NEW STRATEGIES OF HEPARIN IMMOBILIZATION TO IMPROVE BLOOD COMPATIBILITY OF TITANIUM

Janna Kuchinka (1), Thomas Groth (1, 2)

1. Department Biomedical Materials, Martin Luther University Halle-Wittenberg, Germany, Interdisciplinary Center of Material Science Halle, Germany

Introduction

Acute and chronic heart failure are major challenges in modern medicine. Ventricular assist devices (VAD) made of titanium (Ti) alloys as implantable axial pumps have provided solutions to keep patients alive. Long-term application of VAD requires systemic anticoagulation, which decreases the risk of thrombosis but increases that of bleeding. Particularly, the cannula inserted in the ventricular region is prone to thrombotic complications. Therefore, we studied here strategies to improve the blood compatibility of Ti by durable covalent or adsorptive binding of heparin.

Methods

Glass slides were coated with Ti by metal vapor deposition used as model substrata. Subsequently, Ti was oxidized using UV light. Modification of Ti-coated slides was done with organosilanes (OS) providing amino groups for side-on of non-fractionated (HepA) or end-on of degraded (HepB) immobilization of heparin (Hep) [1]. An additional sacrificial coating of Hep was achieved by adsorption of multilayers (PEM) combining polycations with anti-bacterial properties and non-fractionated heparin (pA/Hep; CHI/Hep) [2]. Blood compatibility studies of these coatings was performed with a Factor Xa assay (FXa), [3] a commercial aPTT assay, and by platelet (PLT) adhesion studies [4].

Results

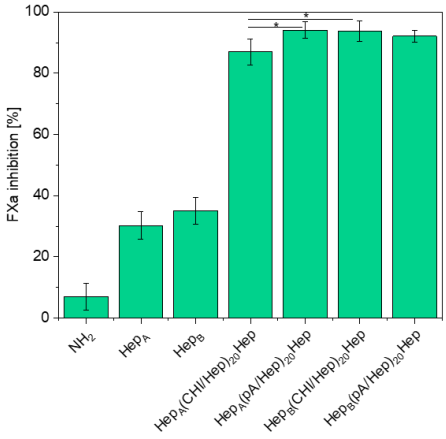

Figure 1: Inhibition of factor Xa by heparinization

Fig. 1 shows the results of FXa assay with an inhibition of its activity already achieved by covalent binding. Indeed, the inhibition was almost complete when a sacrificial layer of heparin was bound as multilayer in combination with polycations like chitosan (CHI). Studies with whole blood clotting assay aPTT yielded comparable results showing that covalently attached heparin, both side-on and end-on bound, prolong clotting times significantly in comparison to oxidized Ti while addition of a sacrificial Hep as PEM inhibited coagulation of human plasma completely.

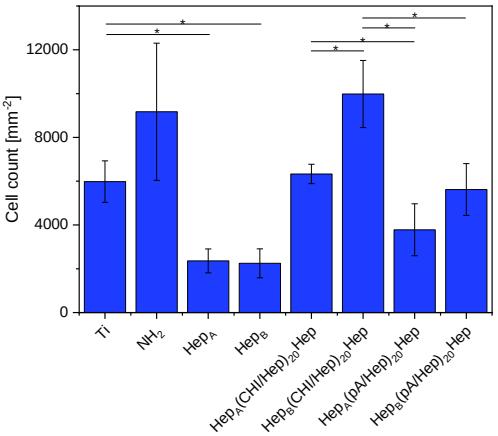

Figure 2: Reduction of platelet adhesion on coatings

PLT adhesion studies were conducted showing that Ti and the OS layer (NH_2) were thrombogenic while platelet number was low on surfaces with covalently bound Hep. PEM with Hep as polyanion increased PLT adhesion, particularly with CHI as polycation which indicated that the flow conditions might be an important further parameter since PLT assay was done under static conditions.

Discussion

The covalent immobilization of OS enabled the durable covalent binding of Hep either in side-on or end-on fashion. The negative charge of the bound Hep also permitted the adsorption of PEM with Hep as polyanion providing a release system with additional anticoagulant activity. Interaction of covalently bound Hep with anti-thrombin III enabled not only direct inactivation of FXa but also increased blood clotting times, particularly when with PEM releasing Hep. The negative charge of covalently bound Hep also decreased PLT adhesion significantly compared to plain Ti.

References

1. Köwitsch et al. Biotech. Appl. Biochem. 58:376-389, 2011.
2. Aggarwal & Groth, JBMR 102: 4224-4233, 2014.
3. Groth & Wagenknecht, Biomaterials 22: 1227-1234, 2001.
4. Huang et al, Marcomol. Biosci. 11:131-140, 2011.

Acknowledgements

This work was supported by grant Gr1290/13-1 to T.G. from Deutsche Forschungsgemeinschaft. We are grateful to Prof. Dmitry Telyshev from MIET Moscow for co-initiating this project.