A novel passive left heart platform for device testing and research

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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 effec-tively 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 interac-tions 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 in-tervention 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 con-trol 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 repli-cate physiological hemodynamic conditions and to allow for effective endoscopic visualization of transcatheter procedures [30]. Neverthe-less, this methodology presents two drawbacks that limit its appli-cability: first, it causes a paradoxical motion of the left ventricular walls during the cardiac cycle; secondly, since the fluid flow is pro-vided 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 im-proper 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 aor-tic 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], di-latation of the annulus [36], and may eventually result in cusps fusion [31,35] and AV insufficiency [13,14,32]. In this preliminary experi-ment, 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 devel-oped an *ad hoc* rapid-prototyped vacuum seal, printed with a Polyjet
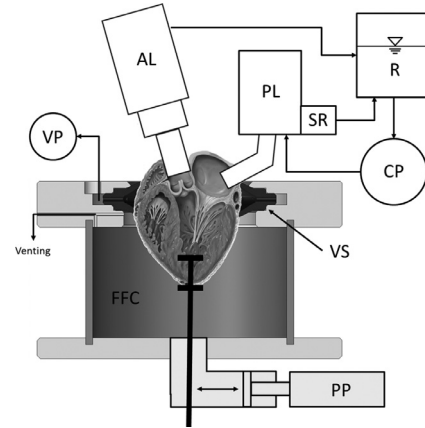

Fig. 1. Schematic of the passive-heart platform: piston pump (PP), fluid-filled cham-ber (FFC), vacuum seal (VS), vacuum pump (VP), afterload module (AL), reservoir (R), centrifugal pump (CP), preload module (PL), starling resistor (SR).
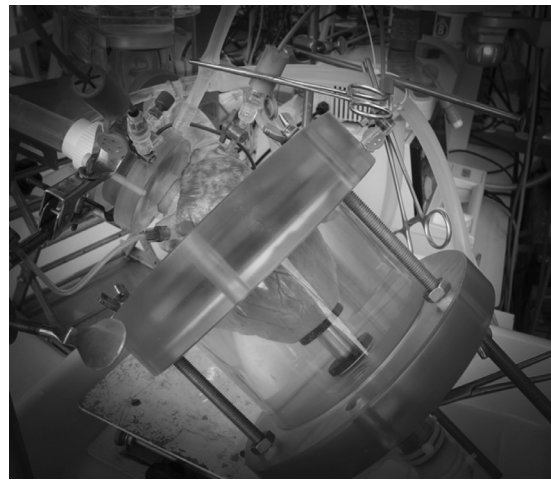

Fig. 2. Picture of the platform showing the heart housed in the fluid-filled chamber.

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, Ver-non 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 mi-tral valve. For the LVAD experiments, a modified hollowed connector was used to allow for the hydraulic connection of the LVAD to the ventricle.

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

for the simulation of different hemodynamic scenarios. The outflow of the afterload drains into a reservoir, from which the fluid is pumped to the preload module by means of a centrifugal pump (Bio-Pump® Plus; Medtronic, Minneapolis, MN, USA). The preload is designed in order to optimize the diastolic filling by actively providing flow to the atrium, thus avoiding negative ventricular pressures during diastole. In particular, the centrifugal pump provides the flow to the preload, and the adjustable Starling shunt maintains the mean atrial pressures at physiological levels also during systole [23]. Moreover, the preload is connected to the left atrium through a compliant silicone tube, aimed at filling the atrial chamber with limited inertial effects.

Accesses for endoscopic visualization and/or transcatheter procedures are provided in the afterload through the aortic polyurethane tube, while the FFC enables the connection of LVADs, the execution of intracardiac endoscopy and the simulation of transcatheter apical procedures.

2.2. Hemodynamic assessment

Fresh entire hearts were harvested at the local slaughterhouse from 100–120 kg pigs, which were killed for the food industry. Pigs were asphyxiated by CO_2, and the hearts were harvested from the production line within 15 min from the death of the animal. The hearts were then submerged in saline solution and transported to the laboratory, where, if no damages and/or pathologies were ob-served, the surgical preparation was performed. Preparation con-sisted of the ligation of the coronary arteries to avoid fluid loss toward the right atrium, and of the connection of the atrium and aorta to *ad hoc* designed connectors. In particular, the pulmonary veins were surgically removed, and the atrium was cut open. Then, a hollowed plastic connector was inserted into the atrial cavity and secured by ty-ing the atrial tissue with cotton laces. Similarly, the aorta was cleaned from any fatty tissue, and separated by the pulmonary artery. A plas-tic connector was then inserted into the ascending aorta and fixed in place with a tie wrap. Finally, the heart apex was also fixed to the respective connector.

The FFC was then filled with room temperature saline (0.9% NaCl) to avoid edema, and the heart was housed in the mock loop with the ventricles submerged in the FFC. Once a correct positioning of the heart was achieved, i.e. with the coronary sulcus aligned with the vac-uum seal, the vacuum pump was switched on and set to 500 mmHg of vacuum pressure. After proper sealing of the heart was ensured, the FFC was completely deaired and the end-diastolic configuration of the ventricular walls was set as follows. With the piston pump hold in its end-diastolic position, fluid was added or removed with a syringe from the FFC in order to maximize the ventricular volume, without creating negative pressures in the FFC itself. This protocol ensured the achievement of a realistic ventricular end-diastolic vol-ume, without inducing unrealistic dilations of the ventricle itself. The aorta and the left atrium were then connected to the afterload and the preload respectively, and the circulatory loop was filled with saline solution, while the right heart was left empty. The piston pump was then gradually activated and the circulatory loop was set to replicate physiologic systemic conditions. In particular, final heart rate was 85 bpm, the afterload module was tuned to obtain physiological aortic pressure tracings (120/80 mmHg), and the stroke volume of the pump was adjusted in order to achieve physiologically relevant cardiac outputs (about 4–5.5 L/min).

Pressures were monitored in the left atrium, in the left ventricle and downstream of the AV with solid state sensors (P10EZ-1; Becton Dickinson Medical, Franklin Lakes, USA). The perivascular sensor for the measure of the pulsatile aortic flow (MA28PAX; Transonic Systems Inc., Ithaca, USA) was integrated in the aortic connector, while the mean cardiac output was measured at the outlet of the after-load circuit (HFM-09-1; LifeTec Group, Eindhoven, The Netherlands). Hemodynamic data were acquired at 1 kHz using a data-acquisition board (PCI 6221; National Instruments, Austin, TX, USA) and running dedicated software (LabVIEW 7.1, National Instruments).

2.3. Pilot study: AV opening in cf-LVAD support

In this preliminary experiment we aimed at replicating *in vitro* the acute post-operative scenario after the implantation of a cf-LVAD. In particular, the hemodynamic and kinematic alterations experienced by the AV were simulated, for different pump speeds, by acquiring hy-drodynamic quantities and high speed video recordings of the valve. A MicroMed deBakey LVAD (MicroMed Technology Inc., Houston, TX, USA) was connected to the apex of the heart through an access in the FFC bottom plate, and ejected directly into the aorta. In order to simulate a realistic clinical scenario, the mock circulatory loop was adjusted to simulate cardiogenic shock hemodynamic conditions, i.e. hypotensive conditions (Fig. 5, top panel) with a cardiac output of 3 L/min. Then, the LVAD was switched on and pump speed was pro-gressively increased from 7500 to 12,500 rpm in 500 rpm steps, with-out changing any of the settings of the mock circulatory loop. Using a 10 mm endoscope (Olympus Europe, Hamburg, Germany), coupled with a high-speed camera (MotionScope M5C; IDT Vision, Tallahas-see, FL, USA) and a light source (Xenon Nova, 300 W; Storz GmbH & Co. KG, Tuttlingen, Germany), AV motion was recorded at 200 frame per second (fps) for every experimental condition, together with hemo-dynamic data. Based on these recordings, the mean AV pressure load and duty cycle, i.e. the fraction of time in which the AV is open during each cardiac cycle, were computed [37].

3. Results

3.1. Mock loop assessment

Fig. 3 shows a representative example of the pressure and flow tracings measured in the mock loop, that were consistent with typi-cal systemic *in vivo* waveforms. In particular, the mean flow rate was 5.2 L/min, the aortic pressure was in the 125/80 mmHg range, ven-tricular pressure was in the 125/0 mmHg range, while the mean atrial pressure was about 18 mmHg.

Regarding the pumping action of the platform, left ventricular stroke volumes showed some variability due to the compliance of the hearts, and were in the range of 46–65 mL, yielding to mean flow rates ranging from about 4 to about 5.5 L/min at 85 bpm, with aor-tic peak flows of 25–30 L/min. Endoscopic visualization of the valves (Fig. 4) qualitatively showed proper leaflet coaptation and no signifi-cant abnormalities in the valve opening and closing dynamics.

3.2. LVAD study

The acute post-operative scenario following the implantation of a cf-LVAD was simulated with the passive-heart platform. Fig. 5 shows the pressure tracings measured in the simulated shock condition (top) and at maximum support (bottom). Mean aortic pressure increased from 62 mmHg to 93 mmHg at maximum pump speed (12,500 rpm), with a significantly reduced pulse pressure (from about 50 mmHg to 15 mmHg). High levels of support also induced negative pressures in both the left atrium and ventricle.

Fig. 6 shows the AV mean pressure load computed over a cardiac cycle, and duty cycle for the different levels of support. As expected, the pressure load acting on the AV increased with increasing pump speed, while the AV duty cycle decreased from physiological levels at no support to zero for pump speeds higher than 12,000 rpm. The high-speed video recordings confirmed these findings and allowed the visualization of AV behavior for the different levels of support. Fig. 7 shows the instances of the AV at its maximum opening for all the tested pump speeds. Consistent with the hemodynamic data, which show a null duty cycle at full support, the AV remained permanently
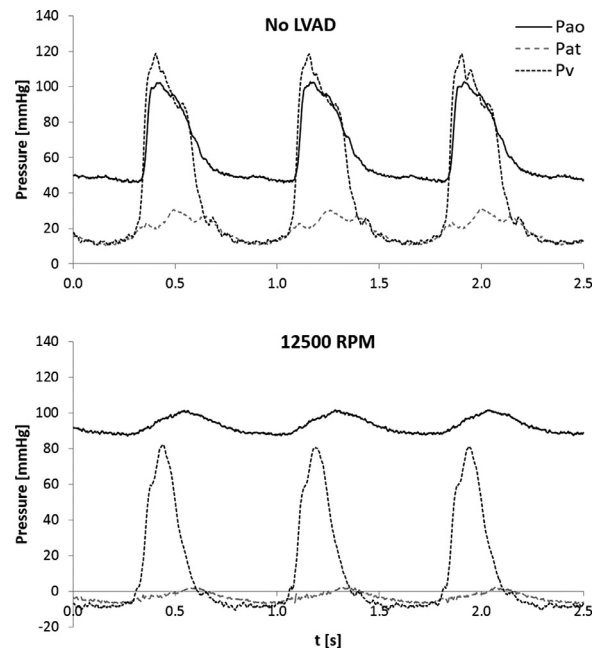
Measured pressures
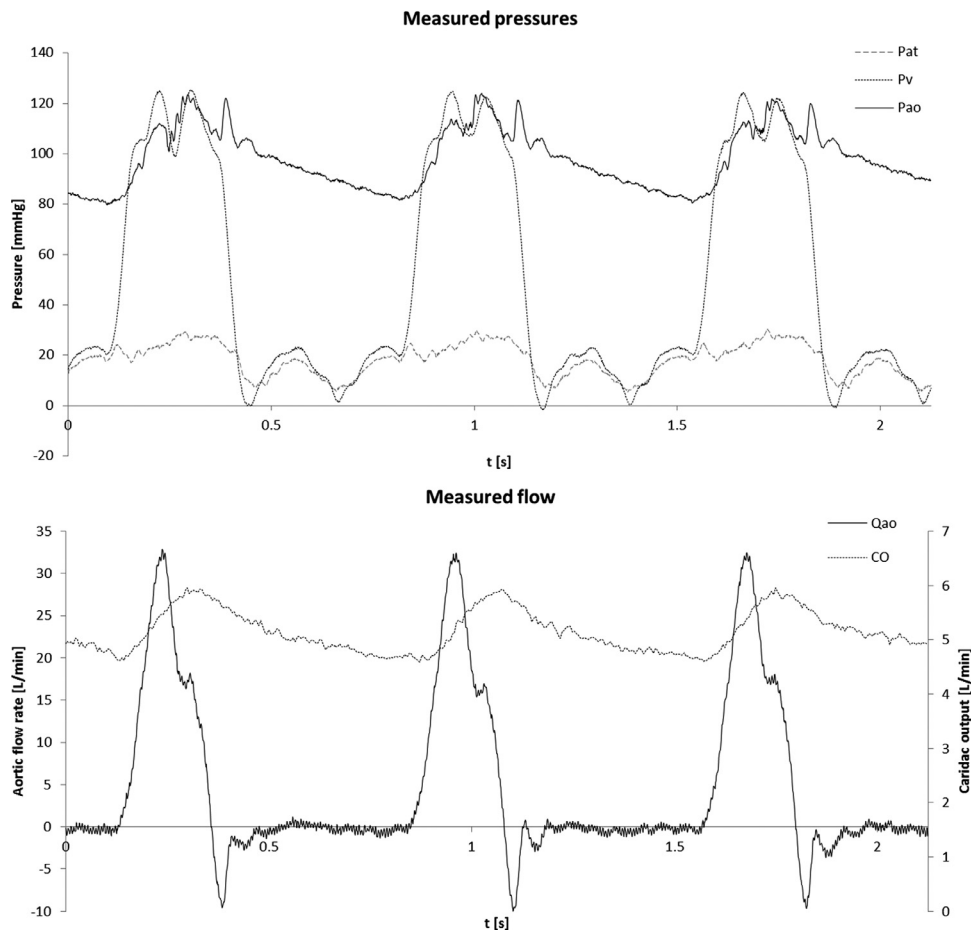
Measured flow

Fig. 3. Representative pressures (top) and flow (bottom) tracings measured in the mock loop. The system was set to simulate physiological systemic hemodynamic conditions. Pat: atrial pressure. Pv: ventricular pressure. Pao: aortic pressure. Qao: aortic flow rate, measured downstream the aortic valve. CO: mean cardiac output, measured downstream of the afterload.
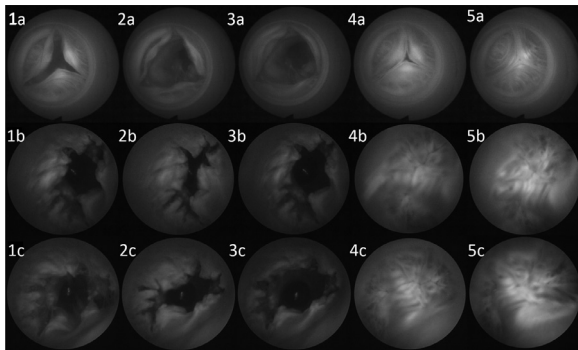

Fig. 4. Representative snapshots of both the aortic (1) and mitral (2–3) valve, recorded with the high speed camera from one of the tested hearts. The five pictures in each line represent different time points throughout the cardiac cycle. In particular, the aortic valve is reported at (1a) beginning of the ejection, (2a) end of the rapid opening phase, (3a) maximum opening, (4a) during the closure phase and (5a) in the closed configuration. The mitral valve is shown (1b–1c) during the E peak, (2b–2c) between the E and A peak, (3b–3c) during the A peak, (4b–4c) at the beginning of the closure and (5b–5c) at peak systole. Line 2 shows the mitral valve with a stroke volume of about 50 mL, showing proper coaptation and a physiological behavior. Line 3 shows the same mitral valve for stroke volumes of 65 mL, with the last snapshot (bottom right) highlighting the prolapse of the anterior leaflet due to the absence of papillary muscle function.

closed only for pump speeds higher than 12,000 rpm. At 11,500 rpm, with a duty cycle of about 5%, AV opening did occur, but without a complete leaflet separation in the commissural region. At 11,000 rpm and lower, with duty cycles higher than 10%, the valve commissures separated completely at peak systole.

Fig. 5. Measured pressures tracings in the cf-LVAD experiment under simulated shock conditions (top) and full support (bottom). Pat: atrial pressure. Pv: ventricular pressure. Pao: aortic pressure.
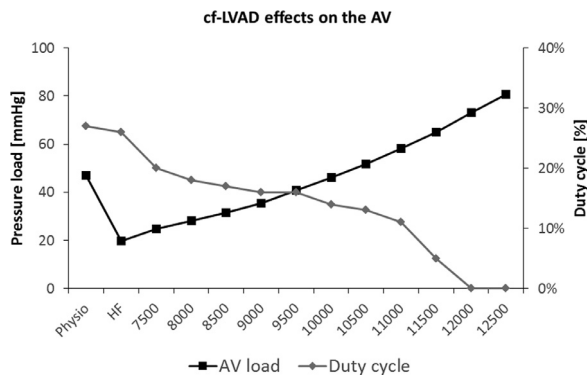
Fig. 6. Mean aortic valve pressure load computed over a cardiac cycle (mmHg) and duty cycle (%) for all the tested condition: physiologic systemic conditions (Physio), heart failure (HF), and different pump speeds.
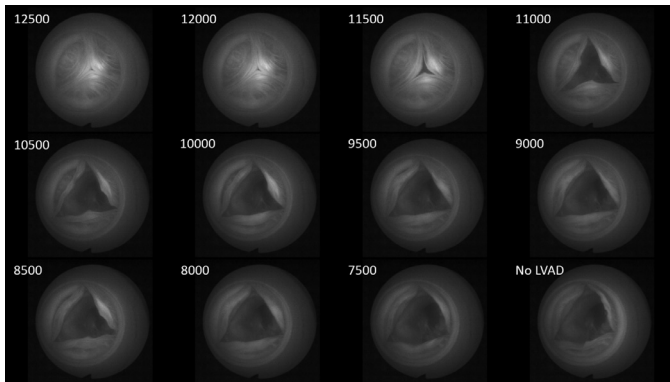
Fig. 7. Snapshots of the aortic valve at maximum opening recorded with the high speed camera for all the tested conditions.

4. Discussion

In this paper, we described a novel *in vitro* platform, able to house an entire swine heart and to simulate its pumping function by driving the motion of the ventricular walls during the cardiac cycle through their dynamic external pressurization. The rationale of the work was to develop a system capable of merging the advantages of the classical hydraulic mock loops, with the preservation of the heart anatomy and with a better mimicking of the *in vivo* pumping action of the heart with respect to the state-of-the-art passive-heart simulators. The mock loop was able to replicate physiological hemodynamic conditions, both in terms of pressure and flow tracings, and showed to be an effective platform for both device-testing and visualization studies.

From a technical viewpoint, the main challenge of the proposed approach was the achievement of an optimal sealing of the pressurized fluid chamber around the coronary sulcus. With respect to this, the design of the flexible rapid-prototyped vacuum seal allowed for an easy, efficient and reliable sealing of the pressurized chamber around the ventricles, enabling physiological ventricular stroke volumes. Together with the hydraulic modules that were used in the mock loop, this ultimately led to the achievement of appropriate hemodynamic conditions in the setup. Moreover, although in this design paper we focused on the simulation of systemic physiological conditions, the wide adjustability of the main circulatory loop components (piston pump, preload and afterload) would reasonably allow for the simulation of different hemodynamic conditions, as demonstrated by the pathological shock scenario that was simulated for the cf-LVAD experiment.

In the experimental assessment, the morphology of all the experimental tracings resembled the typical *in vivo* waveforms. The aortic pressure showed a sharp systolic pressure rise, a dicrotic notch and

a smooth diastolic fall. Similarly, the ventricular and atrial pressure waveforms were as expected, without remarkable oddities. In addition, the measured flow rates were comparable with other *in vitro* state-of-the-art setups [21,23]. Concerning valve function (Fig. 4), endoscopic visualization of the AV showed proper leaflet coaptation and an opening phase qualitatively consistent with other investigations [18,24,27]. Visual inspection of the mitral valve confirmed its conti-nence in all the experimental conditions. However, with increasing stroke volumes, the anterior mitral leaflet progressively exhibited a remarkable prolapse in most of the tested hearts, which occurred without any apparent fluid regurgitation. This behavior was possibly due to two combined reasons: a less-than-physiological tension of the chordae tendineae, caused by the absence of the papillary mus-cle function, and the presence of the vacuum seal that causes a rigid circumferential constrain on the valvular plane. These two aspects could combine and determine a dome-like configuration of the mitral valve during systole, that may explain the tendency of the anterior mitral leaflet to prolapse. This effect showed to become more rele-vant when the ventricular wall motion was more pronounced, i.e. for higher stroke volumes.

The LVAD pilot experiment was meant to demonstrate the potential of the developed mock loop for research, device testing and visualization studies. The passive heart platform was able to effectively simulate the post-operative scenario, allowing hemodynamic measurements with simultaneous visualization of the AV under well controllable experimental conditions. In particular, the hemodynamic and kinematic effects of different levels of mechanical support on the AV function were assessed, obtaining results that are coherent with both clinical observations [33] and published *in vitro* studies [37]. Moreover, the possibility of performing high speed video acquisitions allows deeper insights on the kinematic and morphological alterations that cf-LVAD induce on the AV function. In this experiment, we analyzed AV opening and showed, for duty cycles smaller than 10%, how the AV opens without complete separation of the AV leaflets. This phenomenon only seems to occur in a very narrow pump speed range, just below the speed at which valve opening is completely inhibited (12,000 rpm in our test). This finding may suggest that, for some patients, a fine tuning of the cf-LVAD speed may prevent altered AV opening, still without significantly impairing the support that is given to the patient.

Regarding the behavior of the passive left ventricle, which was the main focus of our design and actuation methodology, the proposed platform represents a more realistic model of the *in vivo* ventricular dynamics if compared to the state-of-the-art passive-heart mock loops. Indeed, the pumping function is obtained avoiding any paradox behavior of the ventricular walls, which is instead typical of the apically actuated platforms [20,21]. However, the complex *in vivo* ventricular physiology that involves a specific distributed, three-dimensional dynamic myocardial contraction with ventricular twisting cannot be mimicked with the proposed approach, which only involves applying a uniform and simultaneous pressure on the whole ventricle epicardium. Similarly, atrial contraction is absent, as the left atrium is not subject to any external load and is only provided with a controlled filling pressure through the preload circuit. Furthermore, our setup was limited to the left heart, and the right ventricle was left unfilled. Although this aspect had reasonably negligible effects on our experimental results, because the behavior of the passive left ventricle are only driven by the pump, ventricular interaction through the septum cannot be studied with our setup.

Some of these limitations could be addressed by future developments. For example, a better simulation of the *in vivo* ventricular dynamics may be achieved with an appropriate and controlled motion of the heart apex, which could be mechanically actuated through the existing apical holder. Also, atrial contraction could be hemodynamically mimicked by actively controlling the preload pressure through an appropriate actuation of the Starling shunt. Future devel-

opments of the proposed platform may also address its evolution into a 4-chamber model of the circulation, facing the challenge of properly managing the different compliances of the ventricles.

With respect to echo imaging, the described setup, at this stage of the design, has some limitations as compared to other passive-heart mock loops [20,21]. Indeed, the access to the heart is inhibited by the presence of the rigid chamber around the ventricles, which could in the future be equipped with an *ad hoc* port. As for the LVAD study, the main limitation lies in the fact that the fluid used, i.e. saline, did not mimic the blood rheology. Indeed, despite the use of saline is widely reported in the literature [28,38,39] it potentially introduces a bias in our findings. Anyway, the mock loop is capable of working with any fluid, including blood. Also, the outflow graft was used to connect the outflow of the LVAD to the aorta was longer than the set of tubes and cannulae used in patients.

In conclusion, the proposed *in vitro* mock circulatory loop represents a valid and cost-effective platform for a wide range of purposes, including devices-testing applications, simulation of valve repair or transcatheter procedures, visualization studies and training.

Conflict of interest

No conflict of interest.

Ethical approval

No ethical approval was required for the present study.

Acknowledgments

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