CARDIAC SAQ 1
HEPARIN / ANTICOAGULATION

N R Burri
A 67 year-old patient is to undergo coronary artery surgery on cardiopulmonary bypass (CPB).

a) What dose of heparin is used to achieve full anticoagulation for CPB and how is it given? (2 marks)

b) Which laboratory and “point-of-care” tests determine the effectiveness of heparin anticoagulation in CPB patients? Give the advantages and/or disadvantages of each test. (10 marks)

c) What are the causes of inadequate anticoagulation in a patient whom it is believed has already received heparin? (5 marks)

b) Describe the possible adverse reactions to protamine. (3 marks)
SAQ Heparin - Weighting

• Dose & How: ..................................................2
• Tests: Lab, POCT, Adv, Disadv:.......10
• Inadequate anticoagulation.............5
• Adverse reactions to Protamine......3
KEY POINTS

- **CPB** triggers Coagulation & Inflammatory Pathways.
- **Heparin** remains the standard anticoagulant for CPB.
- **Activated Clotting Time** – ACT is the standard test.
- **ACT & Thromboelastography** – Point of care tests.
- **Reversal with Protamine** reestabilishes haemostasis.
HEPARIN

- Negatively charged glycosaminoglycan
- MW 3000 – 40000 Da
- Potentiates AT III to inhibit Thrombin
- All fractions of heparin inhibit Xa
- But only longer chains inhibit Thrombin
- Heparin mediates TFPI & Fibrinolysis
ADVANTAGES OF HEPARIN

• Rapid onset of action
• Clinical efficacy
• Rapid neutralization by Protamine
• Safety
• Low cost
HEPARIN RESISTANCE

• Need for higher than usual doses of heparin to achieve adequate anticoagulation

• ATIII deficiency; Protein binding of Heparin.

• If ACT < 480sec @ > Heparin 600 iu/kg: ? ATIII deficit.
CAUSES OF ANTITHROMBIN III DEFICIENCY

- Decreased Synthesis: Liver Cirrhosis
- Increased Excretion: Protein Losing States
- Accelerated Consumption: DIC, Sepsis
- Dilution: CPB
- Drug induced: Heparin
- Familial
AT III DEFICIENCY - MANAGEMENT

• 1000 units AT III increases AT by 30%
• 2 – 4 units FFP is less expensive
ALTERNATIVES TO HEPARIN

• LMWH: Danaparoid
• Lepirudin: Long half life & lack of reversal
• Bivalirudin: Shorter half life
• Ancrod: FFP & Cryo to reverse.
• Argatroban:
STANDARD SEQUENCE FOR ANTI COAGULATION MANAGEMENT DURING CPB

1. ABG sample for baseline ACT
   300 – 400 iu/kg Heparin via CVC

2. ABG for ACT after 3 – 5 minutes.
   Ensure ACT > 3 - 4 times base line (>480sec)
   5000 iu Heparin into CPB prime solution.

3. Monitor ACT every 30 minutes.
   Maintain ACT 400 – 480 sec during CPB

4. Reverse with Protamine 1 mg = 100 iu
   ABG for ACT after 3 – 5 minutes.
ACTIVATED CLOTTING TIME

BLOOD SAMPLE IN THE TUBE
ACTIVATED CLOTTING TIME

- **Monitor:** Heparin anticoagulation since 1970s
- **Glass tube containing an activator & magnet**
- **Activators:** Celite, Kaolin, Glass

- Tube with sample warmed to 37°C & rotated
- **Clotting** - resistance to movement of magnet
- **Normal ACT** = 100 - 140 sec.
PROLONGATION OF ACT

- Hypothermia
- Haemodilution
- Thrombocytopenia
- Platelet Function abnormalities.
- Factor deficiencies
- Lupus antibodies
- GpIIb/IIIa Inhibitors
- Warfarin
- Aspirin
COAGULATION FACTORS

- Factor I: FIBRINOGEN
- Factor II: PROTHROMBIN
- Factor III: TISSUE FACTOR (THROMBOPLASTIN MIX)
- Factor IV: CALCIUM
- Factor V: PROACCELERIN
- Factor VI: ACCELERIN
- Factor VII: PROCONVERTIN (STABLE FACTOR)
- Factor VIII: ANTI HAEMOPHILIC FACTOR
- Factor IX: CHRISTMAS FACTOR
- Factor X: STUART FACTOR (THROMBOKINASE)
- Factor XI: PLASMA THROMBOPLASTIN ANTECEDENT
- Factor XII: HAGEMAN FACTOR
- Factor XIII: FIBRIN STABILISING FACTOR
CONVENTIONAL & OTHER LAB TESTS

• **PT & APTT:** No value during CPB
  A role in Pre op assessment & Post Op Coagulopathy

• **Platelet Count:** Only test to guide platelet use.

• **Heparin Conc.:** With Protamine titration assay

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**ADVANTAGES:**
- Laboratory based
- Inexpensive
- Quality assured

**DISADVANTAGES:**
- Not real time
- Long turn around time
- Information from plasma only.
  (Platelets & Factors interaction - missing)
- Information only up to the first phase of fibrin formation.
EXTRINSIC & INTRINSIC PATHWAYS

EACH PATH LEADING TO Xa & Va which in turn generate IIa (Thrombin)
Extrinsic path in Cell Based Model leads to generation of small amount of Thrombin IIa

Intrinsic path in Cell Based Model Acts on platelet surface to generate Burst of Thrombin IIa needed for stable Fibrin clot
OVERVIEW OF CELL BASED MODEL

EXTRINSIC

INTRINSIC
BASICS OF TEG

- Prolonged R time: Factor deficit & Heparin
- Decreased Alpha: Factor & Platelet Deficit
- Decreased MA: Platelet dysfunction
- LY 30: Measures degree of fibrinolysis
THROMBOELASTOGRAPHY

Amplitude = Clot strength

REACTION TIME
SPEED
STRENGTH
LYSIS

Time
TEG & ROTEM
## TEG vs ROTEM - NOMENCLATURE

<table>
<thead>
<tr>
<th>THROMBOELASTOGRAPHY</th>
<th>ROTATIONAL THROBOELASTOMETRY</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>R time (Reaction time)</td>
<td>CT Clotting Time</td>
<td>Time to get a 2 mm wide Amplitude trace</td>
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<tr>
<td>K Time</td>
<td>CFT Clot Formation Time</td>
<td>Time from 2mm to 20 mm increase in Amplitude</td>
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<tr>
<td>α angle</td>
<td>α angle</td>
<td>Angle between a tangent &amp; horizontal @ 2mm amplitude</td>
</tr>
<tr>
<td>MA Maximum Amplitude</td>
<td>MCF Maximum Clot Firmness</td>
<td>Greatest vertical width of tracing</td>
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<tr>
<td>CL 30 Clot Lysis</td>
<td>LY 30 Lysis</td>
<td>% reduction in amplitude 30 mts after MA</td>
</tr>
<tr>
<td>CL 60</td>
<td>LY 60</td>
<td>% reduction in amplitude 60 mts after MA</td>
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## ADVANTAGES / DISADVANTAGES POCT

<table>
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<th>DISADVANTAGES</th>
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<tbody>
<tr>
<td>Fast turn around compared to lab tests</td>
<td>Measured under artificial conditions</td>
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<tr>
<td>Whole blood = platelets &amp; factors kinetics</td>
<td>Training and competency of staff needed</td>
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<tr>
<td>Real time visual display</td>
<td>Rigorous quality assurance standards</td>
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<td>Reduced non Evidence Based transfusion</td>
<td>May be more expensive than conventional</td>
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TEG

- **R : 4 - 8 mts**: Indicates Concentration of factors
- **K : 1 - 4 mts**: Measure of clot kinetics
- **α: 47 - 74**: Rapidity of fibrin build up / X linking
- **MA: 55-73**: Platelet Number & Fibrinogen
- **CL 30**: Clot stability & fibrinolysis
- **CL 60**: Clot stability & fibrinolysis
PLATELET ASSAY

• COX II Inhibitors: Aspirin
  • Clopidogrel
  • Parsugrel
  • Ticagrelor

• P2Y12 Inhibitors:
  • Abciximab
  • Tirofiban
  • Eptifibatide

• GPIIb/IIIa Inhibitors:
PLATELET ASSAY EQUIPMENT

EQUIPMENT & PRINCIPLE

• PFA -100............................Closure Time (CT)
• Plateletworks®.....................Change in size to count
• Verify Now®.........................Light Transmission
• TEG® Platelet Mapping.MA T/F/AA/ADP
• Multiplate®.........................Impedance aggregometry
PROTAMINE

- Positively charged molecule from Salmon sperm
- 1 – 1.5 mg/kg per 100 iu (1 mg) of Heparin
- Forms 1:1 complex with Heparin
- Administration is associated with

- ARTERIAL HYPOTENSION
- REDUCED CARDIAC OUTPUT
- PULMONARY VASOCONSTRICTION
- ANAPHYLAXIS
SUGGESTED READING

• Management of coagulation during cardiopulmonary bypass
  CEACCP | Volume 7 Number 6 2007

• Conventional and near-patient tests of coagulation
  CEACCP | Volume 7 Number 2 2007

• Point-of-care coagulation testing
  CEACCP | Volume 13 Number 1 2013

• Rethinking the Coagulation Cascade
  Article in current Hematology Reports · October 2005 (pdf) RESEARCH GATE