- Lower dose regimens

04 Therapeutic Interventions and Management of Bleeding Patients

Others

Reversal Agent	Type	Coagulation Factors
Profilnine SD, Bebulin	Unactivated PCC, 3-factor	II, IX, X
Kcentra	Unactivated PCC, 4-factor	II, VII, IX, X
FEIBA NF	Activated PCC, 4-factor	II, VII, IX, X



- Prothrombin complex concentrate (PCC) and fibrinogen concentrate
- Modern 4FPCCs contain the ***25-fold concentration*** of pro-coagulant proteins compared to ***FFP***.

- Synthetic analogue of vasopressin
- enhance platelet function through the release of vWF and multimeric building blocks of vWF

Take home message

- The coagulation and inflammatory systems are so complex
- Restoration of homeostatic balance cannot be achieved by giving blood products alone

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감사합니다.

2024.06.01

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