Published in final edited form as:

Cardiovasc Eng Technol. 2018 September ; 9(3): 339–350. doi:10.1007/s13239-018-0356-z.

Realistic Vascular Replicator for TAVR Procedures

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Abstract

Transcatheter aortic valve replacement (TAVR) is an over-the-wire procedure for treatment of severe aortic stenosis (AS). TAVR valves are conventionally tested using simplified left heart simulators (LHS). While those provide baseline performance reliably, their aortic root geometries are far from the anatomical *in situ* configuration, often overestimating the valves' performance. We report on a novel benchtop patient-specific arterial replicator designed for testing TAVR and training interventional cardiologists in the procedure.

The Replicator is an accurate model of the human upper body vasculature for training physicians in percutaneous interventions. It comprises of fully-automated Windkessel mechanism to recreate physiological flow conditions. Calcified aortic valve models were fabricated and incorporated into the Replicator, then tested for performing TAVR procedure by an experienced cardiologist using the Inovare valve. EOA, pressures, and angiograms were monitored pre- and post-TAVR. A St. Jude mechanical valve was tested as a reference that is less affected by the AS anatomy. Results in the Replicator of both valves were compared to the performance in a commercial ISO-compliant LHS.

The AS anatomy in the Replicator resulted in a significant decrease of the TAVR valve performance relative to the simplified LHS, with EOA and transvalvular pressures comparable to clinical data. Minor change was seen in the mechanical valve performance.

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Compliance with ethical standards

Conflict of interest

Author OR was a consultant for Vascular Simulations LLC. Author BK is partly employed by Vascular Simulations LLC. Author CS has stock ownership in Vascular Simulations LLC. Author BL has stock ownership in Vascular Simulations LLC. Author LG declares that he has no conflicts of interest. Author DB declares that he has no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was waived by the Stony Brook University Institutional Review Board as this study was retrospective and the CT scans for this study were received anonymized. This article does not contain any studies with animals performed by any of the authors.

The Replicator showed to be an effective platform for TAVR testing. Unlike a simplified geometric anatomy LHS, it conservatively provides clinically-relevant outcomes and complement it. The Replicator can be most valuable for testing new valves under challenging patient anatomies, physicians training, and procedural planning.

Keywords

TAVI; Aortic Stenosis; Aortic Valve; Mitral Valve; Prosthetic Valve; 3D Printing

1. Introduction

Calcific Aortic Valve Disease (CAVD) is a progressive cardiovascular disease in which calcifications form at the aortic root and valve. With CAVD progression into severe Aortic Stenosis (AS) the valve leaflets stiffen, and at times may fuse together, up to the point that they cannot open and close properly, leading to aortic insufficiency. CAVD afflicts approximately 0.9% of the United States population with 2.8% of people over 75 years of age having moderate to severe AS [1]. The 2-year survival rate after onset of hemodynamically significant AS in untreated patients is 50% and declines to 20% at 5 years with a rapid decline in survival thereafter [2].

Over the last decade Transcatheter Aortic Valve Replacement (TAVR) has become a life-saving alternative for patients who cannot tolerate open-heart surgical valve replacement [3]. TAVR is an over-the-wire endovascular procedure in which a stented valve is crimped onto a low-profile delivery catheter, then guided into the aortic root location percutaneously via a small incision in a peripheral artery (commonly, the femoral artery in a trans-femoral approach), and deployed inside the calcified valve, pushing the native leaflets aside without removing them. The success of FDA-approved TAVR devices such as the Edwards SAPIEN and the Medtronic CoreValve was promising [4, 5], yet not free of complications such as paravalvular leaks (PVL), bleeding, stroke and platelet activation [6–8] that impede the inclusion of younger and lower risk patients in the newest clinical trials [9]. These persistent complications drive current research and development of newer generation TAVR devices and concepts.

Hydrodynamic testing of transcatheter prosthetic valves is guided by ISO-5840-3, which defines in detail the bench-testing hemodynamic conditions, data recording and processing. Such testing of prosthetic valves (either surgical or TAVR) is usually performed using piston-driven hydrodynamic pulse duplicators that utilize Windkessel elements for replicating physiological flow and pressure conditions across the valve. An example of a piston driven system is the Vivitro Pulse Duplicator (PD) (Vivitro Labs Inc., Victoria, BC), which comprises a simplified aortic root and aorta geometries (straight rigid tube without a native valve). Other commercial simulators include the pulsatile pump systems created by BDC laboratories (Wheat Ridge, CO, USA) which can include simplified ventricle and aorta geometries. Adjustment of the Windkessel compliance and resistance for these simulators require manual adjustment from the operators. While idealized anatomy may provide sufficient baseline for testing and comparing new valve devices, it evaluates valves in an

ideal scenario that is often far from the reality (*in-situ*) of a severe AS patient [10], and lacks the variability of post-procedural outcome due to complex anatomy [11–15]. Thus, overestimation of the valve performance may occur. Modifications to the Vivitro PD, such as custom fabrication of an elastic mock aortic valve for TAVR testing has been described by Rahmani *et al.* [16]. While this made the testing conditions closer to reality, the aortic root anatomy was still being simplified with non-calcified leaflets and straightened ascending aorta. In the academic field, Georgia Tech has developed many novel heart simulators utilizing adaptations to biological specimens of the aortic root and valves, as well as integration of additional imaging modalities of PIV and echo ultrasound [17–21]. Other academic pulse duplicators worldwide commonly share the traditional simplified anatomy [22–25]. With recent improvements in rapid prototyping techniques, fabrication of elastic aortic root anatomy for *in-vitro* testing is becoming more accessible [26–29, 10]. Mock calcified valves for testing of TAVR valves have been reported before, whether homogeneously calcified [30], or even a complete patient-specific calcified aortic root [28, 29], showing promising concepts toward more realistic *in-vitro* testing of TAVR devices.

With TAVR expanding to new indications such as to younger and lower risk patients, growing number of medical centers worldwide adopting its use, and the emergence of new TAVR devices, there is a growing need for a platform that can provide medical and R&D teams with a realistic simulator of the procedure. Such a simulator would allow for direct comparison of valve types and deployment strategies for procedure planning in diverse patient anatomies. Having a stable repeatable simulator would additionally provide an opportunity to develop a consistent training program for physicians.

We report on a new pulse duplicator, aka Replicator, for bench TAVR testing and training, utilizing realistic patient-based anatomy. The emphasis here is on the ability to test TAVR devices in anatomically accurate aortic roots of CAVD patients that are challenging both the procedure as well as the post-procedural outcome, without putting a patient at risk. The Replicator was evaluated in a complete TAVR procedure in the cath-lab using a 24 mm Inovare valve (Braile Biomédica, Br). The valve post-procedural performance was compared to results from an ISO-compliant simulator. Importantly, the patient-based replicator was evaluated here as a complementary method for testing TAVR valves, in addition to the traditional and more simplified pulse duplicators; While the latter evaluate baseline performance of the valves, the former adds the anatomical variability of CAVD patients and may therefore capture associated complications or consequences.

2. Materials and methods

2.1 The Replicator

The Replicator is a compact upper body arterial simulator (iliac arteries to left ventricle, and optionally to the cerebral arteries) designed specifically for catheterization procedures (Fig. 1a). Flow is driven by a pneumatic system that induces compression in the left ventricle model, which along with a compressing atrium, creates a functional left heart system. Flow and pressure are governed by fully automated built-in Windkessel elements (compliance and resistance) to recreate human physiological waveforms, which actively update during the operation leading to no user variability and time effective testing. A feedback mechanism

was designed to maintain consistent 120/80 mmHg aortic pressure at a stable heart rate regardless of the geometry of the silicone anatomy. Flow rate and cardiac output (CO) is controlled by independent control of outflows of the anatomy. The active feedback allows for the capture the nuances of the surgical procedure, for example the occlusion of arteries from the larger catheters and the difficulty of guiding the TAVR into the correct position. The entire procedure can be performed by a physician in a catheterization lab under fluoroscopic guidance. All the silicone mock arteries are reconstructed based on CT scans from patients and molded with consistent compliance. Previously the Replicator has been used for pre-clinical trial planning [31] and as a medical imaging flow phantoms [32].

2.2 Aortic root anatomy

The aortic root and aortic valve geometry are modular, and were designed for quick access and fast removal for an intended use of TAVR training and testing (Fig. 1). Four aortic valves (annulus size 20.5 mm) fabricated from composite elastomer were provided by Vascular Simulations LLC (Stony Brook, NY, USA) and tested in this study: Moderate CAVD flexible (30 Shore-A durometer, aka 'M-CAVD-30'), Moderate CAVD stiff (50 Shore-A, 'M-CAVD-50'), Severe CAVD flexible (30 Shore-A, 'S-CAVD-30'), Severe CAVD stiff (50 Shore-A, 'S-CAVD-50'). The four aforementioned valves are based on CT scans of the same patient, which were provided anonymously by Stony Brook University Hospital after obtaining approval from the institutional review board. Calcific deposits were added to the mold for the severe CAVD (S-CAVD-30 and S-CAVD-50) valves versions (Fig. 1b). The leaflets thickness and the added calcific deposits onto the aortic side of the leaflets are based on data from *ex-vivo* samples of calcified aortic valve leaflets, and available data from the literature [33–35].

2.3 Valve testing

TAVR procedure was performed using a balloon-expandable 24 mm Inovare valve (Braile Biomédica, Br) by an experienced cardiologist. Access and deployment of the Inovare valve were performed by a trans-femoral approach using a 14 Fr delivery system of an Edwards SAPIEN 3 system (Edwards Lifesciences, Irvine, CA, USA). This delivery system was designed to work with the SAPIEN 3 valve. The Inovare valve has very similar dimensions as the SAPIEN 3 valve and is similarly a balloon expandable valve, thus fully compatible for deployment using this delivery system. As the Inovare valve is not intended to be crimped to 14 Fr size like the SAPIEN 3 valve, we have employed a larger French size crimping. The valve was removed from its packaging and rinsed with saline per the manufacturer guidelines. The valve was crimped onto the delivery system less than 20 minutes prior to deployment. Deployment of the Inovare valve was performed once, on the 50 Shore-A severely calcified valve model (S-CAVD-50). For reference, a 29 mm St. Jude surgical Regent™ mechanical valve was mounted in the aortic root location using a 3D-printed custom holder that replaced the aortic valve model.

Prior to the procedure, the Replicator was loaded with 2 liters of a blood analog fluid (50.3% Glycerol, 48.8% dH₂O, 0.9% NaCl, by weight) at a maintained temperature of 37°C, providing blood dynamic viscosity of 3.5 mPa·s. Pressure was monitored and recorded using fluid-filled pressure lines that were connected to the ascending aorta and the left ventricle

(Validyne DP15, Validyne Engineering, Northridge, CA USA) (Fig. 2). Example for pressure recordings with the S-CAVD-50 calcified valve model can be seen in Fig. 3. Importantly, the Replicator was designed to work with severe CAVD anatomical models that might affect the pressure and flow waveforms. Pressure recordings were filtered using a digital low pass filter at 30 Hz cutoff frequency. An 8 mm diameter endoscopic camera was inserted into the Replicator's brachiocephalic artery for monitoring the TAVR valve deployment in real time. Angiography videos (Artis Zeego, Siemens Healthcare GmbH, Erlangen, Germany) of contrast agent injection (Omnipaque® 300, Iohexol, GE Healthcare Inc, Princeton, NJ USA) were taken before and after the procedure by placing a 5F pigtail catheter at the aortic root location, and were used for evaluating feasibility of identifying and quantifying PVL. The injections were performed with a Medrad power-injector with 20 ml of contrast injected at 15 ml/s and pressure of 4 atm. Flow was measured continuously at two locations: cerebral flow and downstream of the iliac arteries with an inline flow probe (MPX6 and MPX10, Transonic Inc., Ithaca, NY USA). Temporal CO was calculated as the sum of the two flows.

Evaluation of the valves performance was done by calculation of the effective orifice area (EOA) per ISO-5840-3, mean trans-valvular pressure drop ($P=P_{Ventricle}-P_{Aorta}$), and aortic regurgitation (AR) evaluated qualitatively using angiograms. 'Pre-treatment' angiograms were acquired with the native valve models (severe or moderate CAVD). 'Post-treatment' angiograms were acquired with the deployed Inovare valve, as well as the mechanical valve. All the valves were tested under varying CO in the range of 1.5-7.0 L/min at 70 bpm.

In order to assess the difference in valve performance in the Replicator to that in an idealized, ISO 5840-3 –compliant, left heart simulator, the Inovare valve was also mounted in a Vivitro PD in similar size aortic annulus (20.5 mm) and tested under equivalent CO. The St. Jude mechanical heart valve was also tested in the Vivitro PD to verify similarity in the hemodynamic conditions between the two simulators. The mechanical valve was expected to be less affected by the patient-specific anatomy of the replicator since the native leaflets are dissected during the actual procedure and thus do not affect the valve deployment and performance. Testing in the Vivitro PD was performed using the aforementioned blood analog at 37°C. Systolic-diastolic ratio was set to 0.35:0.65 at 70 bpm. Pressure measurements were filtered using an analog low pass filter at 30 Hz cutoff frequency. Both in the Replicator and in the Vivitro PD, air bubbles were carefully removed from the pressure lines for ensuring minimum distortion to the pressure recordings. Also, pressure difference between the aortic and ventricular pressure lines was offset to zero to eliminate effects of the height difference between the pressure lines.

3. Results

3.1 TAVR procedure in the Replicator

The TAVR procedure commenced by crimping the Inovare valve onto the balloon-expandable delivery system. We note that since a previously clinically deployed delivery system was used, the balloon was not factory-folded, which lead to a larger overall profile of about 20F. The sleeve of the delivery system was then pushed toward the tip of the catheter to hold the crimped valve in position. No pre-dilatation was used on the mock calcified valve

prior to the TAVR procedure. The loaded delivery system was then introduced into the mock vasculature via femoral access, and was advanced using a pre-positioned guidewire into the aortic root (Online Video 1). At the aortic arch region, bending was added to the tip of the delivery catheter using the control handle, to allow for easier crossing of the arch curvature. Multiple attempts were required to cross the calcified valve (S-CAVD-50); the guidewire naturally positioned itself at the joint region between two calcified leaflets, and taken together with the small opening area of the valve, and the relatively large profile of the crimped Inovare (20F), made it difficult to cross. The TAVR valve was then moved gently along the aortic valve axis until the interventionist was satisfied with its position. The left ventricle pumping was then ceased as an alternative to the rapid pacing that is traditionally used for minimizing the aortic root motion. We used this simplified approach in order to avoid excessive pressure in the left ventricle during the inflation of the balloon. The balloon was then inflated using a power-syringe, and immediately deflated thereafter (Online Videos 2-3).

3.2 Valve performance

Fig. 4 depicts the performance of the mock valves mounted in the Replicator system, either moderately or severely calcified, for both the 30 Shore-A or the 50 Shore-A polymeric formulations, respectively. Negligible effect on EOA is evidenced between the 30 and 50 Shore-A elastomer formulations for both the moderately and severely calcified valves. Slight effect was noticed on the pressure drop between the M-CAVD-30 and the M-CAVD-50 valves, with the former reaching higher CO. As expected, the severely calcified valves had lower EOA and higher mean pressure drop, exceeding the 40 mmHg that classifies severe aortic stenosis [36, 37]. Due to the higher resistance of the severe CAVD models, the maximum CO reached was only about 3 L/min. The moderate CAVD models reached EOA in the range of 0.7-1.3 cm² and pressure gradient in the range of 20-31 mmHg, which are also in compliance with the clinical classification of moderate AS [36, 37].

Post-procedural evaluation of the TAVR valve was performed using angiography and contrast injection. Aortic regurgitation was observed for all the CAVD models as well as post-TAVR in the S-CAVD-50 model (Fig. 5, and Online Videos 4-5), yet it was difficult to determine in the post-TAVR case whether the source of the regurgitation was mainly paravalvular (PVL), transvalvular, or both. The TAVR valve was then extracted together with the mock calcified valve, which revealed two small PVL 'channels' in the commissure regions of the calcified valve leaflets, with estimated diameter < 1 mm (Fig. 5e). The angiography image additionally revealed a slight narrowing at the center of the TAVR valve (eccentric hourglass shape, see Fig. 5d), that likely resulted from the position and the luminal protrusion of the calcific deposits.

Comparison of the Inovare valve performance in the Replicator patient-specific scenario versus in the Vivitro PD- in terms of EOA and average transvalvular pressure gradient, is depicted in Fig. 6. The reduction in performance of the Inovare valve is most prominent here, when moving from the idealized ISO-standard testing to the patient-specific scenario, with mean pressure drops increasing by about 5-10 mmHg, and EOA dropping from values >2 cm² to 1.5-1.8 cm². Images of the Inovare valve during peak systole and diastole both in

the Vivitro PD and in the Replicator can be seen in Fig. 7 and in Online Video 6. Fig. 7 also depicts the deployed Inovare valve in both the Replicator and Vivitro annulus fittings after extraction from the systems. In the Replicator, the opening of the Inovare valve looked a little restricted in comparison to the wide opening seen in the Vivitro. The 29 mm St. Jude mechanical valve was used as a reference surgical valve, and relative to the TAVR valve showed minor increase in mean pressure drops (up to 2.5 mmHg) and decrease of 0.4 cm² in EOA from the Vivitro PD to the Replicator.

Summary of the regurgitation values for the Inovare and St. Jude valves in the Vivitro is presented in Table 1. Total regurgitation values for the Inovare ranged from 17.2% to 6.7% for CO of 2 L/min to 7 L/min, respectively. The regurgitation volume itself was very similar for all the CO tested (~7 ml). Closing regurgitation, which is the fluid volume flowing back into the left ventricle during closure of the leaflets, had a slightly greater contribution to the total regurgitation volume than the leakage volume.

4. Discussion

Bench testing of TAVR procedures is a critical stage for evaluating performance of TAVR valves, for feasibility and proof of concept of new valve technologies, and for the training of physicians. The ISO-compliant left heart simulators that are routinely used for evaluation of prosthetic heart valves provide critical baseline evaluation of valve performance and consistent test conditions for comparing valves performance. Such simulators, however, are limited for testing under simplified anatomy that is usually healthy, and are inadequate for procedural training purposes. For this reason, they tend to overestimate TAVR valve performance. The importance of testing TAVR valves under realistic patient conditions is tightly coupled to the valve performance that is impaired by the diseased anatomy [38, 10]. Lack of realistic bench testing methods forces valve manufacturers to perform multiple experiments in animal models, yet these are time-consuming, costly, and also limited to healthy animal models anatomy. Having a reliable and consistent *in vitro* method for testing valves in realistic and modifiable AS anatomies can be highly valuable in the early research and development stages and help improve future TAVR devices. It can also help to improve procedural outcomes by allowing training, practicing and procedural planning for heart teams performing the procedure in patients with challenging anatomies.

In the present study, we evaluated a novel patient-specific Replicator for TAVR testing, both on the TAVR procedure itself as well as post-procedural evaluation of the valve performance in realistic scenarios of extreme AS anatomies. Acknowledging the importance of testing prosthetic valves first under consistent anatomical conditions for obtaining baseline performance, the Replicator is tested here as a complementary platform for TAVR testing in severe patient cases. Based on feedback from an experienced TAVR interventional cardiologist the procedure felt very realistic with similar challenges and difficulties that are met in the catheterization laboratory. The procedure described here was performed by visually looking through the transparent silicone anatomy. X-ray fluoroscopy was used only before and after the procedure for evaluating and quantifying aortic regurgitation and paravalvular leak. As evidenced from the angiographic images quality, performing the entire procedure blindly using X-ray fluoroscopy guidance is additionally feasible. Evaluation of

TAVR valve performance was done with a 24 mm Inovare valve in an ISO-compliant simulator (the Vivitro PD) as well as in the Replicator, with the purpose of assessing changes in hydrodynamic parameters when moving to a realistic diseased anatomy. For reference, we also tested a 29 mm St. Jude mechanical heart valve, which was expected to be less affected by the patient specific anatomy since it replaced the native valve model.

In the current configuration of the Replicator, transient flow rate was not measured directly from the left ventricle outflow tract (e.g., like in the Vivitro PD) and therefore it was not feasible to quantitatively compare the aortic regurgitation values, or the associated effect of aortic regurgitation on the EOA and transvalvular pressure drop between the two simulators. Moving from the Vivitro PD to the Replicator, the EOA was decreased and pressure drop increased. This trend was expected and is attributed mainly to the non-optimal deployment of the TAVR valve, specifically the resultant post-deployment diameter and shape. In contrast to the Vivitro PD where the TAVR valve is deployed in soft silicone fitting of simplified aortic root anatomy, in the Replicator the mock calcified anatomy restricted the Inovare valve expansion and shape. This was further supported by the angiography images that revealed an eccentric hourglass-like shape, which indicates a certain degree of narrowing. Such narrowing could easily increase transvalvular pressure drops by 5-10 mmHg, both due to the obvious effect of a smaller orifice (pressure drop is affected by the fourth power of the diameter according to the Poiseuille model), and might also be due to non-optimal functionality of the leaflets at this distorted conformation of the valve. This is evident in Fig. 7 and Online Video 6 where slight restriction on the leaflets opening can be seen in the Replicator testing. Importantly, in both simulators the native aortic annulus size was identical, and changes in the overall deployed TAVR valve diameter and shape were a result of secondary parameters such as the presence of the native leaflets (that are commonly excluded in commercial pulse duplicators), and mostly by the presence of calcific deposits. The EOA values measured in the Vivitro were in the range of 1.6-2.7 cm², while in the Replicator the values dropped to 1.5-1.8 cm², depending on the CO. The latter values are in agreement with clinical measurements of other TAVR valves [39–41]. Mean transvalvular pressure drops were increased from a range of 3.5-11.0 mmHg to 10.2-18.2 mmHg, respectively. Comparison to clinical data with the Inovare of 14.1 ± 8.0 mmHg from 90 high risk patients [42], confirms that the results in the AS patient case modeled were very realistic and lied in the middle of the clinical range. It should be noted though that while the 24 mm Inovare was the most common device size used in this study, direct comparison to our results could not be performed per equivalent valve size and CO, as this data was not provided. The 29 mm St. Jude bileaflet mechanical valve showed to be less affected by the patient-specific anatomy, yet still experienced slight reduction in performance relative to the idealized Vivitro PD geometry. The fitting that connected the mechanical valve in the Replicator did not hold it similar to how it is sutured to the aortic annulus *in-situ*, nor as in the Vivitro PD. Rather more as a cylindrical tube with the valve seated in the middle, that possibly caused some increase in the pressure drop. Both in the Replicator and in the Vivitro PD, the mean pressure drop and the EOA of the mechanical valve are in agreement with clinical data (9.86 ± 2.9 mmHg, and 2.81 ± 0.57 cm², respectively) [43]. The results with both the mechanical valve and the TAVR valve confirm the sensitivity of the latter to the calcified aortic valve

anatomy, and emphasize the importance of testing TAVR valves under such conditions for proper evaluation of their actual expected performance.

In addition to the TAVR testing, several polymeric formulations for the mock aortic valves were evaluated. Hydrodynamic testing of these valves revealed that for the two formulations tested (30 Shore-A or 50 Shore-A) the polymer durometer had negligible effect on the performance of the progressing disease CAVD valve models. Rather, the valve geometry and the presence of calcific mass were dictating the performance of the valve models. The durometer had slightly larger effect on the moderate CAVD valve models, where the least severe case (M-CAVD-30) was able to reach normal CO of 5 L/min.

A limitation of this study was the lack a quantitative mean for measuring aortic regurgitation (AR) in the Replicator, e.g., flow measurement in the left ventricle outflow tract (as commonly measured in pulse duplicators), or echocardiographic imaging (as in the clinical setting). The angiographic imaging was clear enough for visualizing AR presence, but could not provide the quantitative data for comparison with the Vivitro PD measurements. Due to size and design mismatch, the valve with the deployed TAVR device could not be tested in the Vivitro PD for quantification of aortic regurgitation. Both echocardiographic imaging and incorporating direct flow measurements in the Replicator are currently under investigation. Another limitation of this study is related to the accuracy of native valve modeling. The term patient-specific is used here to describe modeling of the aortic root and leaflets geometry, and to some extent also mimic their material properties, but does not indicate a complete equivalence to the source. Evaluation of how well these models simulate *in-vivo* scenario before and after TAVR were presented in this study, and showed promising results that complies with clinical data. Finally, the limited availability of TAVR valves limited us to deploy the Inovare valve only in a single CAVD valve model. We avoided multiple deployments with the same Inovare valve as this might have permanently damage it and affect the results. It is important to note thought that the limited number of CAVD models tested in the current study is less critical for the aim of this study, which was to demonstrate the importance of complementary testing TAVR valves in patient-based CAVD model, and not to thoroughly test the Inovare valve performance.

5. Conclusions

In the present study, a new patient-specific aortic Replicator is introduced and evaluated for TAVR procedures. The critical need for an *in-vitro* testing method of TAVR valves with realistic diseased anatomy is demonstrated by comparing TAVR valve performance in the Replicator to that in an idealized ISO-compliant simulator. The Replicator system does not serve as a replacement for the available simplified left heart simulators but rather as a complimentary system. The current simulators utilize simplified geometries to narrow down the influencing variables during valve testing. By doing so they provide excellent tool for evaluation of the baseline hydrodynamic performance of prosthetic valves. The downside of the anatomical over-simplification is that these simulators tend to overestimate valve performance. The Replicator complements this by offering procedural variabilities and physician variation. Importantly, it offers an opportunity for TAVR testing since clinically relevant animal models are not available and while still being an *in vitro* model, it eliminates

the biological variation that is present in clinical trials. The ability to reliably replicate patients' diseased anatomy for testing TAVR devices and procedures may also set the basis for future research with advanced hemodynamic analysis based on patient-specific anatomical criteria, as well as for training on a 'patient' before the actual procedure. Based on the promising results and the realistic experience that the Replicator provides, it can become an essential tool for R&D valve testing, physician training, and pre-procedural practice and planning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to acknowledge Braile Biomédica from Brazil, for providing us with the 24 mm Inovare TAVR valve.

Funding

This project was supported by NIH-NIBIB Quantum Award Phase II-1U01EB012487 (DB) and NHLBI STTR R41-HL134418 (DB).

Abbreviations

AS	Aortic stenosis
AR	Aortic regurgitation
CAVD	Calcific aortic valve disease
CO	Cardiac output
EOA	Effective orifice area
LHS	Left heart simulator
PD	Pulse duplicator
PVL	Paravalvular leak
TAVR	Transcatheter aortic valve replacement

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FIGURE 1.

(a) – Vascular Simulations upper body arterial Replicator. (b) left – reconstruction of ascending aorta and aortic root based on a CT scan of a patient, based on which the aortic root models, shown on the right, were developed. (c) - Moderate (left, M-CAVD-30 and M-CAVD-50) and severe (right, S-CAVD-30 and S-CAVD-50) CAVD models, (d-e) - the modular valve model (red colored for visibility) fitted into the aorta and left ventricle.

FIGURE 2.

Illustration of the arterial model from the iliac arteries to the left ventricle, and the location of pressure lines, flow sensors, and endoscopic camera. P_v and P_{AO} are the left ventricle and aortic pressures, respectively, that were used for the calculation of transvalvular pressure. Empty arrows represent flow directions.

FIGURE 3.
Example of the aortic and ventricular pressure recordings measured with the S-CAVD-50 calcified valve model.

FIGURE 4.

Forward flow hydrodynamic performance summary for the native aortic valve models in the Replicator. (a) – Effective orifice area (EOA) as function of CO. (b) – Mean transvalvular pressure drop (ΔP) as function of CO. M/S-CAVD-30/50 correspond to Moderate/Severe CAVD models with elastomer durometer of 30/50 Shore-A.

FIGURE 5.

Subtracted angiographic pictures of the thoracic aorta model with contrast dye injection. (a) – The S-CAVD-50 calcified valve model before TAVR intervention, (b) – post-TAVR intervention, (c) – post-TAVR without contrast injection for comparison purposes. (d) – Eccentric hourglass shape with narrowing of the deployed TAVR. (e) – Picture of the extracted S-CAVD-50 valve model post-TAVR. Black arrows in (a) and (b) indicate aortic regurgitation. Red arrows in (e) mark location where PVL channels were identified. The original, non-subtracted, angiograms can be seen in Online Videos 4-5.

FIGURE 6.

Forward flow hydrodynamic performance summary of the TAVR and mechanical valves, both in the Replicator and in the Vivitro PD. (a) – Effective orifice area (EOA) as function of CO. (b) – Mean transvalvular pressure drop (ΔP) as function of CO. Significant reduction of EOA and increase in pressure drop was seen for the Inovare TAVR valve when moving from the Vivitro PD to the patient-specific Replicator. The S-CAVD-50 valve model is also presented here as a reference to the pre-TAVR performance.

FIGURE 7.

The Inovare valve deployed in the Replicator (a-d) and in the Vivitro PD (e-h) during peak systole (c, g) and diastole (d, h). Both cases were captured at CO of about 5 L/min. The black wire seen in images (c-d) is the guidewire that was used during the TAVR procedure.

Regurgitation values of the Inovare TAVR valve and the St. Jude mechanical aortic valve in the Vivitro PD. CO – Cardiac Output.

TABLE 1

	Inovare TAVR valve				St. Jude mechanical aortic valve		
	2	3.5	5	7	2	3.5	5
CO [L/min]							
Regurgitation closing [%]	9.7	6.9	6.1	5.0	9.7	4.25	4.5
Regurgitation leakage [%]	7.5	4.2	2.9	1.7	11.9	10.35	6.9
Regurgitation total [%]	17.2	11.1	9.0	6.7	21.6	14.6	11.4