SNS COLLEGE OF ALLIED HEALTH SCIENCES

SNS Kalvi Nagar, Coimbatore - 35

Affiliated to Dr MGR Medical University, Chennai

DEPARTMENT OF CARDIO PULMONARY PERFUSION CARE TECHNOLOGY

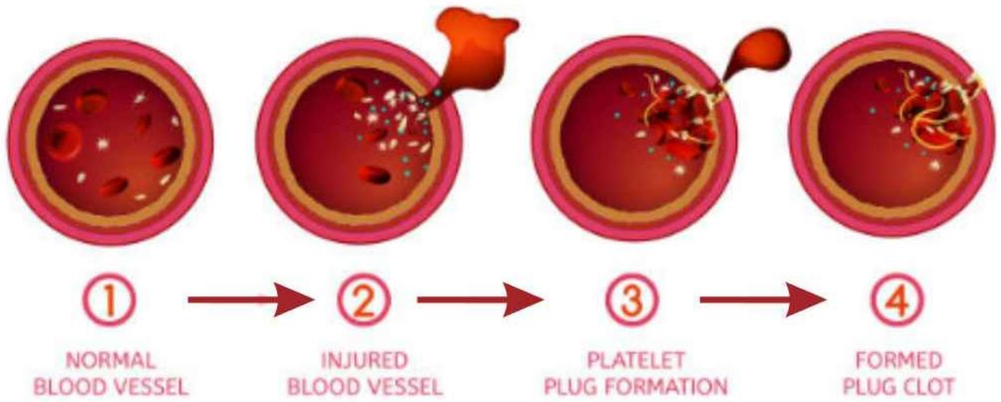
COURSE NAME : PRINCIPLES OF PERFUSION PART 1

2ND YEAR

TOPIC : ANTICOAGULANTS FOR CPB

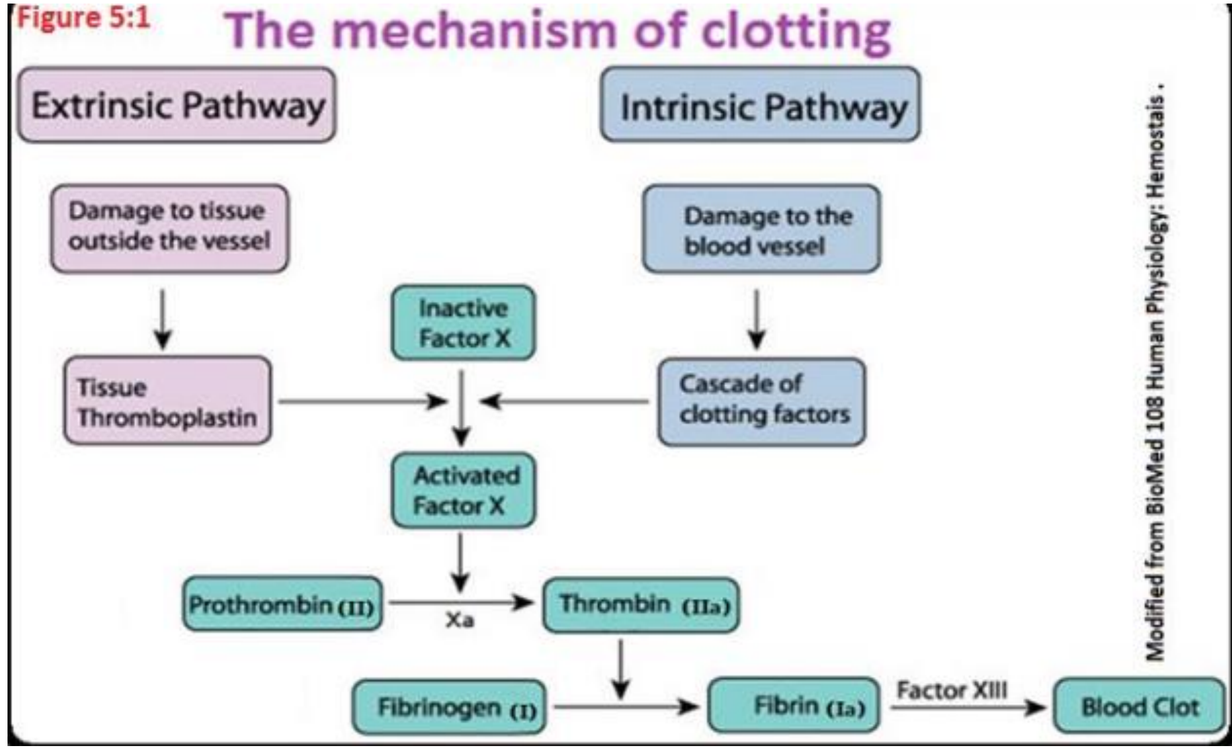
COAGULATION

- It is a complex process by which blood changes from a liquid to a gel (clots).
- It is an important part of hemostasis
- The mechanism of coagulation includes platelets activation (adhesion, and aggregation) to seal a damaged blood vessel wall, and clotting factors responding to form fibrin which strengthen the platelet plug and begin repair of the damaged vessel.
- There are two ways of fibrin formation, the tissue factor pathway (extrinsic pathway), and the contact activation pathway (intrinsic pathway).



COAGULATION (cont)

- The extrinsic pathway begins with trauma to the tissues outside the blood vessels, whereas the intrinsic pathway begins with trauma to the blood itself when it comes into contact with damaged or roughened vessel walls.
- Then both pathways result in the activation of factor X that converts prothrombin to thrombin with help from factor Xa.
- Thrombin converts fibrinogen to first soluble fibrin, which is then made insoluble by the activation of Factor XIII.



Heparin

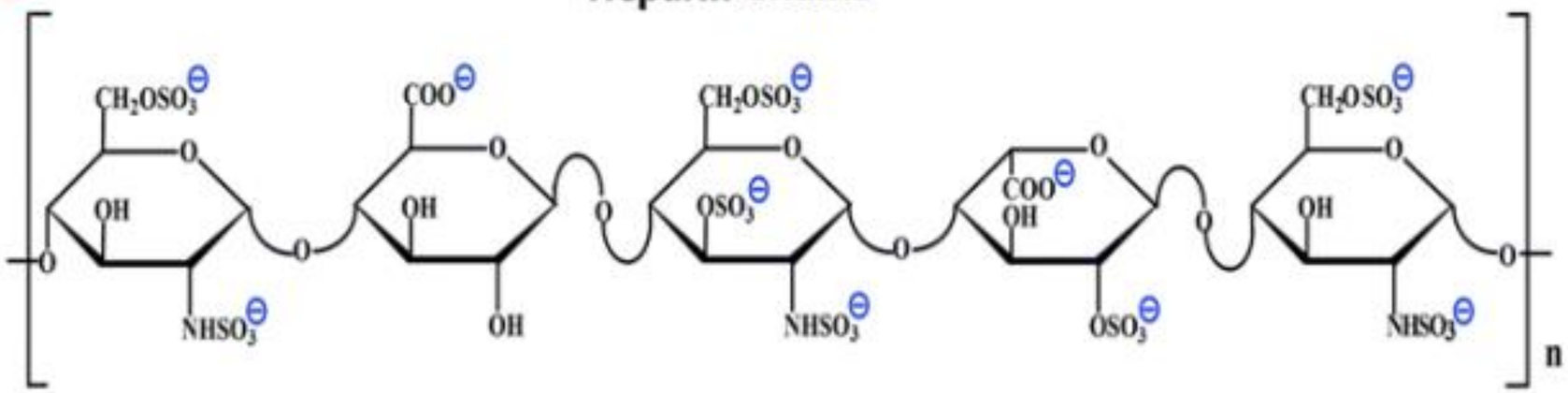
- The heparin is an anticoagulant discovered in 1916, it was isolated from liver cells, hence the name (heparin) from the Greek "hepar", which means liver.
- The commercial heparin most often derived from pigs intestinal mucosa (porcine mucosal heparin) and lung heparin from cattle lung (bovine lung heparin)
- Both bovine lung heparin and porcine intestinal heparin have been widely used as anticoagulants for CPB.

Heparin (cont)

- It is a compound of highly sulfated polysaccharide located in mast cells, and has the highest negative charge density of any known biological molecule which is strongly acidic, and is widely used as an injectable anticoagulant
- Heparin: was used in cardiopulmonary bypass as an anticoagulant, because of its clinical effectiveness as an anticoagulant
- It is rapid, and can be rapidly neutralized by protamine.

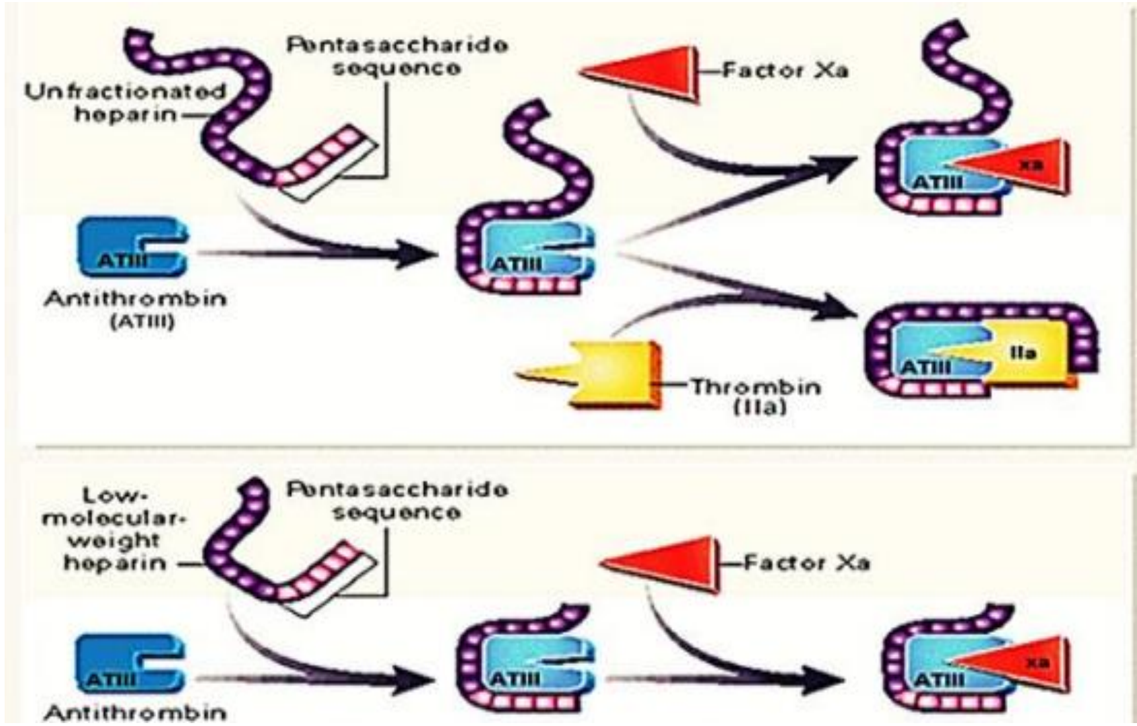
Figure 5:2

Heparin Chains



Mechanism of Heparin Action

- The mechanism of heparin action is to prevent thrombin formation, by increasing the activity of the antithrombin factor (AT III), to inhibit transformation of prothrombin to thrombin through inhibition of factors IIa (thrombin) and Xa.
- **Antithrombin Three Factor (AT III)**: is glycoprotein found in plasma.
- Heparin binding with AT III leads to increase in the ability of AT III to inhibit thrombin to 1,000 times or more
- Longer heparin chains effectively inhibit II a and Xa, whereas shorter heparin chains preferentially inhibit Xa



Mechanism of Heparin Action (cont)

- Heparin is also associated with the second helper factor (cofactor II), cofactor II is a glycoprotein that can cause inhibition of thrombin independently of the ATIII.
- This reaction occurs slowly and requires larger doses of heparin compared with AT III.
- Heparin association with cofactor II is important for anticoagulation, especially in patients with AT III deficiency .

Heparin Dosing

- Inadequate dosing of heparin leads to inadequate anticoagulation.
- Inadequate anticoagulation may cause thrombosis, intravascular clotting, oxygenator dysfunction, and consumption of clotting factors
- The initial dose of heparin in an adult patient has been determined by the patient's weight
- Heparin doses in milligrams (mg) based on patient's weight:

Adult Heparin dose = 3 × weight in Kg

Heparin Dosing (cont)

- The AT III concentration in healthy newborns is only half that of adults.
- Using a standard dose (Adult doses) of heparin may result in inadequate anticoagulation and intravascular coagulation.
- The initial doses of heparin in pediatric patients in mg determined by the weight or body surface area of patients.
- To calculate heparin doses in mg for pediatric:

  Pediatric Heparin dose = 4× weight in Kg or

  Pediatric Heparin dose = 90 × BSA.
- Extracorporeal circuit Heparin doses usually from 2000to 3000 IU per Liter of priming fluid, or 1 mg per kilogram. (1mg Heparin = 100 IU)

Side Effects of Heparin

Large doses of heparin induce

- platelet dysfunction (abnormalities of hemostasis)
- stimulation of tissue factor pathway inhibitor
- facilitation of fibrinolysis
- increases surgical bleeding
- decrease in systemic vascular resistance (hypotension can occur if given rapidly).
- Higher cardiopulmonary bypass heparin concentrations predisposed to postoperative heparin rebound effect, that requires treatment with additional protamine.

Monitoring the Activity of Heparin

- There are number of tests that we can use to monitor the activity of heparin.

- These tests fall into two categories, heparin effect "**the activated clotting times**" (ACT), and **measurements the heparin concentration** in blood or plasma

1. **The Activated Clotting Times**(ACT): ACT has been used as the standard test by many centers because it is not expensive and very simple to use.

But because of the hemodilution and hypothermia during CPB, the sensitivity of the ACT to heparin is increased, and this test becomes inaccurate **blood or plasma** .

- A normal ACT before heparin administration is in the region of **110-120 seconds**.

Monitoring the Activity of Heparin (cont)

- During CPB ACT should be maintained at **greater than 480 seconds** to minimize the risk of **intravascular coagulation.**

- The simplest clinical guideline is to exceed ACT value 400s during CPB for cardiac surgery, and a minimum ACT of **180 seconds** had been suggested for patients undergoing **long-term extracorporeal oxygenation for pulmonary support**(ECMO).

- The perfusionist must regularly(**Every half hour**) measures the ACT level to maintain it at greater than 480 seconds, Because the **heparin is metabolized** during cardiopulmonary bypass.

2- Heparin Concentration:

- To measure the heparin concentration in plasma or blood is the **automated protamine titration** method
- Both heparin and protamine doses are calculated based on the patient's blood volume.
- Protamine titrations measure heparin concentration by identifying the reagent concentration that optimally neutralizes heparin, judged by the fastest clot formation under standardized conditions; so the tube or cartridge with the shortest clotting time represents the closest match between heparin and its neutralizing agent.
- This information can be converted to heparin concentration because the neutralization ratio of protamine to heparin is known (usually 1.0 to 1.2 mg of protamine to 100 U of heparin).
- **Heparin concentration in whole blood on cardiopulmonary bypass must be maintained greater than 4.0 U/ml.**

Alternatives to heparin

- Bivalirudin
- Lepirudin
- Danaparoid
- Argatroban.
- These alternatives were all used successfully in different situation, such as **allergy to heparin or in patients known to have heparin-induced thrombocytopenia (HIT).**

Anticoagulation Management in CPB

1. Administer heparin 300 U/kg for adult, and 90mg x BSA for pediatric patients intravenously by anesthetist.

(The Perfusionist have added heparin to CPB circuit prime at a dose approximately 2- 3 U/ml).

2. After **3 to 5 minutes** from heparin administration take an arterial sample for ACT.
3. If the ACT is less than the target range give additional heparin as needed to achieve an ACT above 400 seconds before initiating CPB and to maintain an ACT above 480 seconds during CPB.
4. Monitor the ACT every 30 minutes during CPB
5. If ACT decreases below the desired minimum value, supplemental heparin doses of 50 to 100 U/kg most often sufficient to prolong the ACT

Heparin Resistance

- Heparin resistance: **is need for higher-than-normal heparin doses** to induce sufficient anticoagulation (above 480 seconds) for the safe conduct of CPB.

Reasons of Heparin Resistance in Clinical Situations:

1- familial AT III deficiency.

2- Ongoing heparin therapy (induced thrombocytopenia).

3- Extreme thrombocytosis (platelet count >700,000/L).

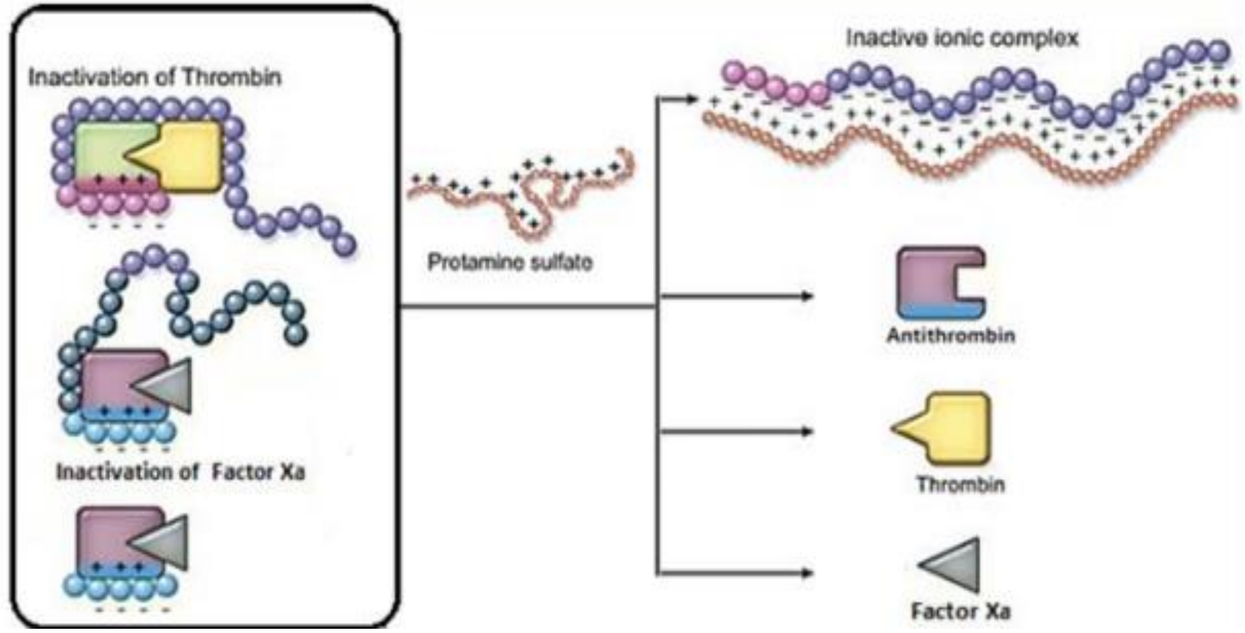
4- Septicemia.

5- Eosinophilia syndrome.

6- Antiphospholipid Syndrome.

Reversal of Anticoagulation

- Protamine: Is a protein derived from **salmon sperm**, it is a **strongly alkaline** compound, contains many **positive ions**.
- Positive ions in the protamine attract negative ions in the heparin, sufficiently to separate it from its binding site on ATIII and reverse its anticoagulant effect.



Calculation of Protamine Dose

- The dose of protamine needed may decreases with time due to the continuous metabolism to heparin in the body (the half-life of heparin is 60-90 minute)
- Improper protamine dose may result in **inadequate reversal, protamine anticoagulation**, or adverse side effects.

Methods for calculating the protamine dose

1. Fixed Protamine Dose Method

- Use a fixed ratio of protamine to the total or initial dose of heparin.
- This method involves giving 1.0 to 1.2 mg of protamine for each 100 U of heparin.
- Advantage - simplicity.
- Disadvantage - the considerable variability in the half-life of heparin, that makes it difficult to predict the status of the coagulation system immediately preceding heparin neutralization

Calculation of Protamine Dose (cont)

2. Protamine Titration Method

- Calculation of protamine dose methods used tubes with several dilutions of a standard protamine solution, a fixed volume of whole heparinized blood is added to these tubes, the lowest protamine concentration resulting in the shortest clotting time is represents the optimal neutralization of heparin.

Advantages for this method:

i. Administration of a lower protamine dose than with a fixed-dose method.

ii. Absence of excessive postoperative bleeding response, and heparin rebound despite reduced protamine doses

Side Effects of Protamine

- Inhibition of plasma coagulation and platelet function
- Protamine overdose can lead to further platelet dysfunction lasting several hours into the post bypass period

Protamine Reactions

1. ***Pharmacologic Histamine Release***:
   - Histamine release is principally related to rapid administration of protamine and can result in bradycardia, vasodilation, sudden fall in blood pressure, pulmonary hypertension, and possibly myocardial depression.

2. ***True Anaphylaxis (IgE-mediated):***
   - True anaphylaxis can result from previous exposure to protamine, which is demonstrated only in diabetic patient who's taking intermediate duration insulin preparations that contain protamine.

3. ***Anaphylactoid reactions (Non . IgE-mediated).***

THANK YOU