https://doi.org/10.60115/11055/1195

Intravenous heparin and non-cardiac anaesthesia

Andrew Emanuel MBBS(Hons), BMedSc, FANZCA
Department of Anaesthesia, Liverpool Hospital, Sydney, NSW, Australia

Dr Andrew Emanuel is a cardiac anaesthetist and medical perfusionist with special interests in simulation, education, and perioperative medicine.

Edited by Dr YEE EoT CHEE

INTRODUCTION

Heparin is documented as being discovered in 1916,[1] and is the oldest anticoagulant[2] used for the prevention and treatment of venous and arterial thrombosis. In anaesthesia, heparin is commonly given for the prevention of thromboembolic complications (TEC) during cardiac and vascular surgery. It is also used as an anticoagulant for extracorporeal circulations, whole blood transfusion, dialysis, cell salvage, and as an anticoagulant in laboratory blood samples. Although unfractionated heparin has greater inter-individual variation in pharmacodynamic effects compared to low molecular weight heparin, its low cost, short half-life, and rapid reversibility with protamine makes it the anticoagulant of choice when careful perioperative control of anticoagulation is needed. This article will focus on non-cardiopulmonary bypass uses of heparin in anaesthesia, as its application in cardiopulmonary bypass has recently been covered in depth.[3]

Pharmacology of heparin

Heparin sodium contains a heterogeneous mixture of negatively charged, sulphated glycosaminoglycan molecules ranging from 3000 to 30,000 Da in molecular weight (mean ~15kDa), which corresponds to approximately 45 saccharide units.[4-6] Due to this heterogeneity, the bioactivity and physiologic action of unfractionated heparin (UFH) can be broad and unpredictable.[7] The WHO standard for UFH has a potency of 122IU/mg of heparin, and since 2008 this has been adopted by the United States Pharmacopeia (which previously used its own standard of 150 IU/mg).[8] This reduced potency is worth noting when looking at heparin doses from older resources. Heparin is prepared from porcine lung and intestinal mucosa (bovine, porcine, or sheep, although porcine is the predominant source worldwide), but it is acceptable to most Jewish and Islamic patients due to its non-enteral route and its medical necessity.[9]

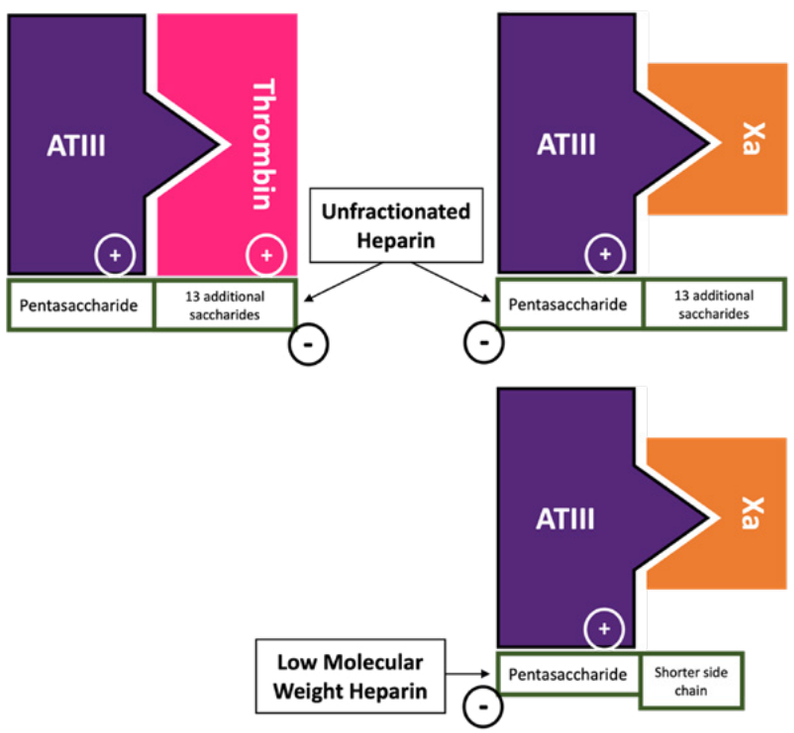
Low molecular weight heparin (LMWH), such as enoxaparin, is prepared via controlled enzymatic cleavage of UFH to produce smaller molecules (mean ~5kDa) with shorter chains (~15 saccharide units) and more predictable actions. LMWH is thus usually the preferred heparin for outpatient and ward-based administration due to its improved bioavailability, lower protein binding, more precise pharmacokinetics, and thus lower requirement for monitoring.[7] Ultra-low molecular weight heparins (ULMWH) have subsequently been developed, but have not gained widespread use due to their lower benefit-to-cost ratio.

The presence of a unique five-sugar sequence (i.e., pentasaccharide) is required for any type of heparin to bind to antithrombin and exert its anticoagulant activity.[10] Binding of this pentasaccharide to Antithrombin III (AT) induces a conformational change, converting it from a slow to a rapid inhibitor of serine proteases and thus enhancing its anticoagulant activity 1000-4000-fold.[10] However, the pentasaccharide-bound AT inhibits only factor Xa. A longer polymeric chain containing 18 or more polysaccharide units is required to bind both antithrombin and thrombin to form a ternary heparin/AT/thrombin complex (Figure 1) in order to inhibit thrombin activity.[2,10,11] This explains why LMWH preferentially inhibits factor Xa than thrombin in a 2:1 to 4:1 ratio, depending on the composition of the chain lengths in a given preparation. Whereas UFH inhibits both factor Xa and thrombin, with its overwhelming effect on thrombin.

Approximately one-third of UFH molecules in the usual clinically administered dose possess the unique pentasaccharide sequence responsible for its anticoagulant effect described above.

However, at concentrations higher than those administered clinically, heparin chains with or without the pentasaccharide sequence start to catalyse thrombin inhibition by a second plasma cofactor, heparin cofactor II.[12] At even higher concentrations, low-affinity heparin impairs factor Xa generation through AT- and heparin cofactor II (HCII)-independent mechanisms.[13] By inactivating thrombin or attenuating its generation, heparin not only prevents fibrin formation from fibrinogen but also inhibits thrombin-induced activation of platelets and thrombin-induced activation of factors V, VIII, and XI.[14,15] Heparin also prevents the formation of a stable clot by inhibiting the activation of fibrin stabilising factor (XIII). The primary locations of common clinically used anticoagulants are presented in a simplified form in Figure 2.

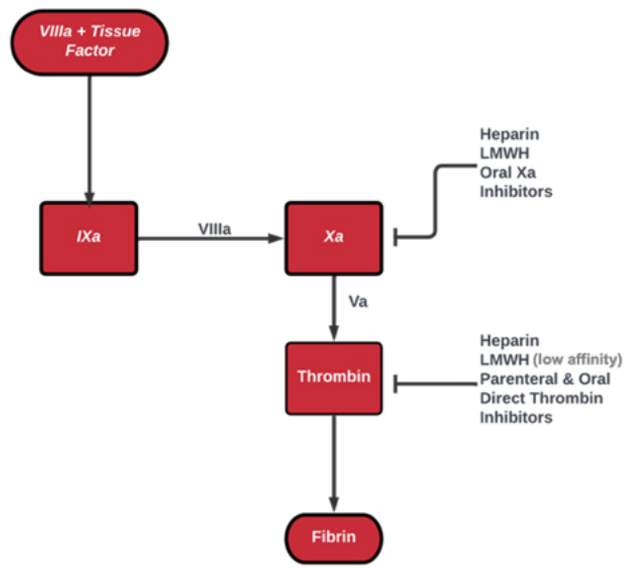
Figure 1. Pharmacology of heparin and low molecular weight heparin[10,16]



The unfractionated heparin/ATIII complex binds to non-fibrin bound thrombin (IIa) at a high affinity and inactivates it. The same complex inactivates factor Xa, but the heparin molecule only binds to ATIII in this situation. In contrast, the ATIII/LMWH complex inactivates factor Xa in a similar fashion, but at a much greater affinity compared to UFH. There is clinically insignificant binding of LMWH/ATIII to thrombin.

The pharmacokinetics of heparin are complex. It is extensively bound to plasma proteins, and it also binds to endothelial cells, macrophages, and von Willebrand factor which inhibits von Willebrand factor-dependent platelet function.[10] Heparin is degraded by heparinases and cells in the reticuloendothelial system. Initial clearance of heparin at lower doses is rapid and linear but at higher doses the clearance becomes non-linear. The apparent biological half-life of heparin is thus dependent on the dose given (Table 1 and Figure 3)[10,17] and this should be taken into consideration when determining protamine dosage required for reversal (if quantitative testing for heparin concentration is not in use).

Figure 2. Anticoagulant effects on the coagulation cascade (simplified)

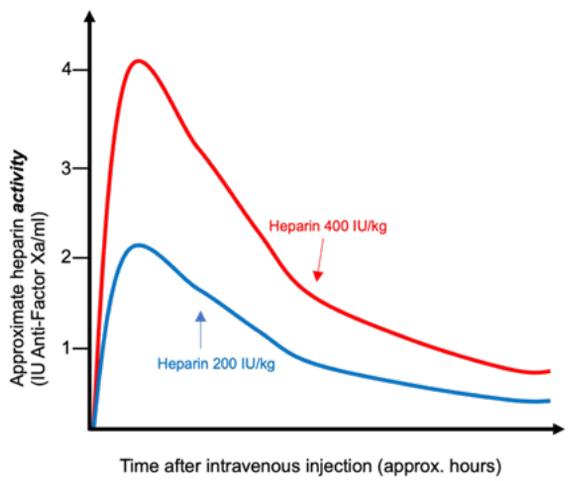


Anticoagulant activity of commonly used clinical agents occurs at two primary locations in the coagulation cascade.

Table 1. Heparin dose and variability in duration of action

Heparin dose (IU/kg)	Approximate apparent biological half-life (mins)
25	30
100	60
400	150

Figure 3. Schematic representation of heparin dose and impact on anti-Xa pharmacology



The pharmacology of heparin's anticoagulant activity varies based on the amount (and subsequent concentration) administered.[18,19] Reproduced with permission from Dr Bruce Cartwright.

The dose of heparin utilised varies markedly with different clinical indications. Very low doses of heparinised saline (10U/ml) are used to keep intravascular devices patent. For arterial vascular surgery, 100U/kg is often recommended, aiming for an ACT approximately 200-250 seconds as a standardised dose of 5000 units is often inadequate.[20] Targeting higher ACT levels, up to 350 seconds, may increase bleeding complications without reducing thrombotic complications.[21] When heparin is used for cardiopulmonary bypass a higher dose of 300-400U/kg is used whilst aiming for an ACT of >480 secs. Heparin is excreted in the urine, but in contrast to LMWH, there is no renal dose adjustment required. There is insufficient evidence to make recommendations for dose adjustment in obesity, although it has been suggested that adjusted body weight (ideal body weight + 40% of excess) could be used.[22]

Heparin does not cross the placenta and isn't excreted in breast milk. Bleeding time is usually unaffected and clotting time is not measurably affected by low dose heparin but is prolonged by therapeutic doses. Patients older than 60 may have a longer APTT prolongation for a given dose of heparin. Half-life may be slightly prolonged in renal impairment and either increased or decreased in hepatic impairment. Heparin does not have fibrinolytic activity and as such, should not be used to lyse existing clots.

Clinical monitoring of heparin effect

The anticoagulant effect of therapeutic parenteral heparin is traditionally, and most accurately, monitored using clot based or chromogenic laboratory tests such as Activated Partial Thromboplastin Time (APTT) or anti-Xa assays respectively (see Table 2). Additionally, in cardiac surgery, whole-blood heparin levels may be determined using an automated protamine titration device (Hepcon).[23]

Heparin infusions are commonly titrated to achieve a "therapeutic" APTT of 1.5-2.5x the normal range, corresponding to a heparin level of 0.2-0.4 IU per ml by protamine titration.[6] The processing time required for protamine titration (typically thirty minutes or more) usually make these tests impractical for intraoperative use. Although there are instruments available to measure point of care APTT, these have shown poor precision and comparability to the laboratory standard.[24] Activated clotting time (ACT) is widely available and familiar in the theatre environment and gives rapid results.

Table 2. Functional (clot-based) and chromogenic assays

	Clot-based assays	Chromogenic assays
Point of care examples	ACT, TEG, ROTEM	-
Laboratory examples	PT, APTT, TT	Anti-Xa
Advantages	Simple, fast, some are point of care	Quantitative
Limitations	Semi-quantitative, result less specific – e.g., High Factor VIII levels could underestimate heparin effect. Presence of lupus anticoagulant will overestimate it.	Lab based. Need specific assays for different anti-coagulants. Longer processing times.

ACT tubes use clot-promoting reagents such as celite or kaolin to standardise and quicken fibrin formation induced by contact activation of the coagulation protein factor XII. The ACT test results reflect the ability of a blood sample to clot in this fashion and the ACT is thus prolonged in the presence of heparin. The more prolonged the ACT result is from baseline or normal values the greater the degree of anticoagulation. The ACT result is not entirely specific and can be affected by haemodilution, hypothermia, pharmacologic compounds, and various coagulopathies. There are numerous different machines available in Australia such as Actalyke (HELENA laboratories), Haemochron (Werfen), and ACT Plus (Medtronic) (Table 3). Different cartridges/tubes should be used depending on the clinical application – for example 'low range' (LR) during haemodialysis/ECMO or 'high range' (HR) during vascular surgery or cardiopulmonary bypass. Using the incorrect cartridge can be misleading, as the ratio of activators to heparin concentration determines the response curve of ACT vs plasma heparin concentration. For example, at a heparin concentration of approximately 1.2IU/ml a HR cartridge may show an ACT of approximately 180 seconds whereas a LR cartridge may produce an ACT of 350 seconds. The use of a heparinase/control cartridge after protamine administration can help the clinician decide if there is ongoing heparin effect or other factors causing the ACT to be prolonged.

Point of care viscoelastic testing such as TEG or ROTEM also allows for additional assays to be run with heparinase added. This can be used alongside the ACT to guide protamine administration, although it should be noted that viscoelastic assays are relatively insensitive to low range heparin concentrations, below 0.3 IU/ml.

Table 3. Examples of point of care testing

Instrument	Manufacturer	Sample	ACT activator	ACT clot detection method	Alternative analyses available
Haemochron Signature Elite	Accriva Diagnostics	Capillary or whole blood (WB) (native or citrated)	ACT+ test uses a mixture of silica, kaolin, and phospholipids; ACT-LR test uses Celite activator.	Optical/ mechanical	ACT HR or LR, POC INR & APTT
iSTAT	Abbott	WB	Kaolin, celite	Electrogenic, amperometry	ACT, POC INR
Actalyke Mini II	Helena Laboratories	WB	Celite, kaolin, glass beads	Magnet rotation	
ACT Plus	Medtronic	WB (native or citrated)		Plunger motion	ACT HR or LR, heparinase

Adapted from[24]. Whole blood (WB), Point of care (POC).

Heparin resistance

Heparin resistance is usually defined as the need for greater than 35,000 units of heparin in 24 hours to reach a therapeutic APTT[25] (in non-cardiopulmonary bypass). It is more common in patients undergoing cardiopulmonary bypass (up to 20%) where it is defined as the need for more than 500 units per kilogram of body weight to achieve an activated clotting time of 400 to 480 seconds.[26] Measuring a baseline ACT does not appear to help predict heparin resistance preoperatively.[26]

Causes of heparin resistance

- Antithrombin (AT) deficiency
  - Congenital
    - ~1:5000 incidence
    - AT levels of 40-60% of normal
  - Acquired
    - Heparin therapy - the thrombin-antithrombin complex is cleared by the reticuloendothelial system - AT levels decline by ~5-7% per day.
    - Liver disease
- Upregulated coagulation system
  - Disseminated Intravascular Coagulation (DIC)
  - SARS-CoV-2
- Non-specific binding
  - Anionic heparin molecules bind many different proteins including platelet factor 4, glycoproteins, von Willebrand factor, fibrinogen, and factor VIII.
- Platelet interactions
- Andexanet alpha
  - Xa decoy - apixaban/rivaroxaban reversal agent
- Pseudo (apparent) heparin resistance

Although most heparin resistance is due to antithrombin deficiency, supplemental antithrombin doesn't always raise ACT, suggesting there is also an anti-thrombin-independent mechanism.

Management of heparin resistance

When heparin resistance is discovered, the first step is to determine whether there is true heparin resistance (*in vivo* blunting of heparin's anticoagulant effect) or pseudo (apparent) heparin resistance, where there are subtherapeutic APTT/ACT values despite therapeutic *in vivo* anticoagulation. To help differentiate true from pseudo heparin resistance, the APTT and anti-Xa assay levels should be measured on the same blood sample. The anti-Xa assay relies on free factor Xa (i.e., not bound by the antithrombin-heparin complex) and, unlike the APTT and ACT, it is not affected by other clotting factors (e.g., high factor VIII levels as seen in SARS-CoV-2 patients[27]) or acute-phase reactants.[28] True heparin resistance, where both APTT/ACT and anti-Xa levels are concordantly lower than expected, is most commonly due to decreased antithrombin activity. Antithrombin chromogenic functional assays are the best first test for antithrombin deficiency with a normal range being approximately 80-130%. Additional specialised tests to differentiate type 1 (quantitative deficiency) vs type 2 (dysfunction) are not standard but are available in some laboratories. Unfortunately, it is often not practical to wait for formal anti-Xa or antithrombin III assays during surgery and empirical treatment is often used. As antithrombin III deficiency is the most common cause of heparin resistance, empirical treatment with 1000 units of purified human antithrombin III concentrate is expensive but usually effective in achieving a therapeutic ACT.[29] If antithrombin concentrate is not available, fresh frozen plasma (FFP) can be used with 1ml of FFP containing approximately 1 IU of antithrombin.

Andexanet alpha (a factor Xa decoy) is a new reversal agent for rivaroxaban and apixaban, but it also binds to antithrombin III reducing the thrombin III-heparin complexes which could preclude adequate anticoagulation with heparin. Administration of antithrombin III or bivalirudin could be considered in this settting.[30]

Protamine

Protamine sulfate is a positively charged basic protein, originally isolated from salmon fish sperm but increasingly manufactured with recombinant technology.[31] Protamine neutralises the effect of anionic heparin through electrostatic binding in a 1:1 ratio to form a protamine-heparin aggregate. As neutralisation is dependent on molecular weight, protamine will only partially neutralise low molecular weight heparin.[32] Protamine has a rapid onset of action, within 5 minutes, and a short half-life of approximately 10 minutes. 1mg of protamine will neutralise 100 units of heparin but as heparin is being continuously excreted, the dose of protamine should be reduced if more than 15 minutes has elapsed since the heparin administration. If excessive protamine is given it will have anticoagulant effects via interference with platelet function, clotting factors, and enhanced fibrinolysis.[31] Adverse effects to protamine (Table 4) can be non-immunologic or immunologic and are highest in patients with previous protamine exposure (including in some insulin formulations) and patients with vasectomy or fish allergies. The haemodynamic effects of protamine administration are greatly reduced if it is given by slow infusion.

Table 4. Adverse effects of protamine administration

Adverse effect	Clinical sequelae
Vasodilation	Hypotension
Pulmonary vasoconstriction	Pulmonary hypertension or right ventricular dysfunction
Anaphylaxis or Anaphylactoid reactions	Hypotension, bronchospasm

Heparin induced thrombocytopaenia

Heparin induced thrombocytopaenia (HIT) has two main types. Type 1 (sometimes simply referred to as "heparin associated thrombocytopaenia" to avoid confusion) affects up to 10% of patients exposed to heparin and usually causes a mild thrombocytopaenia within 1-4 days of heparin administration. It is due to a direct and non-immune mediated activation of platelets causing clumping or sequestration but carries no increased risk of thrombosis.[33] In contrast, Type 2 HIT, which occurs in approximately 0.3% of vascular surgical patients,[34] causes a delayed (typically 5-11 days post heparin exposure) and more severe reduction in the platelet count as it is immune mediated. IgG develops in response to formation of a heparin-platelet factor 4 (PF4) antigen. This can cause irreversible aggregation of platelets and progress to the development of arterial and venous thromboses and mortality in up to 30% of patients. If a diagnosis of HIT is suspected, a pre-test probability can be estimated using the 4T scoring system (Table 5) prior to performing heparin-PF4 antibody testing, as it not necessary (or usually recommended) for patients with low pre-test probability.[33] If a patient has intermediate or high-risk probability, heparin should immediately be discontinued, and haematological advice sought as further testing with immunoassays and/or functional assays should be strongly considered. Low molecular weight heparin (LMWH) cannot be used in patients with HIT due to the strong cross reactivity of the HIT antibody with LMWH-PF4 complex. Alternative anticoagulants, such as bivalirudin (a direct thrombin inhibitor), should be used for all patients with suspected, acute, or subacute HIT. Patients are said to have "Remote HIT" if enough time has elapsed such that both functional and immunoassays are unable to detect anti-PF4 or anti-heparin antibodies. In these patients it is reasonable to use heparin in emergency settings if non-heparin anticoagulants are not available or clinical experience is lacking.[35]

Table 5. 4T Scoring System

	2 points	1 point	Not significant
Platelet fall	>50% Drop by 20-100	>30-50% Drop by 10-19	<30% fall Drop <10
Timing	Onset 5–10 days	Outside 5–10 days by 1 day	<4 days
Thrombosis	Skin necrosis, new DVT/PE	Progressive or recurrent (e.g., new defect with existing PE)	None
Other cause of thrombocytopenia	None	Possible – e.g., haemodilution	Definite

Low risk <3 points; Intermediate risk 3-5 points; High risk >5 points

Bivalirudin is a synthetic direct thrombin inhibitor first introduced for percutaneous coronary intervention (PCI) in the early 1990s. It has the theoretical advantages of inhibiting fibrin-bound thrombin, a predictable effect of anticoagulation and a short half-life of approximately 30 minutes if renal function is normal.[36] Unlike heparin, it lacks a specific reversal agent, and its half-life is significantly prolonged in renal impairment. Argatroban can be used as an alternative in patients with severe renal impairment (Table 6).

Table 6. Heparin alternatives – pharmacology and suggested dosing

Heparin alternative	Mechanism	Half-life (mins)	Indication	Dose	Dose adjustments
Bivalirudin	Direct thrombin inhibitor	25	HIT/Acute coronary syndrome (ACS)	0.1-0.15mg/kg then 0.25mg/kg/hr	Reduce dose in renal impairment.
			Percutaneous coronary intervention (PCI)	0.75mg/kg then 1.75mg/kg/hr	
Argatroban[37]		50	HIT/ACS	2mcg/kg/min	Reduce dose in hepatic impairment.
			PCI	250mcg/kg then 15-25mcg/kg/min	Consider 100mcg/kg bolus titration to effect.

In a meta-analysis comparing bivalirudin (0.75mg/kg loading + 1.75mg/kg/hr) versus unfractionated heparin (50-100 U/kg) for peripheral endovascular procedures (PEP) there were no significant differences in rates of procedural success, major and minor bleeding, transfusion requirements, perioperative TIAs, or haemorrhagic strokes.[36] Another meta-analysis of retrospective studies showed that bivalirudin used for PEP may be associated with lower all-cause mortality and bleeding complications but further large RCTs were considered necessary to confirm these results.[38]

Heparin allergy

The most common adverse effect of heparin is haemorrhage. Late side effects can include alopecia, osteoporosis, lipodystrophy, and raised liver enzymes. Although true allergy to heparin is rare, all types of allergic reactions have been described. The most common allergic mechanisms are cell mediated type IV (e.g., erythematous cutaneous plaques) and antibody mediated Type II reactions (e.g., HIT type 2, as previously discussed).[39] Immediate Type I reactions are very rare. Heparin necrosis, a differential diagnosis of Type IV mediated rashes, can also occur and is the cutaneous manifestation of the severe form of HIT Type 2.

Perioperative management of heparin infusions

For patients on therapeutic heparin infusions, if the APTT is in the therapeutic range (typically 55-90 seconds) it is usually recommended to cease the infusion six hours prior to surgery. This may vary depending on the clinical assessment of the patient's relative risk of bleeding compared to their risk of TEC.

The American Society of Regional Anesthesia (ASRA) recommend cessation of intravenous heparin six hours prior to neuraxial blockade or epidural catheter removal.[40] It should be noted that if the APTT is above the therapeutic range, a longer cessation time is required, and normal coagulation status should be verified prior to neuraxial blockade or surgery with critical bleeding risk (e.g., neurosurgery).

ASRA recommend waiting at least one hour after neuraxial anaesthetic procedures before restarting a heparin infusion. Recommencing heparin infusions post-surgery is largely based on surgical preference and again must consider the patient's bleeding versus TEC risk profile.

CONCLUSION

Intravenous heparin is a familiar drug that is widely available, low cost, and rapidly reversible. It has numerous applications in anaesthesia and perioperative medicine, and understanding its advantages, shortcomings, and nuances is valuable for all anaesthetists and perioperative staff.

REFERENCES

1. Mclean J. The discovery of heparin. Circulation. 1959;19:75-78.
2. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337:688-698.
3. Cartwright B, Mundell N. Anticoagulation for cardiopulmonary bypass: part one. BJA Educ. 2023;23:110-116.
4. Johnson EA, Kirkwood TB, Stirling Y et al. Four heparin preparations: anti-Xa potentiating effect of heparin after subcutaneous injection. Thromb Haemost. 1976;35:586-591.
5. Andersson LO, Barrowcliffe TW, Holmer E, Johnson EA, Sims GE. Anticoagulant properties of heparin fractionated by affinity chromatography on matrix-bound antithrombin iii and by gel filtration. Thromb Res. 1976;9:575-583.
6. Hirsh J. Heparin. N Engl J Med. 1991;324:1565-1574.
7. Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: Past, Present, and Future. Pharmaceuticals (Basel). 2016;9:38.
8. Royston D. Pharmacology and Physiology for Anesthesia Anticoagulant and Antiplatelet Therapy. In: Hemmings HC, MD, PhD, FRCA, Egan TD, MD2019. p. 870-894.
9. Datz H. Religious-related concerns and animal-derived medications during anesthetic care. Anaesthesia, Pain & Intensive Care. 2018
10. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e24S-e43S.
11. Levy JH, Connors JM. Heparin Resistance - Clinical Perspectives and Management Strategies. N Engl J Med. 2021;385:826-832.
12. Tollefsen DM, Majerus DW, Blank MK. Heparin cofactor II. Purification and properties of a heparin-dependent inhibitor of thrombin in human plasma. J Biol Chem. 1982;257:2162-2169.
13. Hirsh J, Weitz JI. New antithrombotic agents. Lancet. 1999;353:1431-1436.
14. Béguin S, Lindhout T, Hemker HC. The mode of action of heparin in plasma. Thromb Haemost. 1988;60:457-462.
15. Ofosu FA, Sie P, Modi GJ et al. The inhibition of thrombin-dependent positive-feedback reactions is critical to the expression of the anticoagulant effect of heparin. Biochem J. 1987;243:579-588.
16. Hirsh J, Warkentin TE, Shaughnessy SG et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest. 2001;119:64S-94S.
17. Weitz JI. Blood Coagulation and Anticoagulant, Fibrinolytic, and Antiplatelet Drugs. In: Brunton LL, Knollmann BCNew York, NY: McGraw-Hill Education; 2023.
18. Despotis GJ, Summerfield AL, Joist JH et al. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg. 1994;108:1076-1082.
19. Qi Y, Zhao G, Liu D et al. Delivery of therapeutic levels of heparin and low-molecular-weight heparin through a pulmonary route. Proc Natl Acad Sci U S A. 2004;101:9867-9872.

20. Doganer O, Jongkind V, Blankensteijn JD, Yeung KK, Wiersema AM. A Standardized Bolus of 5 000 IU of Heparin Does not Lead to Adequate Heparinization during Non-cardiac Arterial Procedures. Ann Vasc Surg. 2021;71:280-287.
21. Kasapis C, Gurm HS, Chetcuti SJ et al. Defining the optimal degree of heparin anticoagulation for peripheral vascular interventions: insight from a large, regional, multicenter registry. Circ Cardiovasc Interv. 2010;3:593-601.
22. Myzienski AE, Lutz MF, Smythe MA. Unfractionated heparin dosing for venous thromboembolism in morbidly obese patients: case report and review of the literature. Pharmacotherapy. 2010;30:324.
23. Raymond PD, Ray MJ, Callen SN, Marsh NA. Heparin monitoring during cardiac surgery. Part 1: Validation of whole-blood heparin concentration and activated clotting time. Perfusion. 2003;18:269-276.
24. Wool GD. Benefits and Pitfalls of Point-of-Care Coagulation Testing for Anticoagulation Management: An ACLPS Critical Review. Am J Clin Pathol. 2019;151:1-17.
25. Heparin resistance. [editorial]. Br J Anaesth 2002;88(4):467.
26. Staples MH, Dunton RF, Karlson KJ, Leonardi HK, Berger RL. Heparin resistance after preoperative heparin therapy or intraaortic balloon pumping. Ann Thorac Surg. 1994;57:1211-1216.
27. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2.[letter]. Int J Lab Hematol 2020;42 Suppl 1(Suppl 1):19-20.
28. Downie I, Liederman Z, Thiyagarajah K, Selby R, Lin Y. Pseudo heparin resistance caused by elevated factor VIII in a critically ill patient. Can J Anaesth. 2019;66:995-996.
29. Williams MR, D'Ambra AB, Beck JR et al. A randomized trial of antithrombin concentrate for treatment of heparin resistance. Ann Thorac Surg. 2000;70:873-877.
30. Pauls LA, Rathor R, Pennington BT. Andexanet Alfa-Induced Heparin Resistance Missing From SCA Blood Management in Cardiac Surgery Guidelines.[letter]. J Cardiothorac Vasc Anesth 2022;36(12):4557-4558.
31. Boer C, Meesters MI, Veerhoek D, Vonk ABA. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. Br J Anaesth. 2018;120:914-927.
32. Schroeder M, Hogwood J, Gray E, Mulloy B, Hackett A-M, Johansen KB. Protamine neutralisation of low molecular weight heparins and their oligosaccharide components. Analytical and Bioanalytical Chemistry. 2011;399:763-771.
33. Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. Postgrad Med J. 2007;83:575-582.
34. Chaudhry R, Wegner R, Zaki JF et al. Incidence and Outcomes of Heparin-Induced Thrombocytopenia in Patients Undergoing Vascular Surgery. J Cardiothorac Vasc Anesth. 2017;31:1751-1757.
35. Cuker A, Arepally GM, Chong BH et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360-3392.
36. Hu Y, Liu AY, Zhang L et al. A systematic review and meta-analysis of bivalirudin application in peripheral endovascular procedures. J Vasc Surg. 2019;70:274-284.e5.
37. Lewis BE, Wallis DE, Berkowitz SD et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation. 2001;103:1838-1843.- Cruz-Gonzalez I, Sanchez-Ledesma M, Osakabe M et al. What is the optimal anticoagulation level with argatroban during percutaneous coronary intervention. Blood Coagul Fibrinolysis. 2008;19:401-404.
38. Olmedo W, Villablanca PA, Sanina C et al. Bivalirudin versus heparin in patients undergoing percutaneous peripheral interventions: A systematic review and meta-analysis. Vascular. 2019;27:78-89.
39. Bircher AJ, Harr T, Hohenstein L, Tsakiris DA. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. Allergy. 2006;61:1432-1440.
40. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43:263-309.