

# Understanding the Heparin/Protamine reaction as applied to cardiac surgery

R K Firmin, DVT Harischandra, Dulan Munasinghe, E.V.C.Jayaliya, G Piyasiri

*Cardiothoracic Unit II, Teaching Hospital Karapitya, Galle, Sri Lanka*

**Correspondence** : Dr Richard K Firmin ; rkfirmin@hotmail.com

**ORCID ID** : <https://orcid.org/0000-0002-5119-7742>

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## Introduction

One of the old aphorisms of cardiac surgery was that post-operative bleeding was caused by either “hypoprolenaemia or hypoprotaminaemia”. In other words, it was surgical or medical; with the emphasis being on failure to neutralise heparin after cardiopulmonary bypass had been concluded. This was true for many years until the use of multiple anti-platelet agents became routine in managing coronary artery disease. Since then, bleeding from anti-platelet agents has, in addition, become a real issue if they are not stopped sufficiently prior to surgery.

## Heparin and Protamine pharmacology

Heparin acts by pentasaccharide binding to anti-thrombin III (AT) accelerating the rate at which AT inactivates thrombin, factor Xa and other serine proteases in the coagulation cascade [1]. As a reactive molecule, heparin will also bind less specifically with other plasma proteins, platelet factors and cellular proteins. If heparin is injected, its effects are seen to last a significant amount of time with a half-life of 30 to 90 minutes [2]. The rate of decline is dependent on factors such as dosage, urine output, obesity and malignancy. However, some heparin activity may be detected for up to 24 hours after administration due to subsequent release from plasma protein binding that had occurred earlier [3]. In patients on ECMO, this may occur for even longer periods, presumably with heparin being released from elements of the circuit as well as from the blood itself (personal observation of senior author).

Reversal of heparin has usually been with protamine sulphate. Although protamine sulphate was initially derived from biological sources, it is now produced by recombinant DNA methodology [4]. It preferentially binds to heparin and neutralises its effects by forming a heparin/protamine complex that no longer affects the coagulation cascade [5]. On its own, protamine can have anticoagulant activity [5], but this effect is weak and is rarely, if ever, of clinical significance. It can also have systemic effects such as pulmonary vasoconstriction, hypotension, and anaphylaxis [6]. Like heparin, protamine is a reactive molecule and will bind to other plasma proteins and blood elements. When injected, its effects only last for 10 minutes in the absence of heparin and five minutes in its presence [7]. Thus, there is a mismatch between the half-lives of heparin and protamine and the reaction between the two, is in essence, a first pass reaction: if protamine does not bind to heparin immediately it is bound to something else. This means that if any heparin appears subsequently, it will not be neutralised. Protamine and heparin molecules that do combine form a stable ionic pair that is inactive and are subsequently removed by the reticuloendothelial system [8].

It has long been known that heparin can re-appear in the circulation after a neutralizing dose of protamine has been administered: a phenomenon called heparin rebound [9]. The mechanisms behind this deserve consideration as excessive bleeding, unnecessary blood transfusion and re-exploration are often avoidable by the simple administration of further protamine. This is preferable to blind administration of clotting products as is a frequent response in some units.

Another factor that allows for heparin rebound is the reliance on the Activated Clotting Time (ACT) to determine heparin reversal. ACT is a crude clotting test of whole blood. Significant heparin effect can be found, even if the ACT is 'normal', with more sophisticated near patient tests such as TEG or ROTEM or laboratory tests such as thrombin time.

Thus, the factors that are likely to contribute to heparin rebound are the following: -

1. The discrepancy between the half-lives of protamine and heparin.
2. Secondary release of heparin after binding to plasma proteins.
3. Inadequate assessment of heparin reversal using ACT.
4. Improvement in peripheral perfusion as the cardiac output improves after surgery and patient warming allowing release of heparin from peripheral circulation and tissues.
5. The presence of heparinised blood if this is administered directly from the pump or subsequently transfused peripherally.

The relative importance and contributions of these factors are unknown.

Typically, protamine has been administered via the intravenous route. Administration via a peripheral vein is deemed to be safer than administration via a central vein given the possible haemodynamic instability and changes in arterial oxygenation. Controlled trials have shown that administration of Protamine via the ascending aorta lead to less haemodynamic instability and changes in arterial oxygenation [10] though it has not yet entered the routine standard of practice.

### **How we do it**

In cases where cardiac function is marginal or pulmonary hypertension a feature, we administer protamine via a 26g needle in the aorta rather than intravenously. This seems to be effective in abolishing reactive hypotension and pulmonary vasoconstriction. Whether this is due to slower

administration through the small needle or due to heparin binding as the protamine goes through the systemic circulation is uncertain.

Furthermore, in response to the understanding of the mechanisms of the action of heparin and protamine, we have evolved a strategy of giving relatively small bolus doses (50mgs) of protamine quite frequently after the initial reversal dose at the time of de-cannulation or formally giving a continuous infusion of 50–100mg of protamine per hour in normal saline over one to three hours. In controlled trials, continuous infusions have been shown to work to significantly reduce blood loss and prevent heparin rebound[[3]. We also use ROTEM as well as ACT to assess bleeding in any case where there is a perceived problem. The presence of a heparinase plot confirms whether, or not, heparin is still present.

### **Conclusion**

Understanding the pharmacology of both heparin and protamine separately and together are important to understand how each can be used optimally. Furthermore, the use of tests additional to ACT should also lead to reduced postoperative blood loss and reduced use of blood and clotting products.

### **References**

1. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of Action and Pharmacology of Unfractionated Heparin. *Arterioscler. Thromb. Vasc. Biol.* 2001; 21:1094-1097. <https://doi.org/10.1161/hq0701.0936862>. Tahir R. A review of Unfractionated Heparin and its Monitoring. *US Parm.* 2007; 32: H26-HS36.
3. Teoh KHT, Young E, Blackall MH, Roberts RS, Hirsh J. Can extra protamine eliminate heparin rebound following cardiopulmonary bypass surgery? *J Thorac Cardiovasc Surg.* 2003;128:211-9. <https://doi.org/10.1016/j.jtcvs.2003.12.023>
4. Boer C, Meesters MI, Veerhoek D, Vonk ABA. Anticoagulant and side-effects of protamine in cardiac surgery: anarrative review. *Br J Anaesth.* 2018; 120(5):914-927. <https://doi.org/10.1016/j.bja.2018.01.023>
5. Sokolowska E, Kalaska B, Miklosz J, Mogielnicki A. The toxicology of heparin reversal with protamine: past,

- present and future. *Expert Opin Drug Metab Toxicol.* 2016; 12: 897-909.  
<https://doi.org/10.1080/17425255.2016.1194395>
6. Kimmel SE, Sekeres M, Berlin JA, Ellison N. Mortality and adverse events after protamine administration in patients undergoing cardiopulmonary bypass. *Anesth Analg.* 2002; 94:1402-8.  
<https://doi.org/10.1213/00000539-200206000-00005>
  7. DeLucia, Wakefield TW, Kadell AM, Wroblewski SK, VanDort M, Stanley JC. Tissue distribution, circulation half-life, and excretion of intravenously administered protamine sulphate. *ASAIO J.* 1993;39(3):M715-8.  
<https://doi.org/10.1097/00002480-199339030-00108>
  8. Stehle G, Wunder A, Sinn H, Schrenk HH, Friedrich EA, Dempfle CE, Maier-Borst W, Heene DL. Complexes of a low-molecular-weight heparin with protamine are predominantly cleared by macrophage scavenger receptor-mediated process in rats. *J Surg Res.* 1995; 58:197-204.  
<https://doi.org/10.1006/jsre.1995.1031>
  9. Gollub S. Heparin Rebound in Open Heart Surgery. *Surg.Gynecol.Obstet.* 1967;124:337.
  10. Chaney MA, Devin Roberts J, Wroblewski K, Shahul S, Gaudet R, Jeevanandam V. Protamine Administration Via the Ascending Aorta May Prevent Cardiopulmonary Instability. *J Cardiothorac Vasc Anesth.* 2016 Jun;30(3):647-55. doi: 10.1053/j.jvca.2015.11.014. Epub 2015 Nov 19. PMID: 26948466