

# Valve-in-Valve Implantation Using a Novel Supravalvular Transcatheter Aortic Valve: Proof of Concept

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**Background.** Transcatheter valve implantation within degenerated bioprostheses is a potentially promising treatment for high-risk surgical patients. Clinical experience is limited; however, we have shown in vitro that currently available transcatheter aortic valve sizes did not provide acceptable hemodynamics in small bioprostheses. The objective of this study was to develop a new transcatheter valve that would provide good hemodynamics within degenerated bioprostheses.

**Methods.** Supravalvular transcatheter valves were created using a Dacron covered stainless steel stent at the base and trileaflet pericardial leaflets in an open stent above the bioprosthesis. The transcatheter valves were implanted within 19-, 21-, and 23-mm Carpentier-Edwards Perimount bioprostheses with simulated degeneration using BioGlue to achieve a mean pressure gradient of 50 mm Hg. Hemodynamics of valve-in-valve implantation were studied in a pulse duplicator.

**Results.** Supravalvular transcatheter valves successfully relieved bioprosthetic stenosis. Acceptable hemodynamics were achieved with a significant reduction in mean pressure gradient of  $54.0 \pm 3.5$  to  $9.2 \pm 6.3$  mm Hg in 23-mm bioprostheses ( $p < 0.001$ ), from  $49.3 \pm 3.1$  to  $14.4 \pm 4.7$  mmHg ( $p < 0.001$ ) in 21 mm, and from  $53.9 \pm 3.8$  to  $28.3 \pm 9.8$  mm Hg ( $p = 0.013$ ) in 19-mm bioprostheses. Effective orifice area after valve-in-valve implantation increased significantly and was comparable to rereplacement with the same size bioprosthesis.

**Conclusions.** Valve-in-valve implantation was performed using a novel supravalvular transcatheter valve, which successfully relieved bioprosthetic stenosis. The hemodynamics were comparable with standard surgical valve replacement. Further studies are required to assess device safety and efficacy in patients.

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The feasibility of transcatheter aortic valve (TAV) implantation within degenerated bioprostheses has recently been demonstrated [1–4]. Although valve-in-valve (VIV) results are encouraging, clinical experience remains limited [1–3]. We have previously shown hemodynamic complications from implantation of currently available TAVs within small-size normal bioprostheses in in vitro experiments [5]. Successful VIV implantation was achieved only when the TAV matched the bioprosthetic size. The oversized TAV was constrained by the rigid bioprosthesis, resulting in TAV stenosis. The TAV was anchored inside the bioprosthesis and could not be dilated beyond the bioprosthetic annulus. Thus, one concern of using TAVs within small bioprostheses is that the effective orifice area may be reduced significantly, particularly when compared with surgical valve replacement of equal size.

We hypothesized that a possible solution to achieve better hemodynamics of TAVs within bioprostheses is to develop a supravalvular TAV where the valve within the

TAV stent is situated above the bioprosthesis (Fig 1). As a result, the TAV is not constrained by the bioprosthesis and a larger valve can be deployed above the bioprosthesis to enhance hemodynamics. The objective of this study was to determine the feasibility and efficacy of supravalvular TAVs in degenerated bioprostheses.

## Material and Methods

### Supravalvular TAVs

The custom designed supravalvular TAV consists of a stainless steel stent covered with Dacron (DuPont, Wilmington, DE) that sits within the bioprosthesis and a valve within an open stent situated above the bioprosthetic posts (Fig 2). To study the efficacy of VIV implantation, six 23-mm supravalvular TAVs were made for implantation within 19-, 21-, and 23-mm Carpentier-Edwards Perimount Magna (Edwards Lifesciences, Irvine, CA) bioprostheses ( $n = 3$  of each bioprosthetic size). Each supravalvular TAV was reusable and functioned well after removal, recrimping, retesting hemodynamics, and reimplantation in a smaller bioprosthetic size.

Three trapezoidal-shaped leaflets (22.5- and 23.5-mm parallel sides, and 15-mm height) were cut from a flat

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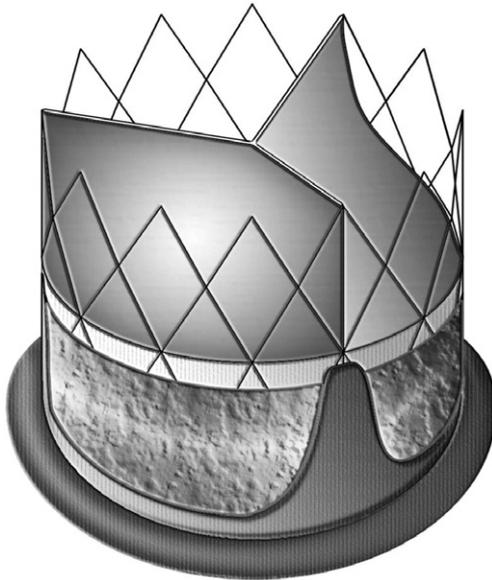


Fig 1. Drawing shows a supra-aortic transcatheter aortic valve within a degenerated bioprosthesis.

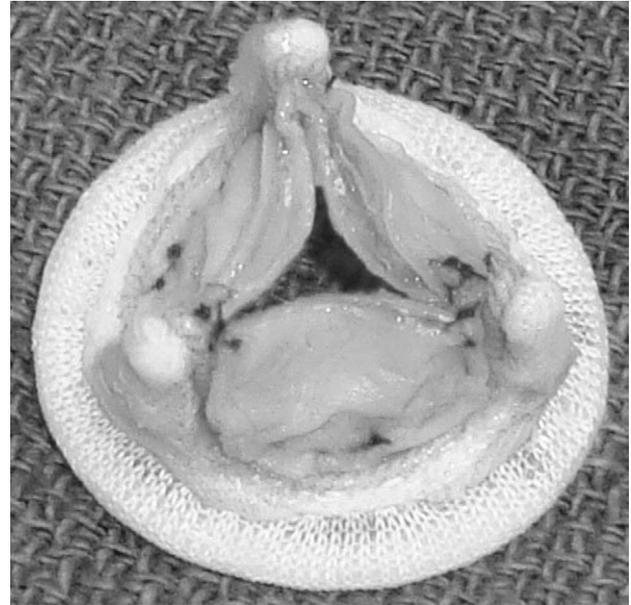


Fig 3. A 21-mm degenerated bioprosthesis in which BioGlue was used to simulate calcification.

piece of bovine pericardium (Edwards Bovine Pericardial Patch, Edwards Lifesciences). The lateral sides of the 3 leaflets were sutured together to create commissures. The base of the leaflets was sutured to a Dacron sheet (69 × 23 mm) at a height of 15 mm using 6-0 polypropylene running suture. Thus, 15 mm of the base of the Dacron sheet was below the valve.

A customized cylindrical stainless steel stent (W.L. Gore and Associates, Flagstaff, AZ), 30-mm height, was dilated to an external diameter of 23 mm. The leaflets and Dacron sheet were secured within the stent. The 3 commissures were anchored at the top of the stent with 4-0 polypropylene interrupted stitches. The Dacron cylinder was attached to the stent at each metal intersection using 5-0 polypropylene interrupted stitches (Fig 2).

#### Degenerated Bioprosthetic Valves

Acquiring explanted degenerated bioprostheses from patients would be unpredictable with respect to pressure gradients as well as bioprosthetic valve sizes, and it would be difficult to achieve the quantity of each size sufficient for statistical analyses at one institution. Therefore, a reproducible model to simulate degeneration of normal bioprostheses was developed to investigate VIV hemodynamics. The model provided consistent transvalvular pressure gradients and reflected the in vivo pathology of the calcified valve.

To simulate calcification, the most frequent mode of failure in pericardial bioprostheses, BioGlue (CryoLife, Inc, Kennesaw, GA) was applied to the leaflets of normal

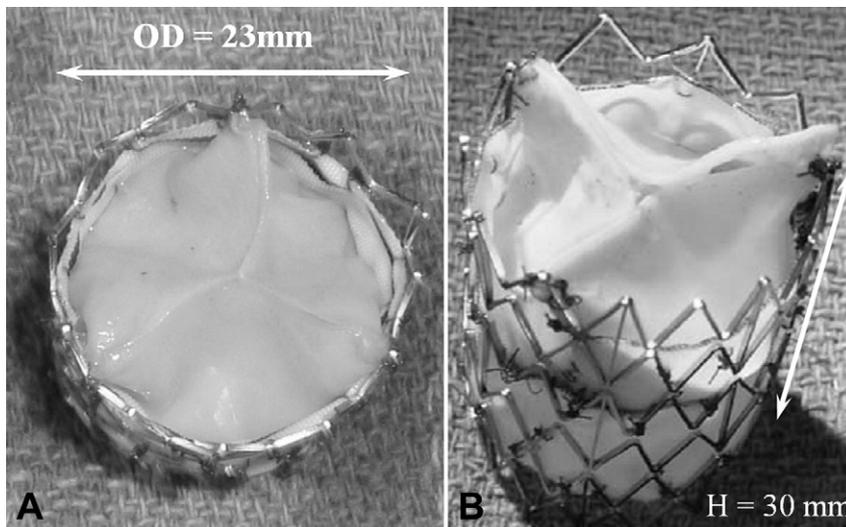


Fig 2. Supra-aortic transcatheter aortic valves are shown in (A) top and (B) side views.

bioprostheses to stiffen the leaflets and imitate calcification [6]. An additional sheet of pericardium was needed to maintain BioGlue adherence and prevent dislodgement during balloon predilatation of the bioprosthesis before TAV implantation. Although various epoxy and commercial glues were used, BioGlue was most effective at simulating degeneration.

Three pieces of Edwards Bovine Pericardial Patch were cut in half-circles with the same diameter as that of the leaflet's free edge. Each piece of pericardium was sutured to 1 of the 3 leaflets of the bioprosthesis on the aortic side by a polypropylene 6-0 running suture along the circular part of the piece, from the bottom of the bioprosthesis sinus to the commissure. No sutures were made on the free edge of the leaflet bioprosthesis in order to create a pocket for the BioGlue. Approximately 2 to 3 mL of BioGlue was then injected into the pockets to reach the desirable pressure gradient (Fig 3). A mean bioprosthetic gradient of 50 mm Hg was set as the goal based on echocardiographic data of degenerated aortic bioprostheses [7, 8]. The bioprosthetic degeneration model reproduced the hemodynamics of a patient with severe bioprosthetic aortic stenosis.

#### Pulse Duplicator System

An in vitro study provides a consistent and well-controlled environment to examine VIV hemodynamics. The valves were tested at room temperature in a custom-built pulse duplicator system developed for TAV implantation (Vivitro Systems Inc, Victoria, BC, Canada). This system is a pulsatile-flow model of the left side of the heart and systemic circulation. Heart rate, blood pressure, and cardiac output were used as control variables for the waveform generator controlling a servo pump. Each stroke of the pump's piston changed the pressure surrounding a compliant silicone left ventricle, causing ejection through the aortic valve. A recirculating fluid of 36% by volume glycerin solution in normal saline solution was used as a blood analogue fluid, which mimicked blood viscosity at 37°C when tested at room temperature. The physiologic circulation was simulated through viscoelastic ventricular contraction, blood-simulating fluid, and control of local compliance and peripheral resistance [9-11]. Pulse duplicator input variables were used to match International Organization for Standardization (ISO) 5840 and Food and Drug Administration standards for testing heart valves: heart rate of 70 beats/min, 35% systolic duration of cycle period, mean atrial and aortic pressures of 10 and 100 mm Hg, and cardiac output 5 L/min [12, 13]. These hemodynamic variables were maintained constant throughout the study.

#### Hemodynamic Measurements

Valve hemodynamics were evaluated with three variables: effective orifice area, mean pressure gradient, and regurgitant volume. Pressure was measured in the left atrium, left ventricle, left ventricular outflow tract, and ascending aorta with strain gauge pressure transducers (Cobe Laboratories Inc, Lakewood, CO). An electromagnetic flowmeter (Carolina Medical Electronics Inc, Old-

town, NC) was used to measure the aortic valve flow rate and the regurgitant volume. Effective orifice area within the TAV was then calculated using the Gorlin equation. Regurgitant fraction was also calculated, defined as the aortic retrograde flow divided by systolic ejection flow. Two-dimensional echocardiography (ACUSON Sequoia C256, Siemens Medical Solutions USA, Inc, Malvern, PA) was used to identify leakage and leakage location and to assess valve opening and closing processes.

#### Data Acquisition and Analyses

To study the efficacy of VIV implantation, the following experiments were conducted in the pulse duplicator: First, supra- and transvalvular TAVs were tested alone in the pulse duplicator to determine the efficacy of the TAV before implantation. Data acquisition was run over 10 consecutive cardiac cycles, and transvalvular pressure gradient, regurgitant volume, and effective orifice area were determined. Then, a normal Carpentier-Edwards PERIMOUNT aortic bioprostheses was tested to obtain a hemodynamic baseline. Subsequently, the same sized degenerated Carpentier-Edwards PERIMOUNT aortic bioprostheses was tested in the pulse duplicator. Finally after balloon predilatation of the degenerated bioprosthesis, the supra- and transvalvular TAV was implanted within the bioprosthesis. Measurements were performed for three bioprosthetic valve sizes (19, 21, and 23 mm; n = 3 of each bioprosthetic size). Hemodynamic measurements were compared using a one-way analysis of variance (ANOVA). Reported values are quoted as mean  $\pm$  standard deviation and statistical analyses were performed using MATLAB 7.0 software (Natick, MA).

#### Results

The 23-mm supra- and transvalvular TAVs made in the laboratory had a mean pressure gradient of  $5.2 \pm 3.7$  mm Hg and an effective orifice area of  $2.5 \pm 0.7$  cm<sup>2</sup> when tested alone in the pulse duplicator. Normal Carpentier-Edwards PERIMOUNT bioprostheses were tested in the pulse duplicator to compare VIV hemodynamics with standard surgical aortic valve replacement. A summary of hemodynamic results from the normal Carpentier-Edwards PERIMOUNT bioprostheses is presented in Table 1. Bioprostheses with simulated degeneration achieved the desired gradient, mean pressure gradient was  $53.9 \pm 3.8$

Table 1. Hemodynamic Characteristics of Normal Carpentier-Edwards PERIMOUNT Bioprosthesis

Normal PERIMOUNT Bioprosthesis	Mean Pressure Gradient, mm Hg	Effective Orifice Area, cm <sup>2</sup>	Regurgitation Fraction, %
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
19 mm	16.2 $\pm$ 2.2	1.28 $\pm$ 0.10	6.1 $\pm$ 1.1
21 mm	11.8 $\pm$ 1.9	1.52 $\pm$ 0.13	8.2 $\pm$ 2.0
23 mm	5.7 $\pm$ 0.9	2.18 $\pm$ 0.17	8.4 $\pm$ 1.8

SD = standard deviation.

mmHg in 19 mm,  $49.3 \pm 3.1$  mm Hg in 21 mm, and  $54.0 \pm 3.5$  mm Hg in 23 mm valves (Fig 4A). The 23-mm supra- valvular TAV reduced mean pressure gradient significantly for all degenerated bioprostheses (Fig 4A). In the 23-mm degenerated bioprostheses, mean pressure gradient decreased significantly from  $54.0 \pm 3.5$  to  $9.2 \pm 6.3$  mm Hg ( $p < 0.001$ ). Furthermore, a significant reduction in the mean pressure gradient was observed after 23-mm supra- valvular TAV implantation in the 21-mm ( $49.3 \pm 3.1$  to  $14.4 \pm 4.7$  mm-Hg,  $p < 0.001$ ) and in the 19-mm degenerated bioprostheses ( $53.9 \pm 3.8$  to  $28.3 \pm 9.8$  mm-Hg,  $p = 0.013$ ).

The 23-mm supra- valvular TAV significantly increased the effective orifice area of all degenerated bioprostheses (Fig 4B). Effective orifice area increased from  $0.70 \pm 0.02$  to  $1.87 \pm 0.55$  ( $p = 0.021$ ) in the 23-mm degenerated bioprostheses, from  $0.74 \pm 0.02$  to  $1.39 \pm 0.22$  ( $p = 0.007$ ) in 21-mm, and from  $0.70 \pm 0.02$  to  $1.00 \pm 0.14$  ( $p = 0.024$ ) in 19-mm degenerated bioprostheses.

However, regurgitant fraction also increased significantly in all bioprosthetic valves after 23-mm supra- valvular TAV implantation (Fig 4C). Regurgitant fraction of supra- valvular TAVs at baseline was determined in the pulse duplicator and found to be  $12.58\% \pm 0.77\%$ . Two- dimensional echocardiography assessment of the valve showed that the leakage was mainly para- valvular. After VIV implantation, regurgitant fraction increased significantly, from  $4.34\% \pm 1.36\%$  to  $17.09\% \pm 1.65\%$  ( $p < 0.001$ ) in 19-mm bioprostheses, from  $4.82\% \pm 1.61\%$  to  $16.86\% \pm 5.35\%$  in 21-mm bioprostheses ( $p = 0.020$ ), and from  $5.87 \pm 1.81\%$  to  $20.58 \pm 3.51\%$  ( $p < 0.001$ ) in 23-mm bioprostheses.

VIV hemodynamics for each bioprosthetic size were compared with hemodynamics of normal Carpentier- Edwards PERIMOUNT bioprostheses to compare VIV therapy with surgical rereplacement with equivalently sized bioprostheses. Supra- valvular TAV reduced mean pressure gradient to  $9.2 \pm 6.3$  mm Hg in the 23-mm degenerated bioprostheses, which was not significantly different than the mean pressure gradient of  $5.7 \pm 0.9$  mm Hg ( $p = 0.422$ ) for normal 23-mm PERIMOUNT bioprostheses. Similarly, VIV mean transvalvular gradient of  $14.4 \pm 4.7$  mm Hg in 21-mm bioprostheses was not significantly different than the  $11.8 \pm 1.9$  mm Hg ( $p = 0.306$ ) of normal 21-mm PERIMOUNT bioprostheses. Even in 19-mm bioprostheses, although the obtained VIV mean pressure gradient of  $28.3 \pm 9.8$  mm Hg was higher than that of the normal 19-mm PERIMOUNT bioprostheses ( $16.2 \pm 2.2$  mm Hg), the difference was not statistically significant ( $p = 0.056$ ).

### Comment

This study describes a supra- valvular TAV designed for treatment of bioprosthetic degeneration. Although current transcatheter aortic valves have demonstrated encouraging results for a 21-mm PERIMOUNT and 23-mm Mitralflow bioprosthesis, published clinical experience remains limited [1–3]. We have previously shown that the current Edwards SAPIEN intravalvular TAV design re-

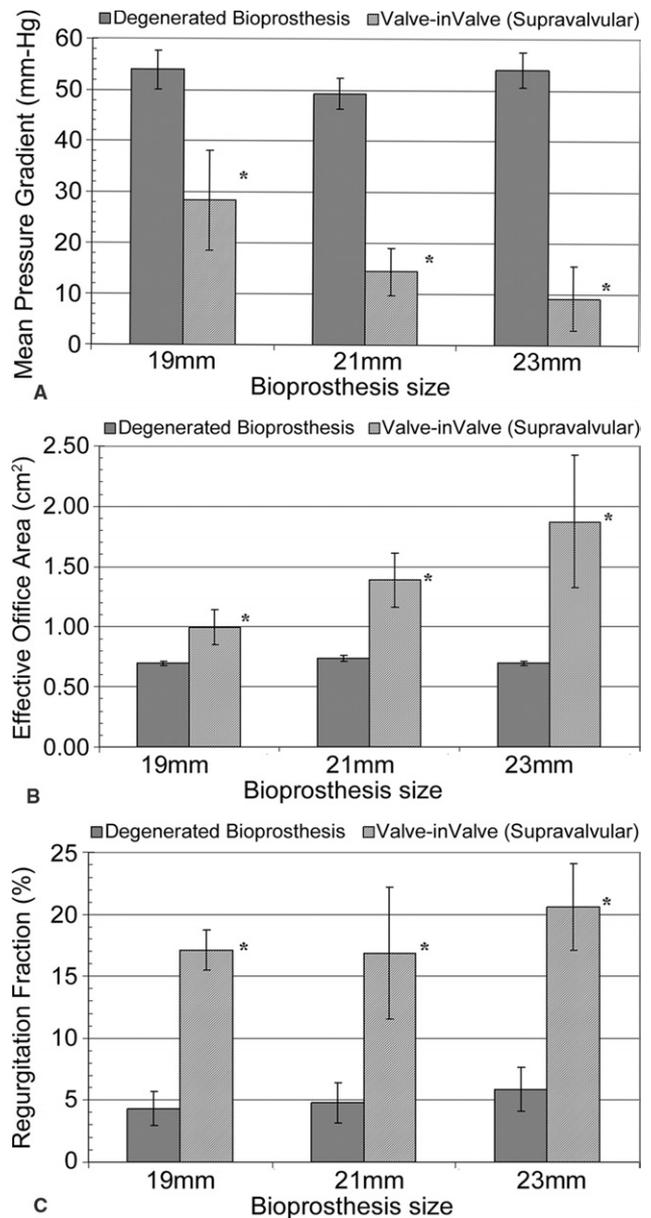


Fig 4. (A) Mean transvalvular pressure gradient of bioprostheses before and after transcatheter aortic valve (TAV) implantation ( $*p < 0.02$ ). (B) Effective orifice area of bioprostheses before and after TAV implantation ( $*p < 0.025$ ). (C) Regurgitant volume of bioprostheses before and after TAV implantation ( $*p \leq 0.02$ ). Mean data are presented with the standard deviation (error bar).

sulted in unacceptable hemodynamics within small normal bioprostheses in in vitro studies, particularly the 19-mm size [5]. The fundamental principle of our supra- valvular design is to move the valve leaflets above the bioprosthesis to avoid constraining the size of the valve by the bioprosthetic annulus and stent posts. A Dacron- covered stainless stent within the degenerated bioprosthesis would yield the maximum circular orifice area achievable within the bioprosthesis and minimize para- valvular leakage, while the valve leaflets within the open

stent above would allow flow into the coronary orifices. In this study, we examined the hemodynamics of our supra- valvular TAV within pericardial bioprostheses degenerated using BioGlue in a pulse duplicator setup.

Hemodynamic performance of 23-mm supra- valvular TAVs was studied within Carpentier-Edwards pericardial bioprostheses. The supra- valvular TAV successfully relieved the bioprosthetic stenosis in all three bioprosthetic sizes. The obtained VIV transvalvular gradients were comparable with standard surgical valve replacement of equivalent size. For a 19-mm degenerated bioprosthetic, however, a lower pressure gradient can be expected from surgical aortic valve replacement with a 19-mm valve. The corresponding difference in effective orifice area of 1.00 cm<sup>2</sup> for VIV in a 19-mm bioprostheses vs 1.28 cm<sup>2</sup> for rereplacement with a 19-mm bioprosthetic may or may not have significant clinical effect depending on the patient's body surface area and comorbidities that affect the risk/benefit ratio of open and minimally invasive procedures.

VIV implantation in these circumstances could still benefit nonsurgical and very high-risk patients. Careful clinical judgment regarding the surgical risks of reoperative valve replacement and the severity of dysfunction of the degenerated bioprosthetic should be taken into account before decisions are made between an operation and VIV implantation in these instances. Overall, our supra- valvular TAVs demonstrated good hemodynamics within small-sized degenerated bioprostheses and were effective in relieving bioprosthetic stenosis.

A potential complication not encountered with surgical rereplacement with a bioprosthetic was the increase in regurgitation with VIV implantation. Regurgitant volume increased significantly after implantation of 23-mm supra- valvular TAVs in all three bioprostheses. The leak was mainly paravalvular, which was assessed using 2-dimensional echocardiography. Intravalvular leak, which was caused by incomplete coaptation of leaflets, was also observed in the 19-mm bioprosthetic. The top portion of the supra- valvular TAV could not be fully expanded in the 19-mm bioprosthetic because the lower portion was tightly constrained by the small size bioprosthetic. Therefore, the TAV leaflets were distorted because of an excess of

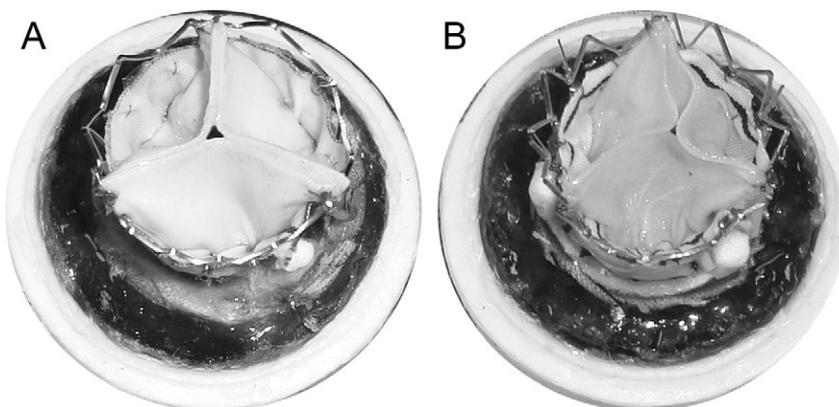
pericardial tissue relative to the stent orifice area (Fig 5). A more flexible stent design using a nitinol stent in the supra- valvular portion may facilitate the expansion of the supra- valvular TAV and improve hemodynamics. Paravalvular leak has similarly been a problem for clinical implantation of Edwards SAPIEN TAV within native stenosed aortic valves [14, 15].

The risks of reoperative valve procedures may have to be weighed against an imperfect result with VIV, where hemodynamic stenosis is relieved with some degree of aortic regurgitation. Owing to the irregularity of the landing zone in both bioprosthetic and native aortic stenosis, complete coaptation of the TAV stent to the bioprosthetic or native annulus would not be expected and some degree of paravalvular leakage would be expected.

The VIV prostheses were stable and no TAV migration was observed. Placing a larger valve above the bioprosthetic helped to avoid any TAV displacement, especially during the diastolic phase where the dominant drag force was applied to TAV [16, 17]. Furthermore, because the lower portion of the stent was to hold the TAV within the bioprosthetic and the valve was located above the bioprosthetic, no TAV leaflet distortion or traumatic injury to the leaflets by calcification was observed within the 21- and 23-mm bioprostheses. Zegdi and colleagues [18] described such leaflet distortion during TAV implantation within native aortic valves.

The next step for determining the effect of the supra- valvular TAV on bioprosthetic stenosis is to document the effect of this design on coronary flows after implantation. It is unknown whether movement of the valve above the bioprosthetic improves hemodynamics but adversely affects coronary flows. The height of the supra- valvular TAV in relation to the height of the aortic sinuses is crucial for successful implantation of the 23-mm supra- valvular TAV. Ideally, the supra- valvular portion remains within the sinus; however, if it extends into the ascending aorta, the diameter of the ascending aorta above the sinuses is also a critical variable. The supra- valvular TAV completely within the aortic sinus or smaller in diameter than the ascending aorta if extending to the ascending aorta should not obstruct coronary flow

Fig 5. (A) A 23-mm supra- valvular transcatheter aortic valve (TAV) implanted within a 21-mm bioprosthetic. (B) A 23-mm supra- valvular TAV implanted within a 19-mm bioprosthetic.



because the open stent would allow blood flow through the stent during valve closure.

In some patients, the coronaries reside close to the sowing cuff of the bioprosthesis or near the stent posts. Because the bioprosthetic cuff and stent posts constrain the TAV expansion in this region, we hypothesize that the covered Dacron stent would not obstruct the coronaries unless the degenerated bioprosthetic leaflets themselves had sufficient bulky calcification to obstruct low lying coronaries. The open valve stent of the TAV above the bioprosthesis expanded to full 23-mm size would allow flow into the sinus and coronaries during diastole while maximizing orifice area, particularly in small sized bioprostheses.

The effect of this design in altering the amount of coronary flow during diastole and pattern of flow should be studied not only experimentally but computationally. Precise echocardiographic measurement is required to determine the size of the ascending aorta and sinuses before TAV implantation. Future *in vitro* pulse duplicator and *in vivo* animal studies are required to address the effect of supra-avalvular TAV on coronary flow before safety trials in humans.

The primary limitation of the study is that the bioprosthetic valves used in our experiments were not degenerated and we used BioGlue to simulate calcification. TAV implantation within degenerated bioprosthesis could be more complicated due to leaflet calcification, stent deformation, or pannus. Although we cannot directly extrapolate our results to clinical practice, our *in vitro* study suggests that the 23-mm supra-avalvular TAV provides acceptable hemodynamics in 19-, 21-, and 23-mm degenerated bioprostheses. The regurgitant volume for VIV was higher than for a bioprosthesis, but the pressure gradient and effective orifice area were comparable with surgical valve replacement. The paravalvular leakage may have arisen from various sources, such as the suture line between the leaflets and Dacron sheet of the TAV itself, gaps between the tip of bioprosthetic leaflet and the base of the supra-avalvular TAV leaflet, or gaps between the bioprosthesis and TAV stent. Nevertheless, lower regurgitant volume is expected using blood instead of the working fluid, which does not have any coagulation properties.

In conclusion, we have developed a supra-avalvular TAV designed to treat bioprosthetic degeneration. This novel TAV consists of two components: a Dacron-covered stainless steel stent that sits within the bioprosthesis and a valve situated above the bioprosthesis. Successful VIV implantation was performed using this supra-avalvular TAV for treatment of bioprosthetic stenosis. The 23-mm supra-avalvular TAV successfully relieved bioprosthetic stenosis, and the obtained transvalvular pressure gradient was comparable with standard surgical valve replacement of equivalent size. Further studies are mandatory to examine the effect of the supra-avalvular TAV on coronary flows as well as device safety and efficacy in patients.

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