Antiplatelet Agents Efficacy after Exposure to Dynamic Shear Stress Profiles

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Despite their efficacy, mechanical circulatory support (MCS) systems remain plagued by post-implantation thrombosis. Patients with implanted devices are burdened with complex, life-long anticoagulation therapeutic regimens, which include conventional anti-platelet agents, i.e. Aspirin, Pentoxifylline, and Integrilin (Eptifibatide) aimed at limiting platelet activation. The efficacy of these drugs in reducing thrombotic complications, as a result of non-physiological flows and high shear exposure, is not well understood. We hypothesized that despite efficacy at low shear, conventional anti-platelet agents will be inadequate in limiting platelet activation resulting from high shear stress exposure such as that in MCS devices. **Methods.** Platelets were collected from healthy drug-free donors, gel filtered and incubated with varying concentrations (mimicking human therapeutic blood levels) of each anti-platelet agent for 10 min. Treated-platelets were exposed to a dynamic shear stress waveform extracted from numerical simulations of a DeBakey VAD utilizing a Hemodynamic Shearing Device [1] for up to 10 min, with non-drug treated platelets as control. Platelet activation at 2, 5 and 10 min was measured utilizing the PAS assay [2]. **Results.** At the shear stress level tested none of the anti-platelet agents investigated provided significant inhibition of shear-mediated platelet activation. **Conclusion.** Despite being a standard-of-care when examined under controlled conditions current conventional anti-platelet agents provide little to no inhibition of shear-mediated activation, at levels of shear actually experienced in MCS devices. Opportunity exists for developing agents and strategies to specifically modulate high shear- mediated platelet activation as occurs in MCS devices.

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[2] Jesty J, Bluestein D. *Acetylated prothrombin as a substrate in the measurement of the procoagulant activity of platelets: Elimination of the feedback activation of platelets by thrombin.* Anal Biochem. 1999;272(1):64-70.