ANTIPHOSPHOLIPID SYNDROME AND CARDIAC SURGERY

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Overview

- Case presentation
- Antiphospholipid syndrome (APLS)
- Cardiac manifestations of APLS
- Intraoperative management of cardiopulmonary bypass in APLS patients
The Case

- Mrs LH
- Dr Jessica Precce, Pathology Intern
Antiphospholipid syndrome

- Complex autoimmune disease
- Young patients (median age <42)
- 3:1, female : male predominance
Antiphospholipid syndrome

- Clinical features
  - Recurrent thromboses
  - Fetal loss
  - Other: heart valve disease, pulmonary hypertension, livedo reticularis, thrombocytopenia, neuropathy

- Laboratory features
  - Autoantibodies against plasma proteins (β2GP1, cardiolipin) dependent on negatively charged phospholipids
  - Prolongation of clotting tests (APTT, dRVVT, KCT, etc) despite prothrombotic state
Antiphospholipid syndrome

Table 1
Updated classification criteria for APLS [1]. APLS is present if at least one of the clinical and one of the laboratory criteria that follow are met.

I. Clinical criteria
1. Vascular thrombosis
   Arterial, venous or small vessel thrombosis in any tissue or organ, to be confirmed by objective validated criteria (imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
   One or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation or
   One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or preeclampsia or placental insufficiency
   Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation.

II. Laboratory criteria (positive test on two or more occasions at least 12 weeks apart, standardised procedures)
1. Lupus anticoagulant present in plasma
2. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL)
3. Anti-beta2Glycoprotein1-antibodies of IgG and/or IgM isotype in serum or plasma

GPL: immunoglobulin G (IgG) anti-phospholipid units, MPL: immunoglobulin M (IgM) antiphospholipid units.

Ammended Sapporo criteria (2006) 

Coagulation testing and APLS

- Antiphospholipid Ab prolong clotting times by interfering with phospholipids in test systems.
- Standard clotting tests depend on calcium and phospholipids for adequate activation of clotting cascade (e.g., APTT, dRVVT).
- Times do not normalise with mixing studies but normalise with adding an excess of phospholipid.
Cardiac manifestations of APLS

- **Coronary artery disease**
  - Fulfils thrombosis criteria in Sapporo classification

- **Valve lesions frequent in 1° APLS**
  - Vegetations, valve thickening and dysfunction in 30-40% \(^1\)
    - More common in APLS patients with arterial thromboses
  - Lesions in 1° APLS predominantly thrombotic or fibrotic/calcified
    - Compared with inflammatory (ie Libman-Sacks in SLE) or infectious lesions
    - Believed to arise as a result of microthrombi formation and subsequent fibrosis from valvular sheer stress and exposed phospholipid
  - Aortic and mitral valves equally affected
  - Thromboembolic risk

The problem

- APLS patients are at a very high risk for VTE complications peri-operatively and in particular following cardiac surgery\(^1\)
- Thromboembolic complications can arise
  - Preoperatively with reversal of anticoagulation
  - Intraoperatively due to inadequate anticoagulation on cardiopulmonary bypass
  - Posoperatively prior to reinstatement of adequate anticoagulation or as a result of catastrophic APLS and multiorgan failure

The problem

- Cardiac/heart valve surgery in APLS patients relatively infrequent
- Approach to perioperative management currently empirical with high morbidity and mortality
  - Literature limited to case reports and small case series (n ≤10)
  - Post operative mortality 7-12% in first 3 years
  - Post operative complications 58%
    - Largely related to prothrombotic events (CVA, AMI, IVC thrombosis)
    - Direct valve related complications in 20% (valve thromboses)

Intraoperative management of coagulation during cardiopulmonary bypass (CPB)

- What usually happens?
  - Cardiopulmonary bypass requires extensive anticoagulation to prevent clot formation and pump failure.
  - Usually attained by supra-therapeutic doses of heparin (~300 U/kg) prior to cannulation.
  - Intraoperative management of anticoagulation is monitored with the aid of a point-of-care activated clotting time (ACT).
  - ACT is measured at ~30 minute intervals and additional boluses of heparin administered as necessary.
  - Heparin subsequently reversed by protamine (dosed based on total amount of heparin used) with a repeat ACT to ensure that baseline levels are reached.
Activated clotting time (ACT)

- Test of whole blood that uses a strong contact activator of the coagulation cascade (celite or kaolin)
- Used in CPB as ACT is linearly responsive to high concentrations of heparin used in CPB
  - Normal baseline **90-150**
  - Target ACT during CPB > **450**
- ACT times also affected by antiphospholipid Ab and APLS patients may have prolonged baseline ACT
  - Degree of effect on ACT dependent on initiation substrate
  - Potentially makes ACT an unreliable marker of adequate anticoagulation

ACT machine
Intraoperative management of coagulation during CPB in APLS

- No consensus, published reports empirically based with wide variability in approach
  - Heparin generally used as good safety profile and widest clinical experience
  - Approaches generally adopt higher than necessary levels of anticoagulation for CPB rather than inadequate anticoagulation
  - Antifibrinolytics generally avoided as theoretical risk of increased thrombotic events
Approaches to monitoring anticoagulation during CPB in APLS

- Empirically administering at least as much heparin as usual and titrating heparin aiming for at least twice baseline ACT or twice upper limit of normal \(^1\)
- Baseline prolonged ACT can render ACT monitoring unusable intraoperatively (>analyzer range)
- Uncontrolled approach with empirical dosing based on body weight
- ACT response to heparin may not be reliable and doubling of ACT may not represent adequate anticoagulation for CPB \(^2\)
- Successful outcomes in published case reports

Approaches to monitoring anticoagulation during CPB in APLS

- Pre-operative testing to establish a heparin-ACT dose response curve\(^1, 2\)
  - Heparin administered intraoperatively according to established target ACT
  - Heparin concentration of >3U/ml assumed sufficient for effective anticoagulation on CPB
  - Analyser specifically designed to analyse dose-response available commercially
  - Difficulties again with ACT >analyser range in APLS

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Approaches to monitoring anticoagulation during CPB in APLS

- Using point of care testing for circulating heparin concentrations on CPB circuit
  - 3mg/kg heparin calculated as required concentration
  - Not a measure of heparin effect (other factors may influence heparin concentration vs effect)
  - Requires point-of-care analyzer capable of monitoring heparin concentrations (indirect measure of protamine reversible heparin activity)

Approaches to monitoring anticoagulation during CPB in APLS

- Using anti-Xa levels to monitor anticoagulation on CPB
  1, 2

  - Reliable, reproducible results using chromogenic anti-Xa
  - ‘Gold standard’ laboratory measure of heparin therapy in situations where APTT may be adversely affected 2
  - Target anti-Xa > 4.0 U/ml for CPB
  - Not available for point-of-care use in theatre with longer turn around times
  - At Alfred, reference curve only calibrated for anti Xa <2.0 U/ml. Unclear if further dilutions to extend reference curve will adversely affect reproducibility of results.

Approaches to monitoring anticoaguation during CPB in APLS

- Empirical use of alternative anticoagulants (bivalirudin) in a patient with concurrent HIT
Back to Mrs LH