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A calcified polymeric valve for valve-in-valve applications

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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

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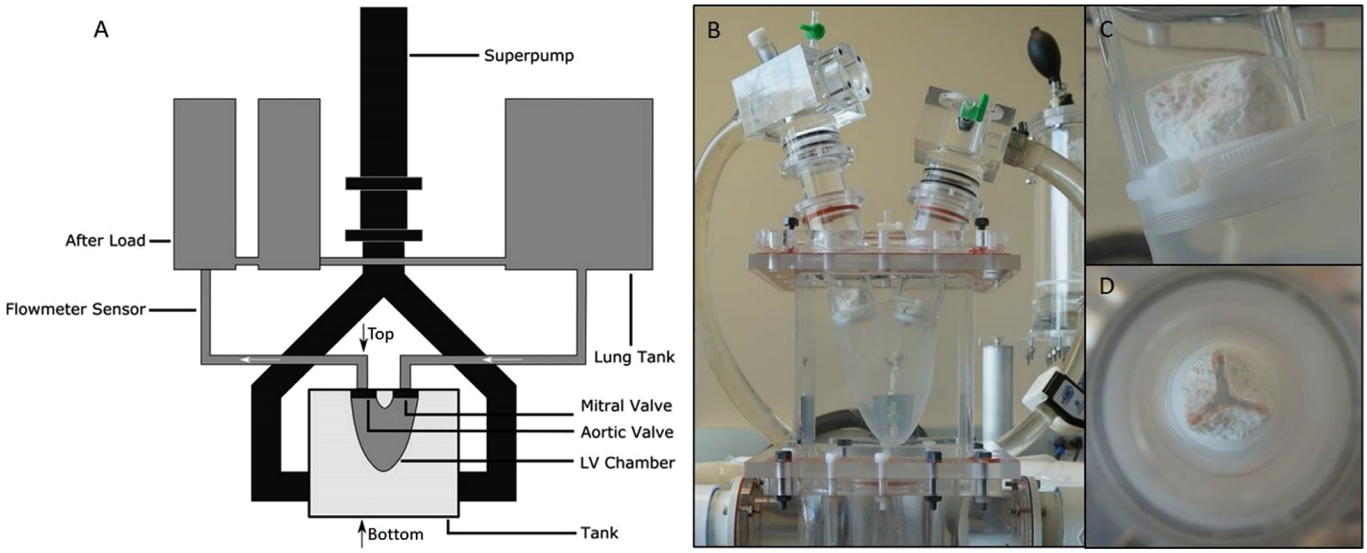

Fig. 1. The heart flow simulator used as the experimental setup, including LV chamber, mitral valve and aortic valve models. (A) and (B) show the experimental setup and the position of the 4V-D GE probe used for echocardiographic studies at the bottom of the chamber. (B), (C) and (D) show the aortic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

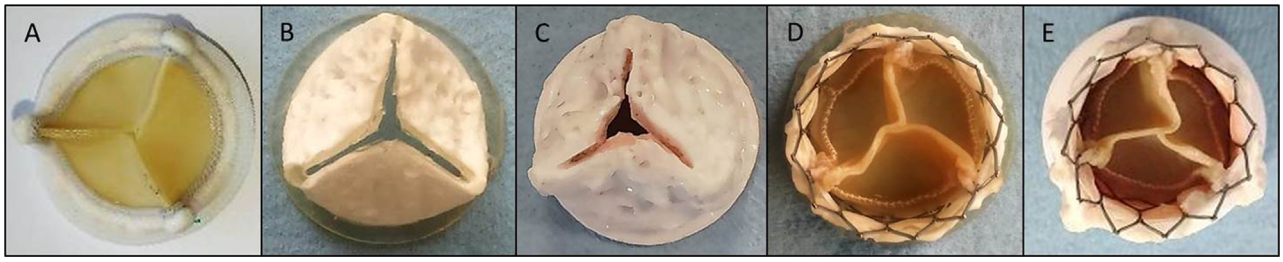

Fig. 2. Aortic valves used in this study: (A) control bioprosthetic valve; (B) moderately-stenotic calcified polymeric valve; (C) severely-stenotic calcified polymeric valve; (D) FoldaValve™ deployed in the moderately-stenotic calcified valve; and (E) FoldaValve™ deployed within a severely-stenotic calcified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