Microfluidic emulators of ventricular assist device shear stress patterns: Lab-on-a-Chip test benches for platelet activation under dynamic device-like shear flow

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INTRODUCTION. Ventricular assist devices (VADs) are currently used to provide restoration of hemodynamics in patients with heart failure. However, VADs have been frequently affected by thrombosis, mainly due to the altered shear stress conditions they expose platelets to [1, 2]. VAD patients are treated with anti-thrombotic drugs, but these therapies often turned out to be ineffective. Many research have been conducted on this issue, which highlighted the need for frequently monitoring the thrombotic risk of patient blood under dynamic shear flow conditions and under the effect of different drugs, with the aim of allowing personalization of anti-platelet therapies and enhancing device performances and patient safety. In this context, we designed and realized novel PDMS-based microfluidic platforms able to replicate significant shear stress patterns of medical devices, with the aim of developing a Lab-on-a-Chip device that can be used as a test bench for platelet activation studies under VAD-like shear stress flow conditions.

METHODS. As a test case, we considered the HeartMateII VAD (HMII, Thoratec Corportation, Pleasanton, CA, USA), that was studied through computational fluid dynamic (CFD) analyses in a previous work [3], in which significant dynamic shear stress waveforms along platelet trajectories were extracted. By means of CFD analyses, we designed a microfluidic channel able to replicate one of those waveforms when perfused at a constant flow rate. First prototypes of PDMS microfluidic platforms were realized through standard soft lithography, starting from the designed channel unit. Preliminary *in vitro* tests were performed with the aim of characterizing the PDMS devices: the platforms were perfused in a closed loop configuration with ovine gel-filtered platelet (GFP) using a peristaltic pump. Platelet activation at different time points was tested using the platelet activity state (PAS) assay [4].

RESULTS. The design of the microfluidic channel unit (HMII microfluidic) is shown in Fig. 1a.

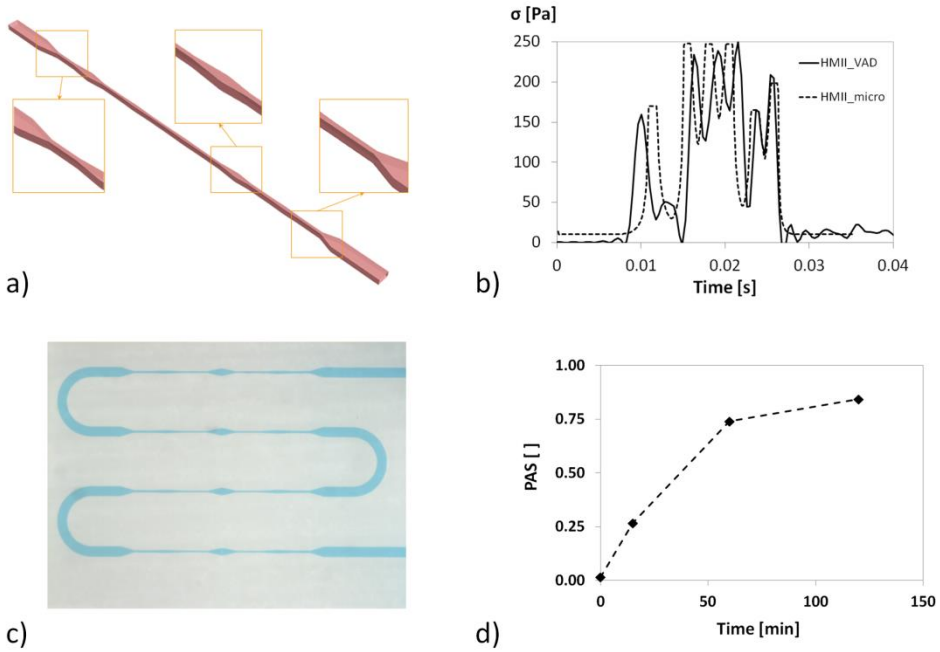

Figure 1. a) 3D CAD of the designed microfluidic channel. b) Significant shear stress waveforms of the microfluidic channel and the HMII VAD. c) Optical microscope image of the PDMS microfludic platform. d) PAS over time obtained from the *in vitro* tests.

The channel is characterized by a constant height (50 µm), while its width was modulated longitudinally in order to generate the desired shear stress pattern. In Fig. 1b, a significant shear stress waveform of the HMII microfluidic is shown and compared to the HMII VAD waveform. The results of the *in vitro* tests performed on the PDMS microfluidic platforms (Fig. 1c) are reported in Fig. 1d, where the PAS is shown at different time points. The platforms induced a high level of platelet activation with a non linear trend, which tended to a plateau close to the maximum level of PAS of the sample.

DISCUSSION. In this work we demonstrated the feasibility of using microfluidic technologies to design microfluidic platforms able to replicate the dynamic shear stress patterns of VADs. We performed preliminary characterization tests of the microfluidic devices. The approach seems promising to develop a novel technology that can be advanced to Point-of-Care devices for monitoring patient thrombogenic risk under realistic shear flow conditions. Current studies are focused on developing and testing an *on-chip* platelet activation assay, with the aim of downscaling and integrating the reading onto the microfluidic platform and advance the approach towards a potential Point-of-Care testing procedure.

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