CORONARY MICROVASCULAR DISEASE: HOW TO ASSESS THE LOCAL HEMODYNAMIC CHANGES

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Introduction

Between 50 and 65% of individuals presenting acute chest pain, but without occlusive pathologies of the epicardial coronary arteries, are affected by coronary microvascular disease (CMD) [1]. CMD is a responsible factor for cardiac perfusion impairment, with the endothelium subjected to an inadequate vasodilatory or pathological vasoconstrictive response. This pathology is characterized by a sensible alteration in the microvasculature local hemodynamics and represents a timely and unsolved clinical problem, due to the current diagnostic and treatment challenges. Due to the microscopic dimension, no current imaging or testing modalities consent *in-vivo* visualization of the vessel morphological and hemodynamic changes, delaying the diagnosis and the (limitedly) possible treatment. Aiming at assessing the perfusion impairment (i.e., the degree of the microvascular obstruction) through local hemodynamic descriptors, we develop an integrative platform based on additive manufacturing and computational fluid dynamics (CFD) providing the tool to analyse the hemodynamic alterations occurring in CMD.

Methods

This work is subdivided into an experimental, a computational, and a coupling phase. First, an idealized model of the coronary microvasculature is created. The bifurcating model (Fig. 1-A) is constructed by following the Murray's branching model [2]. The model (1-mm inlet and 0.4-mm outlet diameter) is employed for both the experimental and the computational analyses.

Second, on the experimental side, a hybrid fabrication protocol based on 3D printing and soft lithography (Fig. 1-B) is created. The substrate material is chosen based on surface reproducibility, cyto-compatibility and the similarity to vessel-like structures. Being the 3D printed material cytotoxic, polydimethylsiloxane (PDMS) and polytetrafluoroethylene (Teflon) were compared. To assess the reproducibility of the fluidic chips, surface profile measurements were conducted. Moreover, the cyto-toxicity of the fabricated chips was preliminarily analyzed by culturing HEK cells.

Third, the microvascular tree model is employed for conducting CFD simulations (steady-state, Ansys Fluent) at different perfusion conditions (Fig. 1-E). The boundary conditions for the *in-silico* model were derived from the *in-vitro* flow testing.

Last, increasing levels of perfusion impairment were created (including the physiological 'control' case) by coupling the *in-vitro* and *in-silico* models (Fig. 1-F).

Results

The fabricated Teflon and PDMS chips resulted to be similar: significant differences (p-value < .03) were found in few regions of the PDMS chips due to manual fabrication. Following the HEK cell culture, no statistical differences were found between the PDMS and Teflon chips at harvesting days 3 and 7.

The experimental analysis of the obstructed scenarios provided the out-split boundary conditions for the CFD model, while an inlet flowrate of about 195 μl/min (set as flat inlet velocity of 0.012 m/s) was imposed. The wall shear stress (WSS) distribution was changing in function of the number and location of the occlusions, in agreement with the *in-vitro* measurements. A compensatory effect (different WSS gradients) was noticed in the upper portion of the microvascular tree as function of the obstructions' localization.

Discussion

The reported integrated platform resulted suitable for the analysis of the hemodynamic changes occurring in the coronary microvasculature dysfunction and obstructions. Combining the potential of 3D printing and CFD analysis, this cost-effective platform can further the CMD biomechanical understanding and link to *in-vivo* measurements of coronary flow reserve.

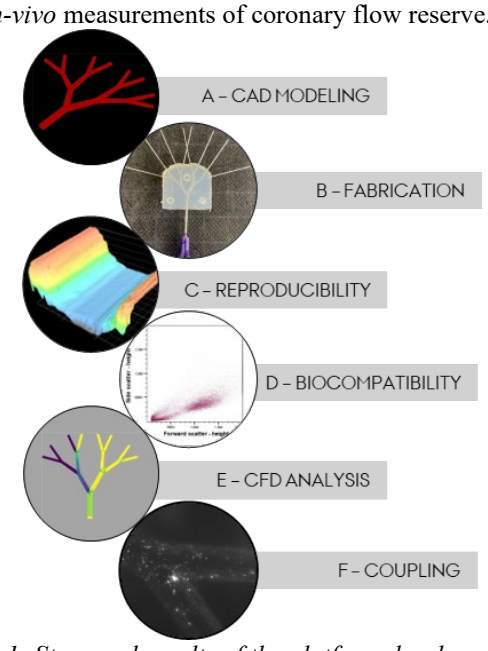

Fig. 1: Steps and results of the platform development.

References

1. Merz et al, Cardiovasc Res, 116:856-870, 2020.
2. Revelling et al, Theor Biol Medical Model, 6(1), 2009.