A Case of Rapid Heparin Resistance with Pulmonary Embolism

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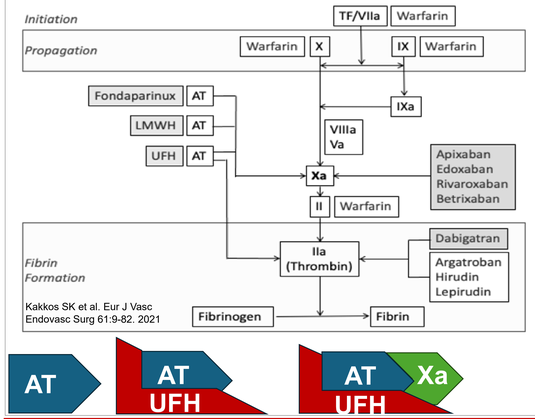
BACKGROUND

Heparin resistance is the failure to achieve a predetermined anti-coagulation goal despite administering an adequate dose (**>35,000 units/day**) of unfractionated heparin (UFH).[1]

- Average of 24 to 48 hours to reach therapeutic UFH levels[2]
- Heparin resistance is usually considered after multiple days of therapy

Potential causes of heparin resistance:

- **Antithrombin (AT) deficiency**
  - **Etiology:** Congenital AT defects, previous heparin exposure, liver or renal disease, acute thrombosis, DIC, surgery, ECMO, hemodialysis
- Elevated coagulation factors
- Thrombocytosis
- Andexanet alfa
- Hypercoagulability (infectious)



Purpose

To gain a better understanding of the onset of heparin resistance in critically ill patients.

Patient Presentation

A 68 year-old male presenting with altered mental status with a past medical history of HFrEF (NYHA III; EF 20%), chronic kidney disease, left ventricular thrombus and cocaine abuse was admitted to the cardiovascular critical care unit for acute decompensated low output heart failure, gram negative bacteremia with sepsis, and a concomitant pulmonary embolism triaged by the PERT team as low risk which prompted initiation of unfractionated heparin infusion.

Pertinent Labs:
BNP: 5774 pg/mL
hsTroponin: 237 ng/L
Lactic Acid: 3.6 mmol/L
tBili: 3.4 mg/dL
SCr: 5.2 mg/dL (baseline 2 mg/dL)

Vitals:
HR:120 bpm
BP:118/81 mmhg
RR:37
Wt: 75 kg

Imaging:
CT-PE: subacute pulmonary emboli in the segmental and subsegmental pulmonary arteries of the right lower lobe with no evidence of right heart strain

Time (hr)	6	12	18	24
Heparin dose (units/kg/hr)	15	18	**21**	24
Units of Heparin per 24 hours	27,000	32,000	**38,000**	43,000
Anti-Xa (goal: 0.3 to 0.7 IU/mL)	<0.10	<0.10	**<0.10**	<0.10

Clinical Course

Heparin Resistance Suspected
- >35,000 units/day
- Unable to achieve therapeutic Anti-Xas

→ Antithrombin assay and augment anticoagulation strategy

→ **Treatment Options:**
Increase heparin dose (no max)
Replete AT
Switch to direct thrombin inhibitor(DTI)

→ **Switched to DTI**
Bivalirudin chosen over argatroban due to hepatic dysfunction

RESULTS

- Antithrombin activity 20% (normal ~80%)
- Therapeutic aPTT levels (50-80) achieved with bivalirudin within first 4 hours of transition

DISCUSSION

Possible reasons for rapid development of antithrombin deficiency:

- Sepsis with increased consumption of AT
- Acute hepatic dysfunction leading to decreased production of AT

Treatment approach:

- Increasing heparin dose (no maximum) is a potential strategy but may delay achieving therapeutic anticoagulation
- Repleting AT can be high in cost, not easily accessible, and lacks standardized dosing
- Direct thrombin inhibitors such as argatroban and bivalirudin inhibit thrombin directly without a requirement for AT which makes them desirable agents for patients with heparin resistance due to AT deficiency
- PE was deemed low risk, so could potentially utilize a direct oral anticoagulant (DOAC) as treatment

Critically ill patients that are unable to achieve therapeutic anti-Xas during the first 24 hours of treatment could potentially be due to rapid heparin resistance as seen in this case.

CONCLUSIONS

This patient case indicates that heparin resistance due to antithrombin deficiency can develop within the first 24 hours of treatment.

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