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Design and Optimization of an In-Vitro Emboli Detector for Flow-Induced Thrombogenicity Evaluation

Ram Shtoltz, Uri Zaretsky
Dept. of Bio-Medical Engineering, Tel Aviv University
Tel Aviv, Israel
ramshtol@mail.tau.ac.il; uriza@eng.tau.ac.il

Shmuel Einav
Dept. of Bio-Medical Engineering, Tel Aviv University
Tel Aviv, Israel
einav@eng.tau.ac.il

Extended Abstract

Ischemic heart disease (IHD) is the most common type of heart disease, responsible for the death of nearly 380,000 people annually in the US alone (Hoyert, D.L et al., 2012). The victims of IHD have invariably been found to have platelet and fibrin thrombi in their myocardium (Frink, R.J et al., 1988). Knowing these numbers, it comes as no surprise that the process of approving an implanted cardiovascular device with the FDA requires extensive thrombogenicity assessment tests.

It is a well-established fact that abnormal shear stress initiates thrombosis (Miyazaki, Y et al., 1996). Flow-induced thrombosis is one of the main areas of interest when evaluating an implantable cardiovascular device, as it is crucial to know whether the device will affect the blood flow regime in a way that would initiate thrombosis.

An in-vitro experimental setup was designed and optimized with the goal of providing a relatively simple, yet accurate, evaluation of the thrombogenicity of different cardiovascular implantable devices.

One of the major difficulties when planning such a system is the positive feedback mechanisms that exist in the coagulation cascade. To be able to assess accurately a thrombogenicity profile, platelets activation mechanisms should be restricted to flow disturbances (e.g., abnormal shear stresses) only. The positive feedbacks of platelet activation are mediated, among other substances, by thrombin, adenosine diphosphate (ADP) and thromboxane A2 (TXA2). K. Hosokawa et al. (2014) recently showed that by adding a PAR1 receptor antagonist (inhibits thrombin-induced aggregation), along with Aspirin (inhibits the production of TXA2) and a $P2Y_{12}$ receptor antagonist (inhibits ADP-induced platelet aggregation), the feedback ability of activated platelets can be significantly reduced. Therefore, platelets activation will be mostly limited to abnormal blood shear stresses.

A flow chamber system was designed with the aim of identifying and measuring the flowing emboli. The flow induced thrombogenicity simulator was comprised of a closed flow loop of 3 mm diameter infusion set tubing and driven by a peristaltic pump. The working fluid was human platelet-rich plasma (PRP) at 37℃. A short segment of the flow loop was comprised of a crystal clear silicone, from which images of embolism formation and build up were continuously captured using a digital camera (uEye®, IDS Imaging Development Systems GmbH, Obersulm, Germany) and recorded using a custom made software (LabView®, NI Corporation, Austin, Texas, USA). For rapid and powerful illumination of the embolism, a pulsatile NdYag 532 nm laser was utilized (New Wave Research, Fremont, California, USA). Post-processing included detection and sizing of emboli and statistical analysis was performed on emboli count and size over time (MATLAB, MathWorks®, Natick, MA, USA). In Vitro tests were performed under a constant flow rate of 19 ml/min, which accounts for mean coronary flow rate at rest

(Re~118). In these tests various compositions of the anti-platelet cocktail were investigated, for optimization of reduction of the platelets' positive feedback.

Preliminary results show that with the reduction of the positive feedback mechanisms, the process of emboli formation was noticeably more gradual. Thus, the flow-induced thrombogenicity footprint of a device can be estimated with increased sensitivity.

Over the past years several other systems have been proposed (Jesty, J et al., 2003). These systems are highly effective for design optimization of the cardiovascular device, yet operating such systems is costly and time consuming. In contrast, the proposed method is aimed to act as a preliminary quick and inexpensive test for rapid evaluation of a device thrombogenicity, before considering stepping into a costly optimization process.

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