10-2016

Heparin Resistance After Cardiopulmonary Bypass

Stanlies D'Souza
Baystate Health, dsouzastan@yahoo.com

Heparin Resistance After Cardiopulmonary Bypass

Francisco J Herrera MD, Mamatha Kadiyala MD, Stanlies D'Souza MD

Department of Anesthesiology, Baystate Medical Center/ Tufts University School of Medicine, Springfield, MA

Introduction

Heparin resistance is defined as the inability to achieve an activated clotting time (ACT) of >400 seconds after an adequate dose of heparin. Its incidence ranges from 3-26% (1). We present a case we recently encountered and discuss our management.

Case Description

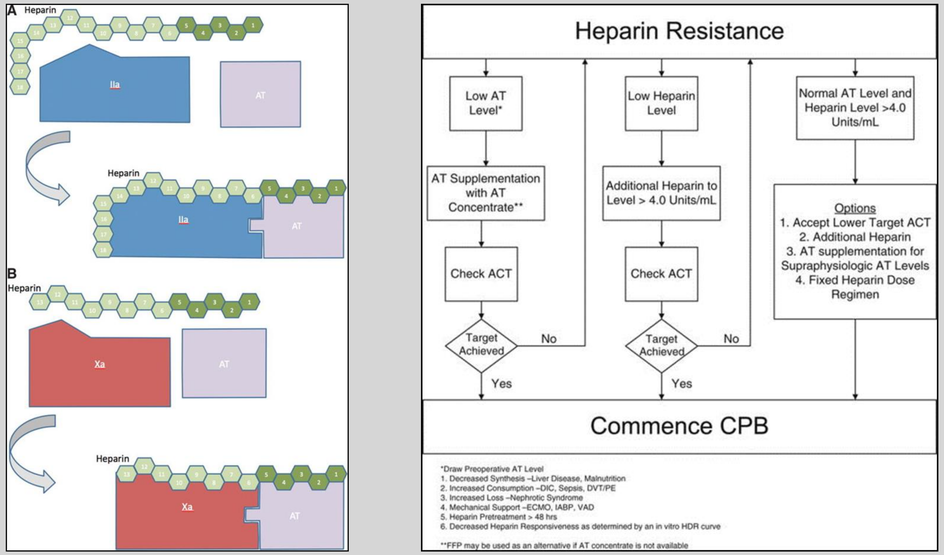
A 70 year old male with severe left main coronary artery disease presented for one vessel CABG with a baseline ACT of 110. After 30,000 units of intravenous heparin, his ACT was 380. An adequate ACT for CPB could not be achieved following 2 additional doses of 10,000 units of heparin. Adequate anticoagulation was achieved with the transfusion of 6 units of fresh frozen plasma and subsequent administration of 10,000 units of heparin. His intraoperative course was complicated by significant coagulopathy, inadequate reversal with protamine and the requirement for the transfusion of blood products.

Etiology

Deficiency of ATIII decreases the ability of heparin to inhibit thrombin and can be either congenital or acquired in etiology. Acquired ATIII deficiency is associated with liver disease, malnutrition, nephrotic syndrome, and previous heparin treatment. Other factors related to heparin resistance include IV nitroglycerine, heparin binding proteins and factor VIII among others.

Pathophysiology

Preoperative heparin (24-48 hours) is commonly thought to contribute to heparin resistance. Heparin-AT complex binds to thrombin and this complex is rapidly consumed and cleared via the reticuloendothelial system resulting in a ATIII level decline by 5-7%. This decline is thought to be the mechanism by which heparin pretreatment increases the incidence of heparin resistance. In addition to ATIII deficiency, there are multiple other potential mechanisms that can lead to heparin resistance that are both poorly defined and nonspecific.



Figure(s) 1 and 2. Alan Finley MD, Charles Greenberg MD. Heparin Sensitivity and Resistance: Management During Cardiopulmonary Bypass. Anesthesia and Analgesia 2013;116(6):1210-1222. Copyright 2015 by International Anesthesia Research Society. Used with permission.

Treatment

Therapeutic approaches include administering additional heparin, supplement ATIII with FFP, supplement ATIII with an ATIII concentrate or accept the ACT and proceed to CPB without any additional treatment. The effectiveness of FFP as treatment in Heparin Resistance is limited and no studies have shown improvement in clinical outcomes. ATIII replacement has been shown to be superior to FFP in increasing ACT, but questions remain based on its increased cost, lack of clinical outcomes improvement and inability to reach the desired ACT in all patients with ATIII deficiency. Accepting below target ACT for CPB, on fixed heparin dose regimens is often not chosen for fear of sub-therapeutic anticoagulation.

Diagnostic Testing

- ACT (activated clotting time)
- ATIII levels (30-60 min)
- High dose thrombin time (more specific for thrombin inhibition)
- Heparin response curve
- Heparin level

References

1. Finley et al. Anesthesia and Analgesia. 2013;116:(6):1210-1222
2. Beattie et al. Interactive Cardiovascular and Thoracic Surgery. 2014;18:117-120
3. Sniecinski et al. Best Practice & Research Clinical Anesthesiology. 2015;29:189-202

Alternative Agents

Direct thrombin inhibitor: Bivalirudin (Angiomax) 1.5-2 mg/kg followed by 0.5-5 mg/kg/h

Conclusions

- **Identification of patients at risk for HR**
- **Besides ATIII levels, multiple factors affect ACT**
- **The minimum ACT required for safe conduction of CPB remains unknown**
- **A rational approach should be taken to evaluate heparin resistance**
- **Research is needed to confirm clinical benefits in treating heparin resistance**