Current Trends in Antithrombotic Therapy During Adult ECMO Presentation Outline

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Conflict of Interest

- No current or recent financial relationships with pharmaceutical or medical device companies exist
- No potential conflicts of interest exist
- The use of medications outside of their FDA approved indication will be included in this presentation

Objective

- Describe current literature for anticoagulant selection, monitoring, and intensity for adults supported with extracorporeal membrane oxygenation (ECMO)

Background

- **Antithrombotic Therapy and Adult ECMO**
  - Fine balance between thrombosis and hemorrhage by regulating multiple prothrombotic and anticoagulant systems
  - Exposure of blood to the non-biologic artificial surfaces of ECMO → complex inflammatory response → activates coagulation pathway + blood elements (platelets, leukocytes)
  - Advances in ECMO have made circuits less likely to activate coagulation/immune responses
  - Certain areas of ECMO circuits remain problematic: adaptors, connectors, access points, hemofilter and its smaller bore tubing and filter membrane
  - Until the risk of thrombosis is eliminated in ECMO anticoagulation will remain a necessary evil
- **Thrombosis and Bleeding During Adult ECMO**
  - Bleeding and thrombosis comprise the majority of all side effects that can occur on ECLS
    - Thrombosis
      - Location: In vivo is not commonly seen clinically, clot in the circuit is common
      - Risk Factors: factor V Leiden, congenital antithrombin, protein C or protein S deficiency, or antiphospholipid antibodies, low flow rates
      - Event Rates
    - Bleeding
      - Location: Always in vivo → cannula sites, surgical incisions, nose, mouth, urinary tract, abdominal or thoracic cavities, lungs and airways, gastrointestinal (GI) tract, and calvarium
      - Risk Factors: blood pressure, concomitant diseases, over anticoagulation, deficiency of coagulation factors, thrombocytopenia, AVWS, platelet function defects, hyperfibrinolysis
      - Event Rates

Considerations for Agent Selection: Direct Thrombin Inhibitors in ECMO

- **Therapeutic Options for System Anticoagulation**
  - Inhibition of FX and prothrombin are the primary coagulation pathways exploited for circuit patency in ECLS
    - Heparin

- Most commonly used anticoagulant drug (likely due to experience with CPB)
- Forms a complex with antithrombin → inhibition of factor Xa and factor IIa.
- Limitations: HIT, binding to other plasma proteins, highly variable half-life, and the population kinetics of heparin, varies widely between individuals

▪ Direct Thrombin Inhibitors

- Off-label but growing popularity
- Binds directly to circulating and clot-bound thrombin
- Exhibits predictable and dose-dependent anticoagulant effect
- Ideal for Heparin induced thrombocytopenia (HIT) or some form of heparin resistance

- **Direct Thrombin Inhibitors in ECMO**
  - Bivalirudin
    - Berei et al. ASAIO J. 2017 Oct 23.
    - Pieri M et al. J Cardiothorac Vasc Anesth. 2013 Feb;27(1):30-4.
    - Ranucci M et al. Crit Care. 2011;15(6):R275.
  - Argatroban
    - Menk M. Ann Intensive Care. 2017 Dec;7(1):82.
    - Beiderlinden M. Artif Organs. 2007 Jun;31(6):461-5.
- **Important Considerations in Using DTIs in ECMO**
  - Role
  - Bivalirudin vs. Argatroban
  - Dosing
    - Bivalirudin: 0.005-0.1 mg/kg/h a target aPTT of 45 to 60 seconds. Renal function dependent
    - Argatroban: 0.2 to 1 mg/kg/min. Hepatic and renal function dependent
  - Lack of antidote in the case of bleeding → half-life is relatively short at 25 minutes but prolongs up to 4 hours in ESRD
  - Inability to monitor a patient's underlying coagulable state
  - Avoiding stasis of blood as this will lead to thrombus formation because the majority undergoes proteolytic enzymatic degradation in plasma (bivalirudin)
  - Costs

Considerations for Anticoagulant Monitoring: Anti-Xa Monitoring and TEG/ROTEM

- **Traditional Monitoring Parameters for Anticoagulation in ECMO**
  - ACT
    - ACT provides a real-time examination of the whole blood's clotting time in the presence of heparin infusion, thrombocytopenia, and other patient condition factors such as inflammation, etc.
    - Advantages: Whole blood clotting time, widely available, POC, quantification of very high heparin levels
    - Disadvantages: Insensitive to low UFH dosages, not specific to heparin, lack of standardization
  - aPTT
    - Advantages: Experience with heparin monitoring, widely available, protocolizable
    - Disadvantages: Not specific to heparin, lack of standardization
- **Heparin Anti-Factor Xa Activity for Heparin Monitoring**
  - The principle of the anti-Xa assay is as follows: a patient's plasma which contains an unknown amount of antithrombin–heparin complexes is added to a mixture with a known amount of FXa → AT–heparin complex in the mixture combines with the FXa in the test sample and inactivates a portion of it in a 1:1 ratio → residual FXa in the sample (that which did not combine with the antithrombin–heparin complex) is now available to react with a chromogenic substrate that is added to the mixture in a known amount.

This substrate is cleaved by the residual FXa, and the product is detected using a spectrophotometer. The signal is then compared against a standard curve to yield a quantitative FXa inhibitory activity.

- There are two types of anti-Xa assays that can be performed
  - In the absence of antithrombin (AT), it measures heparin effect
  - In the presence of AT, it measures heparin concentration
- Advantages: Direct measurement of heparin, stable dosing, protocolizable
- Disadvantages: Overcoagulation with innate coagulopathy, affected by high bilirubin and plasma-free hemoglobin concentrations, higher heparin doses
- No consensus regarding the superiority of the anti-FXa level

- **Viscoelastometry (ROTEM or TEG) for Anticoagulation Monitoring in ECMO**
  - TEG measures the time needed to form a fibrin clot, the strength of the clot (determined by the cross-linking of platelets and fibrinogen), and the eventual breakdown of the fibrin clot (fibrinolysis) in whole blood.
  - Has not replaced conventional coagulation assays using plasma.
- **Important Considerations for Anticoagulant Monitoring**
  - aPTT and anti-Factor Xa activity values are frequently discordant and a disproportionate prolongation of aPTT is the more common discordant pattern
  - As such, ACT should not be expected to represent the heparin effect alone, nor should correlation with anti-Xa levels or aPTTs be expected. There are center-specific ACT ranges that ECLS patients are maintained within (related to device used for testing)
  - The aPTT is most often used to monitor the anticoagulant effect of bivalirudin.

Considerations for Target Intensity

- **Anticoagulant Intensity in ECMO**
  - Goal: find the dose that prevents thrombus formation while minimizing the risk of bleeding
  - Bleeding complications, as defined by ELSO, occurred in more than half of critically ill patients undergoing ECMO and were strongly and independently associated with hospital mortality.
  - Traditional ECMO Anticoagulation Targets
    - aPTT: 1.5-2 or 1.5-2.5 x baseline
    - ACT: 180-220 s
    - Heparin anti-Xa: 0.3-0.7 U/mL
- **Anticoagulation Intensity as a Risk Factor for Bleeding in ECMO**
  - HELP ECMO Pilot Study
  - J Crit Care. 2017 Jun;39:87-96.
  - Ann Am Thorac Soc. 2016 Dec;13(12):2242-2250.
  - Ann Intensive Care. 2016 Dec;6(1):97.
- **Important Considerations for Anticoagulant Intensity**
  - Optimize the tolerability of systemic anticoagulation
    - Platelets, fibrinogen, cannula care
  - ECLS studies in adults have shown good correlation between aPTTs of 1.5–2.5 times normal and UNFH concentrations of 0.2–0.4 U/mL
  - VA vs. VV ECMO
  - Consider patient's underlying disease
  - Don't forget the need for VTE prophylaxis