Journal of Biomechanics 50 (2017) 77–82

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

A calcified polymeric valve for valve-in-valve applications

Ahmad Falahatpisheh [a,1], Daisuke Morisawa [a,1], Taraz T. Toosky [b], Arash Kheradvar [a,*]

[a] The Edwards Lifesciences Center for Advanced Cardiovascular Technology, University of California Irvine, Irvine, CA 92697, USA
[b] Toosky Engineering Models Inc., 2650 Walnut Ave # N, Tustin, CA 92780, USA

ARTICLE INFO

Article history:
Accepted 5 November 2016

Keywords:
Aortic valve stenosis
Calcific polymeric valve
Transcatheter aortic valve replacement
Valve-in-valve

ABSTRACT

The prevalence of aortic valve stenosis (AS) is increasing in the aging society. More recently, novel treatments and devices for AS, especially transcatheter aortic valve replacement (TAVR) have significantly changed the therapeutic approach to this disease. Research and development related to TAVR require testing these devices in the calcified heart valves that closely mimic a native calcific valve. However, no animal model of AS has yet been available. Alternatively, animals with normal aortic valve that are currently used for TAVR experiments do not closely replicate the aortic valve pathology required for proper testing of these devices. To solve this limitation, for the first time, we developed a novel polymeric valve whose leaflets possess calcium hydroxyapatite inclusions immersed in them. This study reports the characteristics and feasibility of these valves. Two types of the polymeric valve, i.e., moderate and severe calcified AS models were developed and tested by deploying a transcatheter valve in those and measuring the related hemodynamics. The valves were tested in a heart flow simulator, and were studied using echocardiography. Our results showed high echogenicity of the polymeric valve, that was correlated to the severity of the calcification. Aortic valve area of the polymeric valves was measured, and the severity of stenosis was defined according to the clinical guidelines. Accordingly, we showed that these novel polymeric valves closely mimic AS, and can be a desired cost-saving solution for testing the performance of the transcatheter aortic valve systems *in vitro*.

1. Introduction

According to epidemiological studies, aortic valve stenosis affects 2–7% of the elderly population (Nkomo et al., 2006). Calcification is by far the major cause of aortic valve stenosis (more than 80%), and among the affected patients, some have certain types of triggering congenital heart defects such as bicuspid valve or a history of rheumatic heart disease (Rayner et al., 2014). Calcific aortic valve stenosis is a progressive disease, which is irreversible and can be fatal if left untreated. Pharmacotherapy cannot currently prevent valvular calcification or help repair a damaged valve, since the valve tissue is unable to spontaneously regenerate. Thus, aortic valve replacement/repair is the only current available treatment.

The introduction of transcatheter aortic valve replacement (TAVR) has revolutionized heart valve replacement procedures by offering minimally invasive treatment options for patients with high-risk who have been considered unfit for traditional open-heart surgery (Kheradvar et al., 2015a) and more recently for patients with moderate-risk (Leon et al., 2016). A narrow range of FDA-approved transcatheter valves is currently being used in patients with calcific aortic valve stenosis (Kheradvar et al., 2015a). Contrary to the surgically-implantable aortic valves, transcatheter valves are not sewn within the aortic annulus but their stent expands within the native calcific aortic valve and the roughness due to the calcific nodules on the native leaflets provides means to hold the stented valve in place. The patterns of calcific nodules developed on the leaflets are completely random and vary in every patient (Goldbarg et al., 2007).

Calcific aortic valve stenosis is mainly a disease of the human and has not ever reported to naturally occur in animals. Very few attempts have been made to develop animal models with calcific aortic valve stenosis that were mainly mouse models, (Cheek et al., 2012; Miller et al., 2011; Zhang et al., 2014) and no large animal model of calcific aortic valve stenosis is yet available. Lack of such an animal model makes the research and development studies related to prosthetic heart valves very difficult and costly. Almost all the technologies related to transcatheter repair/replacement of aortic valve require a calcified heart valve in animals to show their feasibility. Currently, the preclinical studies related to TAVR have been performed on ovine or swine models with normal aortic valve (Emmert et al., 2014, 2012; Kheradvar et al., 2015b; Wendt

* Correspondence to: Biomedical Engineering and Medicine, The Edwards Lifesciences Center for Advanced Cardiovascular Technology, University of California, Irvine, 2410 Engineering Hall, Irvine, CA 92697-2730, USA. Fax: +1 949 824 9968.
E-mail address: arashkh@uci.edu (A. Kheradvar).
[1] Equal contribution

http://dx.doi.org/10.1016/j.jbiomech.2016.11.027
0021-9290/

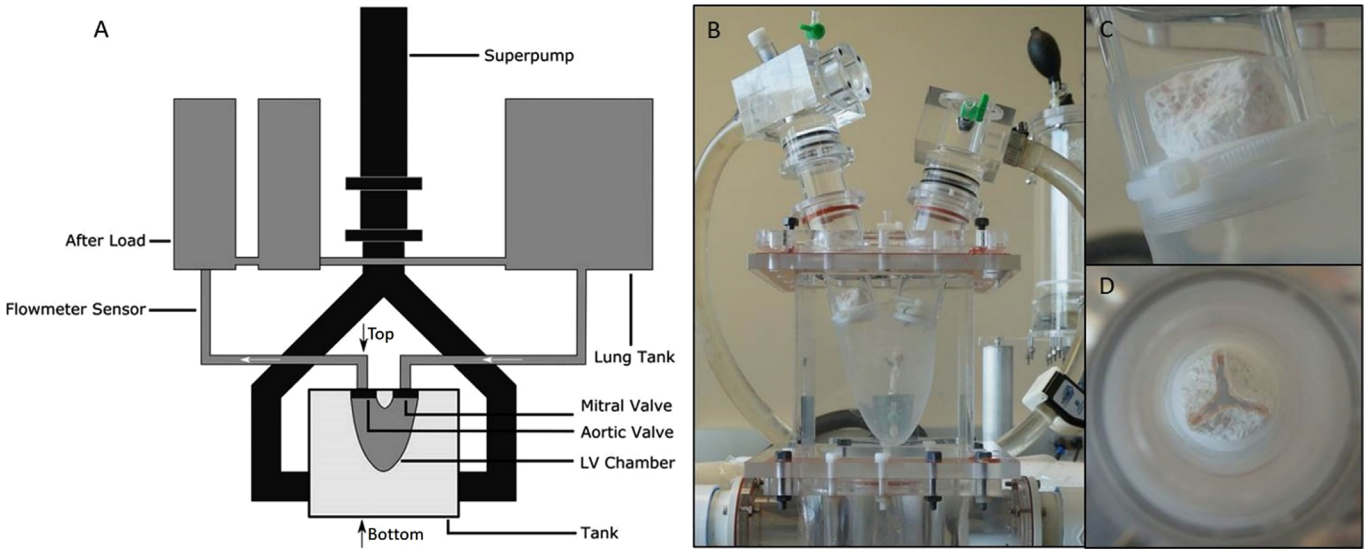

Fig. 1. The heart flow simulator used as the experimental setup, including LV chamber, mitral valve and aortic valve models. (A) and (B) show the experimental setup and the position of the 4V-D GE probe used for echocardiographic studies at the bottom of the chamber. (B), (C) and (D) show the aortic valve model within the Silicone ventricular sac from different views, respectively.

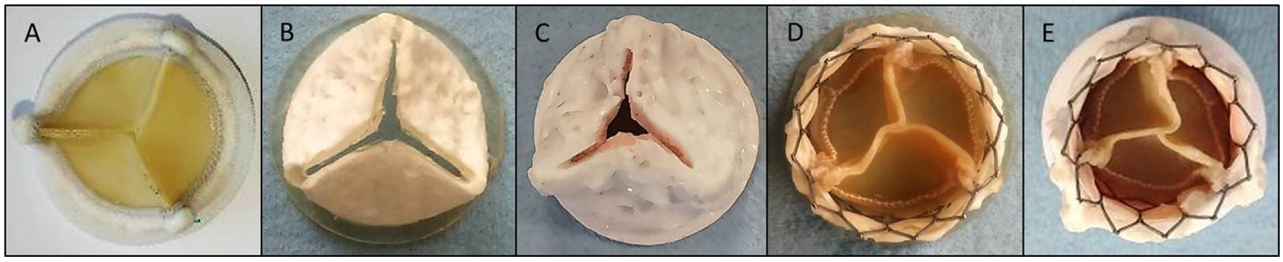

Fig. 2. Aortic valves used in this study: (A) control bioprosthetic valve; (B) moderately-stenotic calcified polymeric valve; (C) severely-stenotic calcified polymeric valve; (D) FoldaValve™ deployed in the moderately-stenotic calcified valve; and (E) FoldaValve™ deployed within a severely-stenotic calcified valve.

et al., 2013). However, the experiments do not closely represent the actual clinical situation, since these animals possess normal aortic valves without any trace of calcification. Therefore, not only a successful implant in sheep does not guarantee that a transcatheter valve can similarly perform in a patient with calcific aortic valve but also a failed experiment due to lack of anchoring in the animal does not necessarily imply that the tested transcatheter valve will fail in a patient with calcific aortic valve stenosis. Furthermore, since the calcific patterns in human aortic valve is remarkably heterogeneous, design and development of the TAVR systems suitable for most patients is extremely difficult due to the lack of a proper experimental model.

Here, we introduce a novel polymeric valve concept whose leaflets possess calcium hydroxyapatite inclusions immersed in them. These valves can be produced to replicate different grades of calcification to test transcatheter aortic valve implantation *in vitro* and may eventually be used for short-term *in vivo* experiments. The present work discusses the performance of these valves *in vitro*.

2. Methods

2.1. Heart flow simulator

We used a heart pulsed flow simulator as previously described for these experiments (Falahatpisheh and Kheradvar, 2012; Groves et al., 2014; Kheradvar and Gharib, 2009a, 2009b; Kheradvar et al., 2006). The system's modular build allows addition of a transparent patient-specific ventricle. The ventricular sac is suspended over the Plexiglas atrium, free-floating inside a rigid water-filled container. The system is connected and actuated by a pulsatile pump system (Superpump system, VSI, SPS3891, Vivitro systems Inc., Victoria, BC, Canada), which operates based on a VSI Wave Generator VG2001 (Vivitro Systems Inc., Victoria, BC, Canada) and controlled by a customized interface according to predefined functions. The circulatory flow is pulsatile and is generated as the ventricular sac's response to input waveforms (Fig. 1). Distilled water along with echocardiographic contrast agent (Optison™, GE Healthcare Inc., Princeton, NJ) was used as the circulating fluid.

2.2. Ventricular model

A transparent ventricular model with the dimensions of 82 mm width, 115 mm height and 69 mm depth was used for this study. The model is made of transparent silicone rubber and was placed in the circulatory system connected to inlet and outlet tubes (Fig. 1).

2.3. Heart valve for mitral position

For the mitral position, a 25 mm bioprosthetic mitral valve (Biocor, St. Jude Medical Inc., St Paul, MN) was used.

2.4. Models of aortic valves

A control and two calcific polymeric valves were used at the aortic position. We used a 23 mm CEP PERIMOUNT Theon PSR pericardial bioprosthesis (Edwards Lifesciences, Irvine, CA; Fig. 2A). This was considered to be the control valve for the study, with no calcification.

2.4.1. Models of calcified aortic valve

We created models of calcified aortic valves with moderate and severe stenosis (Fig. 2B, C). A mixture containing calcium phosphate $Ca_3(Po_4)_2$ was

developed to replicate calcified nodules on the valve leaflets according to the figures reported in the literature (Baumgartner et al., 2009; Novaro et al., 2007). The mixture was based on 1/4 ounce $Ca_3(Po_4)_2$ and 1/8 of ounce Polyurethane (BJB Enterprises, Tustin, CA). 1/8 ounce and 1/4 ounce of the mixture were used to develop moderately- and severely-stenotic valves, respectively. To make the valve, the mixture was applied layer-by-layer and then was set inside a Silicone mold. After several trial and error, a proper mold for each part was made. The process of mixing, pouring, curing and demold time took about eight hours. Molds were manually made according to anatomical figures of native calcified aortic valve. Custom made mold for each level was made by Silicone Rubber with hardness shore 30 A and tensile strength of 700 PSI with a mixing ratio by part A 100% and part B 10%. The two-part mold was set to develop the aortic valve of size 23 mm. Surface area coverage of the calcium-phosphate mixture specify the level of calcification. Eventually, the valves with different grades of stenosis (i.e., moderately- and severely-stenotic) consistent with the guideline of American Society of Echocardiography (ASE) were successfully made by trial and error (Baumgartner et al., 2009). Moderately- and severely-stenotic calcified valves are shown in Fig. 2B and C.

2.4.2. Transcatheter aortic valves

We used FoldaValve™ (FOLDA LLC, Rancho Santa Margarita, CA), a 14 Fr transcatheter aortic valve (TAV) that expands to 25mm, to perform the valve-in-valve procedures (Fig. 2D, E). FoldaValve™ is a self-expandable transcatheter aortic valve that uses a nitinol stent and is made of bovine pericardial leaflets (Kheradvar et al., 2015b).

2.5. Experimental conditions

Five sets of experiments (i.e., using control, moderately-, severely-stenotic calcified polymeric valve, FoldaValve™ in moderately-stenotic calcified polymeric valve and FoldaValve™ in severely-stenotic calcified polymeric valve) were performed to replicate the use of the calcified aortic valves. Flow conditions for all the experiments were set to 70 beats per minute under a physiological waveforms that reproduce the desired Systolic Ratio (SR) of 35% for the LV model; SR is the fraction of time in a cardiac cycle that the LV is in systole (Groves et al., 2014; Kheradvar, 2009; Mason et al., 2007).

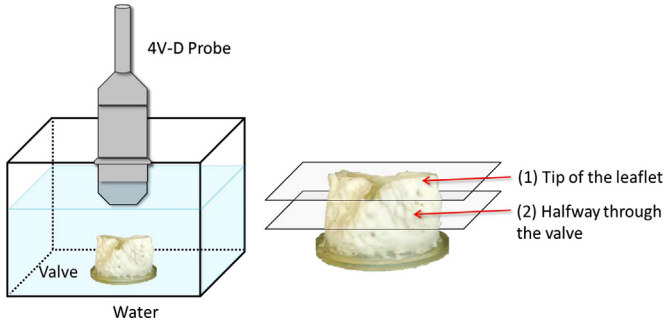

Fig. 3. Schematic of the 3D structural imaging of the aortic valve models. The valves were immersed in a tank filled with water. A GE 4V-D probe was used to statically image the valve's structure in 3D. Tip of the leaflet and halfway through the valve were shown.

2.6. Aortic valve area analysis

Motion of the aortic valve leaflets during the cardiac cycle was recorded by a video camera (Xperia M2 Aqua, Sony, Japan) with a frame rate of 24 fps for all the experiments. Subsequently, the maximum aortic valve area during peak systole was calculated by image processing.

2.7. Echocardiographic studies

We used a GE Vivid E9 system (GE Healthcare, Milwaukee, WI) to perform 2D B-mode imaging, color Doppler imaging, continuous wave Doppler echocardiography, and 3D structural imaging. All acquisitions were performed using a 4V-D GE ultrasound transducer. 2D B-mode images and color Doppler were obtained from the distal throughout the aortic outflow (Bottom arrow in Fig. 1A), and continuous wave Doppler echocardiography was performed by placing the probe at the ventricular sac's apex (Top arrow in Fig. 1A). To obtain structural images, the valves were placed at a tank filled with water to generate hydrostatic pressure in order to capture the valves' structure at their fully closed position (Fig. 3); then the images were acquired at the tip of the leaflets and halfway through the valve as shown in Fig. 5. To compare their echogenicity, we calculated the mean brightness level of the valve images using image processing (Photoshop CS5.1, Adobe, San Jose, CA). Brightness level of a digital image is described as the tonal range of 256 levels, from 0 to 255. Brightness level of 0 and 255 mean pure black and white, respectively. Optison™ was used as the contrast agent to enhance the quality of the images.

3. Results

3.1. Calcified aortic valves

We successfully made and used two polymeric valves of 23 mm according to the shape of the reported native calcified aortic valves (Baumgartner et al., 2009; Novaro et al., 2007) using randomly distributed hydroxyl-appetite inclusions replicating a severely-stenotic and a moderately-stenotic aortic valves (Fig. 2B and C, respectively).

3.2. Aortic valve area

Fig. 4 shows the aortic valve area (AVA) of all the studied aortic valves. The moderately- and severely-stenotic valve's AVA were measured as 1.40 cm^2 and 0.91 cm^2, respectively, versus control valve's 2.17 cm^2. FoldaValve™ was successfully deployed in both polymeric valves and calcium inclusions stayed intact on the valves' leaflets with no calcium dislodgment. Thus, the AVA was improved up to the level of control valve's (2.18 cm^2 and 2.05 cm^2 for moderately- and severely-stenotic valve, respectively; Fig. 4).

3.3. 3D structure imaging

The valves' 3D structrue is shown in Fig. 5 for the control, moderately-, and severely-stenotic valves at two different positions close to the tip and halfway through the valve. The high

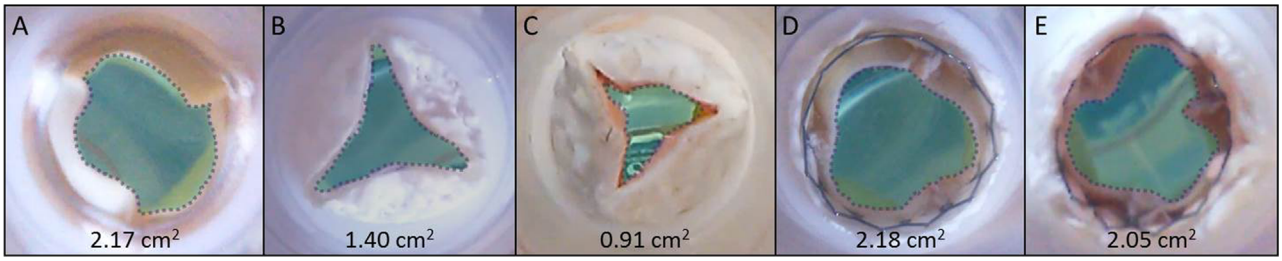

Fig. 4. Aortic valve area (AVA); (A) control; (B) moderately-stenotic calcified polymeric valve; (C) severely-stenotic calcified polymeric valve with significant level of calcification; (D) FoldaValve™ in moderately-stenotic calcified valve; and (E) FoldaValve™ implanted within a severely-stenotic calcified valve.

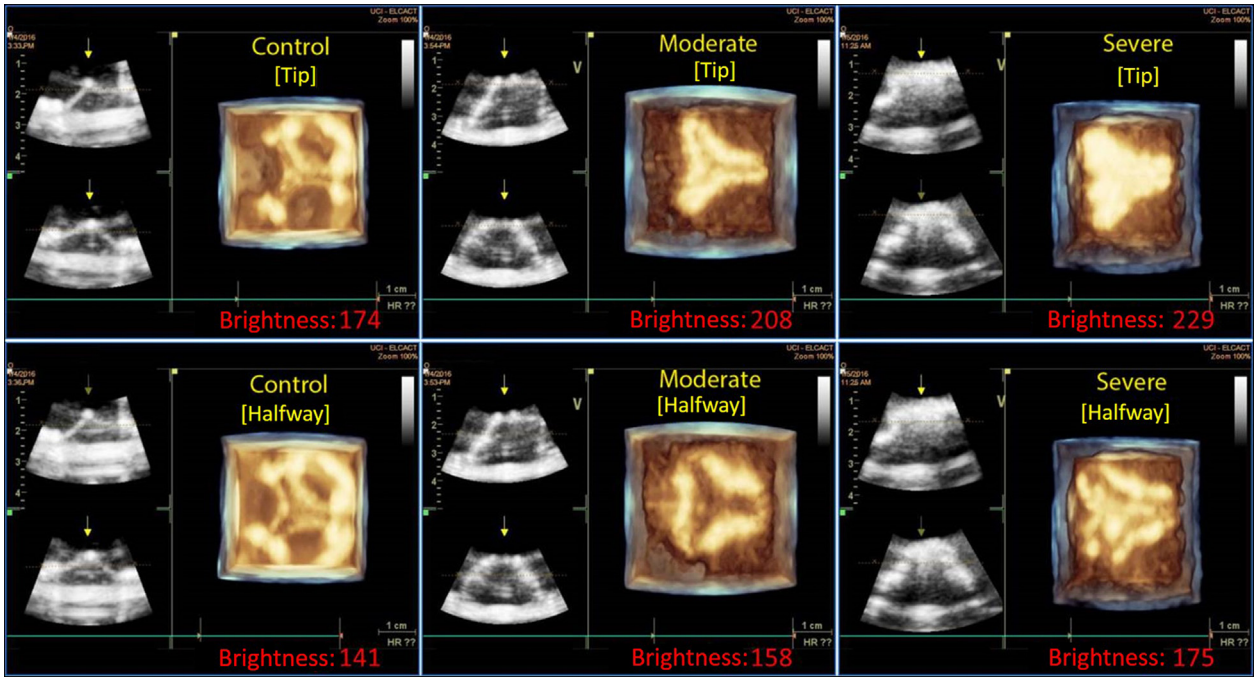

Fig. 5. 3D structural images of the valves acquired at different views of: (left) control, (middle) moderately-stenotic calcified, and (right) severely-stenotic calcified valves. Compared with control, the brightness level in moderately-stenotic calcified valve was higher, and that of the severely-stenotic calcified valve was highest among all.

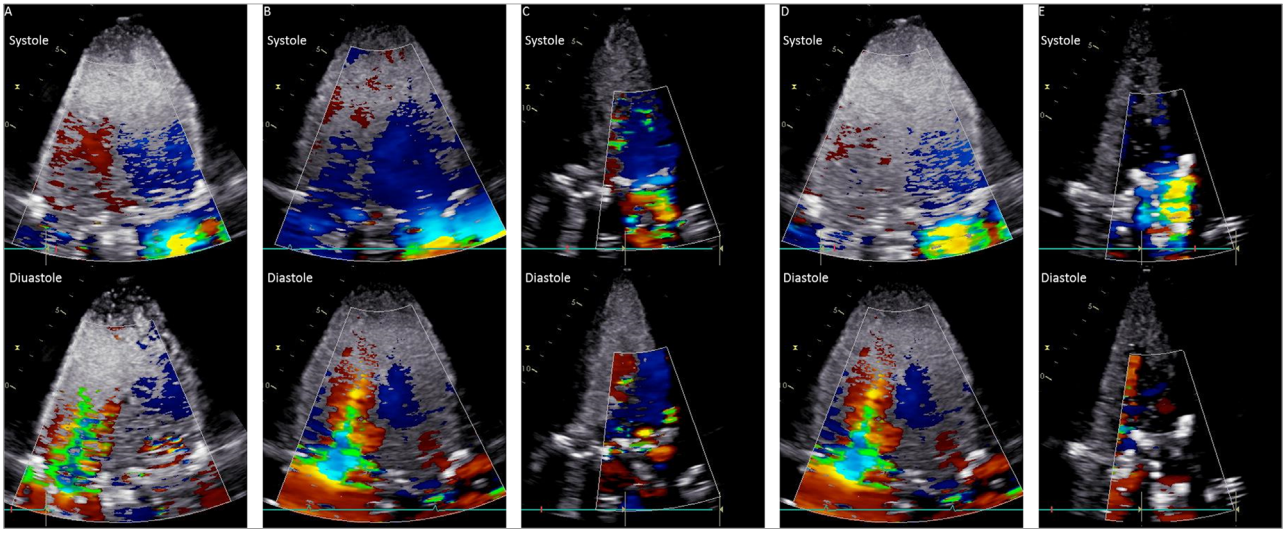

Fig. 6. Color Doppler Imaging was performed to check the presence of valve leakage. Blue color represents jets traveling away from the probe, and the green or yellow signify the jets traveling toward the probe. When there is a leak, green or yellow signal should be observed during diastole. Aortic valve was located at the lower right of each image. No obvious regurgitant color signal was found passing the control valve (A); similarly, no obvious regurgitant color signal was present below the moderately-stenotic calcified polymeric valve (B), FoldaValve™ implanted in the moderately-stenotic polymeric valve (D) and FoldaValve™ implanted within a severely-stenotic calcified polymeric valve (E). However, trace regurgitant signal can be observed below the severely-stenotic calcified polymeric valve (C). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

echogenicity over the leaflets were correlated to the degree of the calcification. Since the control valve does not have any calcification, no region of high echogenicity were observed. Alternatively, high echogenicity regions were observed in both moderately- and severly-stenotic valves. These regions were large and prominent in both calcified valves. In the severely-stenotic valve, echogenicity spread a larger area over the leaflets compared to the other valves, signifying the severity of the calcification and confirming the physical condition shown in Fig. 2. Quantitative evaluation of the valve echogenicity reported the brightness levels of the contol valve at the top and halfaway of the valve were 174 and 141, respectively. For moderately-stenotic and severely-stenotic valves, the brightness at the top and halfway through the valve were 208, 158 and 229, 175, respectively. These results were consistent with the qualitative evaluation (Fig. 5).

3.4. Color Doppler imaging

Color Doppler imaging was performed to test valve leakage. Fig. 6 shows images at peak-systolic and -diastolic phases. As

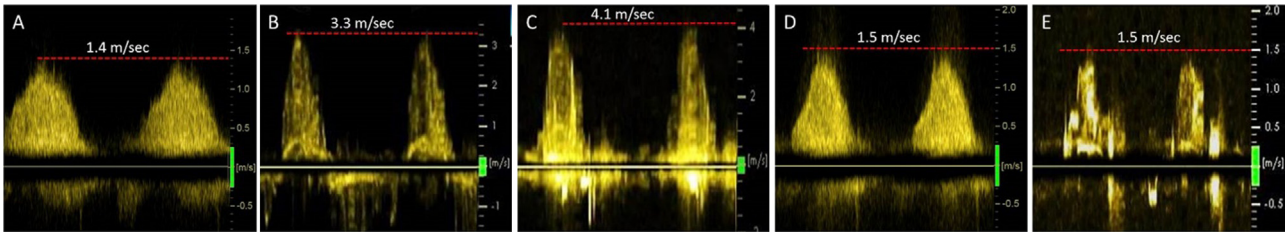

Fig. 7. Continuous wave Doppler imaging was performed to measure the velocity of the aortic valve flow. The peak velocity out of the control valve was measured 1.4 m/s (A); the peak velocity in the moderately-stenotic and severely-stenotic calcified polymeric valves increased to 3.3 m/s (B) and 4.1 m/s (C), respectively. Once FoldaValve™ was implanted in moderately-stenotic and severely-stenotic calcified polymeric valves, the peak velocity reverted back to the control level as shown in (D) and (E), respectively.

anticipated, no obvious backward signal was observed in case of the control valve (Fig. 6A). Alternatively, trivial backward signals were observed in severely-calcified valve, but not observed in moderately-stenotic valve (Fig. 6B, C). After implanting FoldaValve™, the backward signal disappeared in both calcified valves (Fig. 6E, F).

3.5. Maximum aortic valve jet velocity

According to continuous wave Doppler images, peak aortic valve jet velocity of control was measured as 1.4 m/s, which is within the normal range for prosthetic valves (Fig. 7A). The significant increase in peak jet velocity was observed in moderately-stenotic valve (3.3 m/s) and severely-stenotic valve (4.1 m/s) (Fig. 7B and C). Implantation of FoldaValve™ led to reverting the peak jet velocity to normal in both calcified valves (1.5 m/s for both valves; Fig. 4).

4. Discussion

In the past few years, the development of more advanced TAVR systems is enthusiastically progressing but no aortic valve stenosis model is yet available to properly test the implantation procedures. To the best of our knowledge, this is the first report on conception of a polymeric valve with calcium hydroxyapatite inclusions replicating a stenotic aortic valve.

4.1. Severity of aortic valve stenosis

The ASE guideline categorizes severity of aortic valve stenosis into three grades on the basis of AVA (cm^2) and peak aortic valve jet velocity (m/sec). Our polymeric valves showed the restriction of valve opening and elevation of maximum aortic valve jet velocity as 1.40 cm^2, 3.3 m/s and 0.91 cm^2, 4.1 m/s in moderately- and severely-stenotic valves, respectively. Therefore, according to the ASE's guideline, our moderately- and severely-stenotic models are congruent with the moderate and severe aortic stenosis (Baumgartner et al., 2009). After FoldaValve™ deployment, aortic stenosis was improved back to normal similar to the control valve. These results indicate that our novel polymeric valves accurately replicate different grades of aortic stenosis and may be used for testing TAVR systems.

4.2. Echocardiography and valve's echogenicity

To evaluate the severity of valvular stenosis and calcification, echocardiographic examination is commonly performed in patients. In clinical practice, high echogenicity of a native aortic valve generally indicates severe calcification. Here, we found that our polymeric calcified valves show higher echogenicity, compared with control valve, and this echogenicity -represented by brightness level- is associated with the degree of calcification (Fig. 5). Accordingly, the polymeric valve prototypes suitably replicate calcified aortic valve as evaluated by echocardiography.

4.3. Presence of the regurgitation based on Doppler imaging

The color Doppler imaging reports trivial degrees of regurgitation in the polymeric calcified valve models (Fig. 6). This indicates that the polymeric calcified valves not only can replicate the aortic valve stenosis but also can represent aortic valve regurgitation, if needed.

4.4. Clinical implication

The number of TAVR procedures is increasing day-by-day (Dayoub and Nallamothu, 2016). Although many technical problems related to TAVR in high-risk patients have been resolved, paravalvular leakage, valve durability, positioning accuracy, repositioning and retrieval are still considered clinical unmet needs (Maisano et al., 2015; Smith et al., 2011; Webb and Cribier, 2011). Therefore, in the near future, artificial heart valves mimicking valvular disease may play more important role in development of more sophisticated future generations of TAVR systems and improving the existing technologies. The novel polymeric calcified valve introduced here can be used for studies related to valve-in-valve applications. The advantage of this novel polymeric valves is that the calcified surface of their leaflets can be custom-designed by controlling the amount and location of calcium phosphate deposits. In addition, these valves can even be made or 3D-printed according to the patient-specific data acquired by CT-scan and/or echocardiography. Therefore, more precise clinical conditions can be replicated using these valves.

4.5. Study limitations

Although previous studies reported that polyurethane heart valves display adequate biocompatibility, hemocompatibility and durability *in vivo* (Kutting et al., 2011), we did not check whether this novel polymeric valve may evoke any biological reactions *in vivo*. Therefore, use of these valves for *in vivo* application cannot be recommended at the present time and their applications *in vivo* should be tested in future.

5. Conclusion

For the first time, we have developed polymeric calcified valve prototypes that replicate moderately- and severely-stenotic valve conditions. The feasibility of these valves was validated for studies related to transcatheter heart valve implantation *in vitro*. Through multiple experiments, we showed that these calcified valves can suitably mimic the function of a native calcified stenotic aortic valve and can be used for valve-in-valve studies. Finally, we corroborate that using this novel polymeric calcified valve may be a

desired cost-saving solution for testing the performance of new TAVR systems *in vitro*.

Conflict of interest

Prof. Kheradvar is a co-founder of Folda LLC that makes FoldaValve™. He also has an equity interest in Folda LLC, a company that may potentially benefit from the research results. The terms of this arrangement have been reviewed and approved by the University of California, Irvine in accordance with its conflict of interest policies. The other authors have no conflicts of interest to declare.

Acknowledgement

This study is funded by a grant from American Heart Association (16IRG27250078) to Prof. Kheradvar.

References

Baumgartner, H., Hung, J., Bermejo, J., Chambers, J.B., Evangelista, A., Griffin, B.P., Iung, B., Otto, C.M., Pellikka, P.A., Quinones, M., 2009. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am. Soc. Echocardiogr. 22, 1–23 (quiz 101-102).

Cheek, J.D., Wirrig, E.E., Alfieri, C.M., James, J.F., Yutzey, K.E., 2012. Differential activation of valvulogenic, chondrogenic, and osteogenic pathways in mouse models of myxomatous and calcific aortic valve disease. J. Mol. Cell. Cardiol. 52, 689–700.

Dayoub, E.J., Nallamothu, B.K., 2016. Geographic access to transcatheter aortic valve replacement relative to other invasive cardiac services: a statewide analysis. Am. Heart J. 177, 163–170.

Emmert, M.Y., Weber, B., Behr, L., Sammut, S., Frauenfelder, T., Wolint, P., Scherman, J., Bettex, D., Grünenfelder, J., Falk, V., Hoerstrup, S.P., 2014. Transcatheter aortic valve implantation using anatomically oriented, marrow stromal cell-based, stented, tissue-engineered heart valves: technical considerations and implications for translational cell-based heart valve concepts. Eur. J. Cardio-Thorac. Surg. 45, 61–68.

Emmert, M.Y., Weber, B., Wolint, P., Behr, L., Sammut, S., Frauenfelder, T., Frese, L., Scherman, J., Brokopp, C.E., Templin, C., Grünenfelder, J., Zünd, G., Falk, V., Hoerstrup, S.P., 2012. Stem cell–based transcatheter aortic valve implantation: first experiences in a pre-clinical model. JACC: Cardiovasc. Interv. 5, 874–883.

Falahatpisheh, A., Kheradvar, A., 2012. High-speed particle image velocimetry to assess cardiac fluid dynamics in vitro: from performance to validation. Eur. J. Mech. – B/Fluids 35, 2–8.

Goldbarg, S.H., Elmariah, S., Miller, M.A., Fuster, V., 2007. Insights into degenerative aortic valve disease. J. Am. Coll. Cardiol. 50, 1205–1213.

Groves, E.M., Falahatpisheh, A., Su, J.L., Kheradvar, A., 2014. The effects of positioning of transcatheter aortic valves on fluid dynamics of the aortic root. ASAIO J. 60, 545–552.

Kheradvar, A., Gharib, M., 2009a. On mitral valve dynamics and its connection to early diastolic flow. Ann. Biomed. Eng. 37, 1–13.

Kheradvar, A., Gharib, M., 2009b. On mitral valve dynamics and its connection to early diastolic flow. Ann. Biomed. Eng. 37, 1–13.

Kheradvar, A., Groves, E., Goergen, C., Alavi, S.H., Tranquillo, R., Simmons, C., Dasi, L., Grande-Allen, K.J., Mofrad, M.K., Falahatpisheh, A., Griffith, B., Baaijens, F., Little, S., Canic, S., 2015a. Emerging trends in heart valve engineering: part ii. novel and standard technologies for aortic valve replacement. Ann. Biomed. Eng. 43, 844–857.

Kheradvar, A., Groves, E.L., Tseng, E.E., 2015b. Proof of concept of FOLDAVALVE a novel 14Fr totally repositionable and retrievable transcatheter aortic valve. Eur. Interv. 10, 591–596.

Kheradvar, A., Kasalko, J., Johnson, D., Gharib, M., 2006. An in vitro study of changing profile heights in mitral bioprostheses and their influence on flow. ASAIO J 52, 34–38.

Kutting, M., Roggenkamp, J., Urban, U., Schmitz-Rode, T., Steinseifer, U., 2011. Polyurethane heart valves: past, present and future. Expert Rev. Med Devices 8, 227–233.

Leon, M.B., Smith, C.R., Mack, M.J., Makkar, R.R., Svensson, L.G., Kodali, S.K., Thourani, V.H., Tuzcu, E.M., Miller, D.C., Herrmann, H.C., Doshi, D., Cohen, D.J., Pichard, A.D., Kapadia, S., Dewey, T., Babaliaros, V., Szeto, W.Y., Williams, M.R., Kereiakes, D., Zajarias, A., Greason, K.L., Whisenant, B.K., Hodson, R.W., Moses, J. W., Trento, A., Brown, D.L., Fearon, W.F., Pibarot, P., Hahn, R.T., Jaber, W.A., Anderson, W.N., Alu, M.C., Webb, J.G., 2016. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. New Engl. J. Med. 374, 1609–1620.

Maisano, F., Alfieri, O., Banai, S., Buchbinder, M., Colombo, A., Falk, V., Feldman, T., Franzen, O., Herrmann, H., Kar, S., Kuck, K.-H., Lutter, G., Mack, M., Nickenig, G., Piazza, N., Reisman, M., Ruiz, C.E., Schofer, J., Søndergaard, L., Stone, G.W., Taramasso, M., Thomas, M., Vahanian, A., Webb, J., Windecker, S., Leon, M.B., 2015. The future of transcatheter mitral valve interventions: competitive or complementary role of repair vs. replacement? Eur. Heart J. 36, 1651.

Mason, J.W., Ramseth, D.J., Chanter, D.O., Moon, T.E., Goodman, D.B., Mendzelevski, B., 2007. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. J. Electrocardiol. 40, 228–234.

Miller, J.D., Weiss, R.M., Heistad, D.D., 2011. Calcific aortic valve stenosis: methods, models, and mechanisms. Circ. Res. 108, 1392–1412.

Nkomo, V.T., Gardin, J.M., Skelton, T.N., Gottdiener, J.S., Scott, C.G., Enriquez-Sarano, M., 2006. Burden of valvular heart diseases: a population-based study. Lancet 368, 1005–1011.

Novaro, G.M., Katz, R., Aviles, R.J., Gottdiener, J.S., Cushman, M., Psaty, B.M., Otto, C. M., Griffin, B.P., 2007. Clinical factors, but not c-reactive protein, predict progression of calcific aortic-valve disease: the cardiovascular health study. J. Am. Coll. Cardiol. 50, 1992–1998.

Rayner, J., Coffey, S., Newton, J., Prendergast, B.D., 2014. Aortic valve disease. Int. J. Clin. Pract. 68, 1209–1215.

Smith, C.R., Leon, M.B., Mack, M.J., Miller, D.C., Moses, J.W., Svensson, L.G., Tuzcu, E. M., Webb, J.G., Fontana, G.P., Makkar, R.R., Williams, M., Dewey, T., Kapadia, S., Babaliaros, V., Thourani, V.H., Corso, P., Pichard, A.D., Bavaria, J.E., Herrmann, H. C., Akin, J.J., Anderson, W.N., Wang, D., Pocock, S.J., 2011. Transcatheter versus surgical aortic-valve replacement in high-risk patients. New Engl. J. Med. 364, 2187–2198.

Webb, J., Cribier, A., 2011. Percutaneous transarterial aortic valve implantation: what do we know? Eur. Heart J 32, 140–147.

Wendt, D., Pasa, S., Kahlert, P., Delaloye, S., Al-Rashid, F., Price, V., Jánosi, R.-A., Borenstein, N., Behr, L., Konorza, T., Erbel, R., Jakob, H., Thielmann, M., 2013. A New self-expandable transcatheter aortic valve for transapical implantation: feasibility in acute and chronic animal experiments. Scand. Cardiovasc. J. 47, 145–153.

Zhang, B., Casaclang-Verzosa, G., Miller, J.D., 2014. Mouse models of calcific aortic valve disease. In: Rajamannan, N.M. (Ed.), Molecular Biology of Valvular Heart Disease. Springer, pp. 67–80.