Coagulation For Cardiopulmonary Bypass

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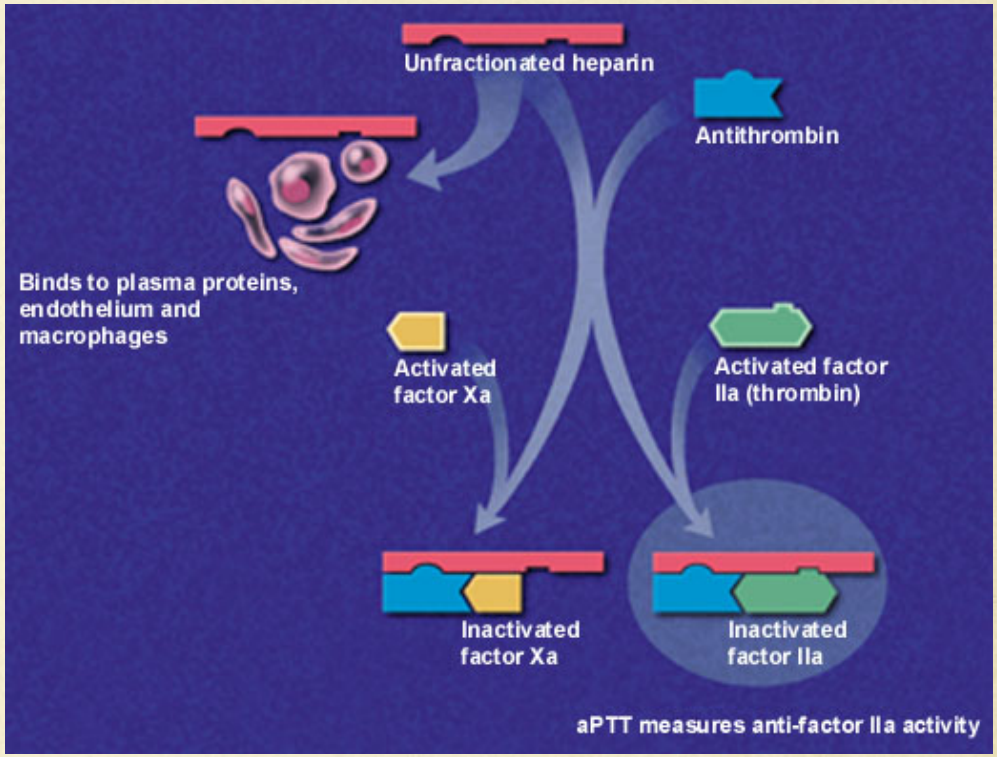
Cardiopulmonary Bypass

- Cardiopulmonary bypass requires high dose anticoagulation since contact of blood with the artificial surfaces of the bypass machine activates the coagulation cascade
- Unfractionated heparin is by far the most commonly used anticoagulant for CPB

Heparin

- Produces anticoagulation by inactivating thrombin and factor X
- It accomplishes this by binding with and upregulating the activity of ATIII



Advantages Of Heparin

(1) High efficacy for preventing thrombosis of the CPB circuit

(2) Rapid and simple intraoperative monitoring by activated clotting time

(3) Easy neutralization of heparin by protamine sulfate

- No other agent meets these requirements

Dosing

- Initial dosing for CPB is 300-400 units/kg (3-4 mg/kg)
- It is usually the goal to achieve an ACT value of at least 480 before initiating CPB, although some evidence shows an ACT as low as 300 may indicate adequate anticoagulation
- An ACT of 400 is typically maintained throughout the CPB course
- Protamine reversal is given after separation from CPB

Heparin Resistance

- Heparin resistance is defined as an excessive demand for heparin (>400-600 units/kg) to achieve an ACT >400-480 seconds
- Occurs in up to 22% of patients undergoing cardiac surgery
- Causes:
  - AT III deficiency
  - Ongoing active coagulation
  - Prior Heparin treatment/current infusion

Heparin Resistance Treatment

- If unable to achieve an ACT >400 with 6 mg/kg of heparin then proceed to one of the following:

1. Antithrombin Concentrate (500-1000 IU – 1-2 vials)
2. 2 units of FFP

Protamine

- Highly cationic peptide
- Initially isolated from salmon sperm but is now produced through recombinant biotechnology
- Binds to heparin, forming a stable ion pair which does not have any anticoagulant activity
- On its own, it does have a weak anticoagulant effect
- Dosage for heparin reversal is 1mg for every 100 units of active heparin

Protamine Reactions

- Hypotension from histamine release – systemic hypotension due to mast cell histamine release
- Anaphylactic reaction – hypotension, bronchospasm, skin reactions caused by preformed antibodies
- Anaphylactoid reaction – similar to anaphylaxis but activates compliment pathway directly
- Catastrophic pulmonary hypertension – precipitous pulmonary htn, RV failure, and systemic hypotension
  - Thought to be caused by thromboxane A2 release triggered by protamine-heparin complexes

Problems With Heparin

- Heparin therapy can be complicated by 2 types of induced thrombocytopenia
- Type I HIT – common, non-immune, fairly benign
- Type II HIT – rare, immune mediated, more serious

Type I HIT

- Occurs in approximately 10% of patients receiving heparin, usually within the first few days of treatment
- Caused by direct interaction of heparin with the platelet membrane, resulting in enhanced platelet aggregation
- The platelet count does not usually decrease below 100,000 and gradually rises to normal levels after several days, even if heparin therapy is not discontinued.
- This form of thrombocytopenia is benign, self-limited, and not associated with bleeding or an increased risk of thrombosis

Type II HIT

- Occurs in up to 5% of patients receiving heparin for more than 4 days, usually presents between 4 and 10 days after starting therapy
- Caused through an immune mediated process by the development of IgG abs that cause platelet activation
- The platelet count progressively decreases to <100,000
- Thrombi and hemorrhage may develop, resulting in sudden myocardial infarction, peripheral arterial thrombosis, pulmonary embolism, DIC, or skin necrosis

Diagnosing HIT

- The diagnosis of HIT requires the following:

1. Thrombocytopenia with a history of heparin therapy within the past five days
2. The exclusion of other causes of thrombocytopenia
3. Recovery of the platelet count after the cessation of heparin therapy
4. Characteristic laboratory findings (ELISA for heparin antibodies)

Patients With Previous HIT

- Heparin induced thrombocytopenia antibodies are transient and usually decline to undetectable levels by 100 days (median, 50 days)
- If heparin is administered to a patient with previous HIT whose antibodies are no longer detectable, several days are required for B lymphocytes to regenerate antibodies, if they are made at all

Patients With Previous HIT

- HIT antibody formation does not recur more quickly or more often in a patient with previous HIT who is re-exposed to heparin
  - There is no immune memory
- Therefore, heparin is the drug of choice for anticoagulation during CPB in patients with a history of HIT who no longer have circulating HIT antibodies

Patients With Subacute HIT

- Subacute (or latent) HIT refers to a patient with a recent episode of HIT who continues to have detectable HIT antibodies
- Such a patient can develop rapid-onset HIT if heparin is administered again
- For these patients in which heparin anticoagulation is considered contraindicated, several off-label approaches exist

Heparin Alternatives

1. Argatroban
2. Lepirudin
3. Bivalirudin

Argatroban

- Synthetic direct thrombin inhibitor that irreversibly binds
- Metabolized by the liver
- Half-life of about 50 min
- ACT can be used for monitoring
- No neutralizing agent

Recombinant Hirudin (Lepirudin)

- Hirudin is a single-chain 65-amino acid polypeptide (7,000 Da) that forms an irreversible 1:1 complex with thrombin
- It is an anticoagulant naturally produced by the salivary gland of the medicinal leech
- The half-life of hirudin greatly depends on renal function, ranging from 80 minutes (normal kidneys) to more than 200 hours (anephric patient).
- No neutralizing agent exists

Bivalirudin

- A 20-amino acid synthetic peptide modeled after hirudin, which consists of two peptide fragments that reversibly bind and inhibit thrombin
- Approximately 25 min half life
- Primarily enzymatic metabolism
- Monitored using ACT
- No neutralizing agent exists

Anticoagulation Options

A. Acute HIT

1. Postpone cardiac surgery for several weeks (then go to C)
2. Bivalirudin (preferable)
3. Lepirudin (can be used if normal renal function, may not be available much longer)
4. Antiplatelet agents (Epoprostenol, Tirofiban) plus heparin

B. Subacute HIT

1. Postpone cardiac surgery for several weeks (then go to C)
2. Off-pump technique using bivalirudin or lepirudin
3. Heparin (if washed platelet activation assay for HIT antibodies is negative or enzyme immunoassay negative or weakly positive)
4. See options listed under A

C. Previous HIT

1. Heparin

Bivalirudin Protocol

- On Pump Cardiac Surgery
  - 1 mg/kg via CVL
  - Check ACT q20 min (ACT goal > 400 sec)
  - 2.5 mg/kg/hr gtt
  - Stop gtt 15 min before d/c CPB
- OPCAB
  - 1 mg/kg via CVL
  - Check ACT q20 min (ACT goal > 360 sec)
  - Re-dose at 0.25-0.5 mg/kg