



Heparin Resistance

Arav Raghunathan, The GTF Group

HSS Day July 19, 2024

Objectives

1. **Define** Heparin Resistance
2. **Define** differences between LMWH and UFH
3. **Explain** the biological mechanisms behind Heparin Resistance
4. **Discuss** diagnostic tests, other testing, and treatment used to measure Heparin Resistance





What is Heparin Resistance?

Heparin Resistance is a prevalent problem but is largely unknown.

01



Heparin Resistance



- **Heparin** is a negatively-charged polysaccharide polymer derived from the porcine intestine (Figure 1). UFH is a mixture of polymers with chain lengths ranging from 3000 to 30,000 daltons. LMWH has a molecular weight of 3500 to 5000 daltons.
- **Heparin Resistance:** The insufficient anticoagulation response received following what is considered a sufficient heparin dose has been administered.
- **Threshold of Heparin Resistance:** Still widely unknown. Some scientists believe that the threshold is more than 35000 U to achieve the desired result, and others believe that it is more 500 U of treatment per kg of body weight to receive a blood clotting time between 400 and 480 seconds.

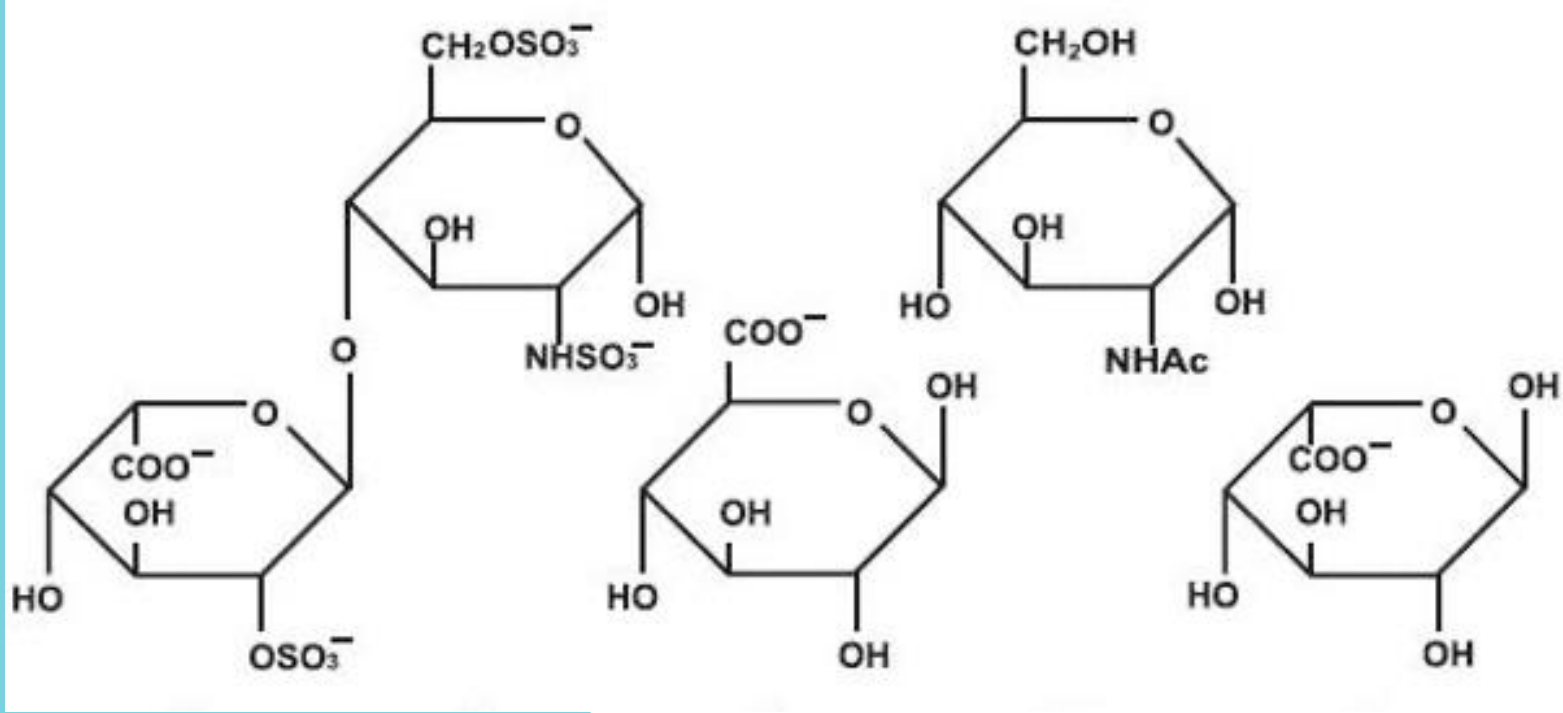


Figure 1: Chemical Structure of Heparin



LMWH and UFH

- **UFH:** The common form of heparin that is unpurified, meaning that it contains varying lengths of polymers.
- **LMWH:** Heparin in its purified, meaning that it contains more uniform lengths of polymers.
- **Effects:** Because of its lengths, unfractionated heparin has unique effect through the inhibition of thrombin, an enzyme that breaks down fibrinogen into fibrin. Both molecules have an effect on Factor Xa levels.



02

Biological Mechanisms of HR

Biological Mechanisms of Heparin Resistance



Non-Specific Binding

- **Non-Specific Binding?:** Non-Specific Binding occurs when a molecule used to bind to a specific proteins binds to another protein, causing unintended effects.
- **Unfractionated Heparin?:** Because of its varying lengths of polymer, unfractionated heparin has the tendency to bind with other molecules, including growth factors, platelet factor IV, and so on.

Antithrombin Deficiency

- **Antithrombin Deficiency?:** Because of conditions that include liver disease and genetic abnormalities, patients may have naturally lower levels of antithrombin, a molecule that inhibit thrombin.
- **Surgery?:** Usually, during surgeries, a level of antithrombin supplement is administered for heparin to have its intended effects.



Biological Mechanisms, contd.

Platelet Interaction

- **Platelet Interaction?:** Studies have shown that certain use of heparin can lead to increased activation of platelets through release of the heparin-binding protein known as platelet factor IV
- **Thrombocytopenia?:** Increased Heparin Levels have shown to induce thrombocytopenia, which is a known cause of heparin resistance.

Elevation of Coagulation Factors

- **Coagulation Factors?:** In certain individuals, clotting factors such as Factor VIII as well as Fibrogen can decrease aPTT in certain individuals.
- **Effects?:** A shortened aPTT means that more heparin is required to prevent clotting from occurring, indicating heparin resistance.



Biological Mechanisms contd.

Andexanet Alfa

- **Andexanet Alfa?:** Andexanet Alfa is a synthetic factor that is usually employed during cardiac surgery and has the capability to reverse the effects of antithrombotic inhibitors.
- **Heparin Resistance?:** The reversal of these effects, some of which are actually caused by Heparin, can render the anticoagulant useless, causing heparin resistance.

COVID-19

- **COVID-19:** Covid-19, as ubiquitous known, is a respiratory illness that causes a variety of unpleasant symptoms in the lungs, similar to a cold or flu.
- **Heparin Resistance?:** Because of its respiratory effects, Covid-19 has been shown into causing an increased expression of coagulation factors, which include Von Willebrand Factor and Factor VIII.

Incidence / Predictors of Heparin Resistance



- **Incidence:** Heparin Resistance occurs in up to 22% of cardiac surgery patients
- **Predictors:** Some of the major predictors of Heparin Resistance include the following:
 - AT activity greater than or equal to 60%
 - Platelet Concentration greater than 300,000
 - Patient's age is greater than 65



03

Diagnostics

Diagnositics



- **Functional Assays:**
 - **Most** functional assays center around how clots grow *in-vitro* (petri dish).
 - **aPTT (Activated Partial Thromboplastin Time)** is the common of the assays.
 - **aPTT** involves collect blood plasma and calcifying the contents. The time from calcification to clot formation is measured.
 - **Higher** concentrations of Heparin that is given leads to sharper increases in aPTT.
 - **Lower** aPTT and Higher Heparin concentrations is generally attributed to Heparin Resistance.



- **Functional Assays (Cont.):**
 - **ACT (Activated Clotting Time)** involves introducing an activated clotting factor to trigger *in-vitro* clotting.
 - **This assay** is sensitive at higher Heparin levels. It is used during cardiopulmonary bypass surgery to carefully monitor how the blood is responding to Heparin.
- **Chromogenic Assays:**
 - **Chromogenic Assays** utilize citrated plasma that is placed in an environment with an excess of clotting factor Xa.
 - **This assay** disregards the levels of other clotting factors such as Factor VIII.
 - **Inverse Relationship** between anticoagulant levels and Factor Xa levels.

Diagnositics

(Contd.)



04

Treatment



Treatment

- **Coagulation Testing:**
 - **Continuous testing** for anti-Factor Xa levels can give a better idea on the amount of Heparin necessary.
 - **Lower anti-Factor Xa** levels should correlate to more Heparin administration.
- **Direct Thrombin Inhibitors:**
 - **Direct Thrombin Inhibitors** inhibit thrombin proteins without affecting antithrombin levels
 - Administered to patients with thrombocytopenia.



05

Conclusion

Conclusion



- **Heparin Resistance**, where Heparin is unable to produce the intended effects for the patients, is a serious clinical condition. 22% of cardiac surgery patients have the condition.
- **It is vital** for doctors and patients alike to understand their medical history and major lingering conditions that potentially could have an effect on Heparin response. This practice will allow patients to receive the most accurate and effective treatment for their thrombotic conditions.



06

Acknowledgements

Acknowledgements



- I would like to thank Dr. Sagar Garud for his mentorship on this project. I would like to thank Loyola Chicago University, Dr. Callahan, and Dr. Fareed for the opportunity to present my research. Lastly, I would like to my parents for their constant support throughout this project



07

References



References

Levy, J. H. & Conner, J. M (2021, August 25). *Heparin Resistance — Clinical Perspectives and Management Strategies*. New England Journal of Medicine.
<https://www.nejm.org/doi/full/10.1056/NEJMra2104091>

National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases (2024, April 9). *About COVID-19*. CDC. <https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19.html>





Thank you!

Do you have any questions, comments,
or concerns?