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A novel passive left heart platform for device testing and research

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ABSTRACT

Integration of biological samples into *in vitro* mock loops is fundamental to simulate real device's operating conditions. We developed an *in vitro* platform capable of simulating the pumping function of the heart through the external pressurization of the ventricle. The system consists of a fluid-filled chamber, in which the ventricles are housed and sealed to exclude the atria from external loads. The chamber is connected to a pump that drives the motion of the ventricular walls. The aorta is connected to a systemic impedance simulator, and the left atrium to an adjustable preload.

The platform reproduced physiologic hemodynamics, i.e. aortic pressures of 120/80 mmHg with 5 L/min of cardiac output, and allowed for intracardiac endoscopy. A pilot study with a left ventricular assist device (LVAD) was also performed. The LVAD was connected to the heart to investigate aortic valve functioning at different levels of support. Results were consistent with the literature, and high speed video recordings of the aortic valve allowed for the visualization of the transition between a fully opening valve and a permanently closed configuration.

In conclusion, the system showed to be an effective tool for the hemodynamic assessment of devices, the simulation of surgical or transcatheter procedures and for visualization studies.

1. Introduction

The use of in *vitro* mock circulation loops for the study of the cardiovascular system and the testing of prosthetic devices dates back to the 1970s [1,2] and finds its rationale in the possibility of performing tests in highly controllable experimental conditions and in a cost-effective way, reducing the need for *in vivo* animal tests. In order to represent realistic models, *in vitro* platforms must be able to effectively replicate the *in vivo* operating conditions the tested device will be subjected to. Being historically associated with the development of mechanical heart valves, the classical approach to the design of mock circulatory systems was purely hydrodynamic-based.

In recent years, however, the need for realistic *in vitro* models has become more stringent due to the substantial changes of the clinical approaches toward reparative, minimally-invasive and transcatheter techniques [3–6]. Moreover, mechanical circulatory support, especially continuous flow left ventricular assist devices (cf-LVAD), has become increasingly adopted, not only as a bridge to transplant but also as a destination therapy [7,8]. For most such applications, the interaction between the implanted device or repaired structure and the *in vivo* environment is not solely limited to the hemodynamics, rather involves broader anatomical and functional aspects that are crucial for the outcome of the procedure. Paravalvular leakage in transcatheter aortic valve (AV) implantation [9,10], complex aortic-mitral interactions following surgical or transcatheter valve treatment [11,12], and AV insufficiency secondary to cf-LVAD implantation [13,14] are only a few examples where an important interplay exists between an intervention applied with a certain therapeutic goal, and the shape and function of the surrounding structures.

Hence, being able to reproduce these aspects is nowadays a challenging, yet fundamental, requirement for any modern *in vitro* mock circulatory loop. In order to model the physiological environment without moving to *in vivo* animal tests, three main experimental approaches are described in the literature: the use of synthetic ventricles [15–17], the integration of passive excised biological samples into artificial *in vitro* setups [18–22], and the use of *ex vivo* beating heart models [23–25]. In particular, the first approach allows for well controllable and repeatable experimental conditions, and is suitable for specific investigational techniques such as particle image velocimetry. At the same time, synthetic ventricles do not allow for the study of surgical approaches, and can hardly reproduce a highly representative

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anatomy. The use of beating heart models allows for a very realistic simulation of the cardiac physiology, still maintaining a good control on the experimental conditions. However, beating heart models are significantly more complex and expensive than classical *in vitro* platforms, thus often representing an effective but inefficient solution either for the evaluation of devices during their early development phase, or for training/educational purposes. With regard to the *in vitro* approach involving passive biological samples, the integration of excised structures into mock circulatory loops is currently evolving from the sole use of excised valves, either aortic [18,26–28] or mitral [19,29], toward the design of platforms able to house entire passive hearts [20–22]. Indeed, the use of entire heart samples ensures a good preservation of the whole cardiac anatomy and allows the testing and analysis of a wider spectrum of devices.

Up until now, the design proposed for passive-heart mock ups consisted of connecting the ventricular chamber through its apex to an external pulsatile pumping system, to attain a cyclical pressurization of its inner volume [20,21]. This approach was shown to fairly replicate physiological hemodynamic conditions and to allow for effective endoscopic visualization of transcatheter procedures [30]. Nevertheless, this methodology presents two drawbacks that limit its applicability: first, it causes a paradoxical motion of the left ventricular walls during the cardiac cycle; secondly, since the fluid flow is provided through the apex, an altered fluid dynamic field inside the left ventricle is produced.

In this paper, we describe a novel *in vitro* platform able to house an entire porcine heart and to mimic the pulsatile pumping function of the left heart through the external dynamic pressurization of the ventricular walls. This represents the complementary approach with respect to that of internally pressurizing the ventricular chamber, and is intended to better simulate the dynamic behavior of the ventricular walls. In order to assess the potential of the passive-heart platform for device-testing applications, we also present a pilot experiment in which a clinical issue was addressed, specifically the interaction between cf-LVAD support and AV functioning. Indeed, clinical data showed that patients under prolonged cf-LVAD support exhibit improper AV function [31–35]. These alterations are related to the level of support and are due to the different hemodynamic environment that the aortic root functional unit is subject to, i.e. dampened aortic pulsatility, increased aortic pressure, decreased left ventricular pressure. This scenario leads to higher pressure load on the leaflets, changes in aortic flow dynamics [32], altered valve opening [33], dilatation of the annulus [36], and may eventually result in cusps fusion [31,35] and AV insufficiency [13,14,32]. In this preliminary experiment, we replicated *in vitro* the acute post-operative scenario after the implantation of a cf-LVAD, showing the potential of the developed system as a platform to carry out research and visualization studies with cardiac devices.

2. Materials and methods

2.1. Mock loop

The functioning principle of the *in vitro* platform (Fig. 1) is to drive the motion of the ventricular walls throughout the cardiac cycle, thus replicating its cyclic pumping function. To achieve this goal, the system should be able to selectively pressurize the left ventricle, while the atria should be excluded from external loads. The setup comprises a fluid-filled chamber (FFC) in which the ventricles of a swine heart are housed (Fig. 2). The FFC is composed of a cylinder ended by two plastic plates that are kept together by three threaded rods, and is connected to a computer-controlled piston pump (PP) (ETB32, Parker Hannifin, The Netherlands), that cyclically injects/withdraws fluid into/out of the FFC, hence directly actuating the ventricular walls.

To achieve the selective pressurization of the ventricle, we developed an *ad hoc* rapid-prototyped vacuum seal, printed with a Polyjet technology (Materialise NV, Leuven, Belgium). This design ensures the sealing of the FFC around the coronary sulcus and constrains the heart so as to avoid its axial displacement under pressure. In this way, proper cyclic actuation of the ventricle is possible. The vacuum seal design was based on anatomical measures carried out on seven porcine hearts, to characterize their typical anatomy and size. It has an ellipsoidal shape and features two flexible lips that allow it to easily adapt to the unavoidable variability in hearts' dimensions and shapes. The connection to the vacuum pump (Air Admiral; Cole-Parmer, Vernon Hills, IL, USA) is ensured through a circular channel in the FFC upper plate, which interconnects the radial holes of the vacuum seal that apply suction on the coronary sulcus epicardium. In order to further improve the stability of the heart, thus avoiding any residual bending and displacement under pressure, the heart apex is fixed to the bottom plate of the FFC by means of a rigid adjustable connector. The connector consisted of a cylinder with a threaded extremity, that was inserted into the left ventricle through the apex, and fixed to the heart with a nut, which was inserted in the ventricle through the mitral valve. For the LVAD experiments, a modified hollowed connector was used to allow for the hydraulic connection of the LVAD to the ventricle.

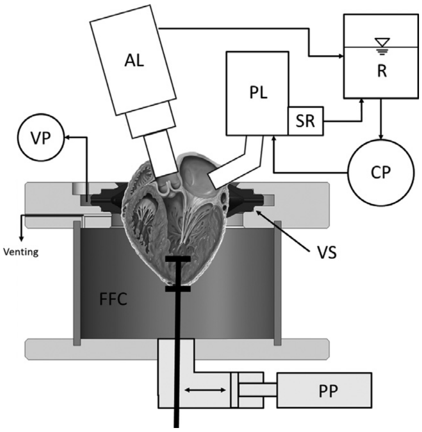

Fig. 1. Schematic of the passive-heart platform: piston pump (PP), fluid-filled chamber (FFC), vacuum seal (VS), vacuum pump (VP), afterload module (AL), reservoir (R), centrifugal pump (CP), preload module (PL), starling resistor (SR).

Fig. 2. Picture of the platform showing the heart housed in the fluid-filled chamber.

As for the hydraulic part of the mock circulatory loop, the aorta is connected to a windkessel afterload module, designed to mimic the human systemic input impedance. In particular, the afterload circuit consists of a compliant polyurethane tube, designed to match the *in vivo* aortic pressure wave speed, and a simple hydraulic module composed of two adjustable resistances and a compliance, so to allow

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