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Published in:
JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY

DOI:
10.1016/j.jtcvs.2019.05.084

Publication date:
2020

Pulmonary versus aortic pressure behavior of a bovine pericardial valve

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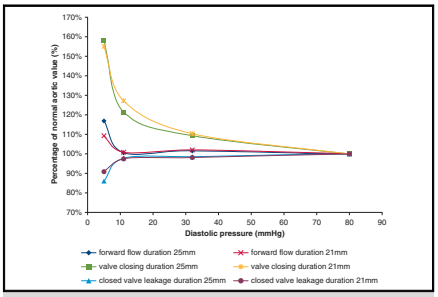
ABSTRACT

Background: The Carpentier Edwards Perimount Magna Ease aortic valvular prosthesis (Edwards Lifesciences, Irvine, Calif) has been among the most frequently and successfully used tissue prosthetic cardiac valves. Furthermore, this prosthesis has been used off-label in the pulmonary position. Until now, there has been a paucity of data regarding the functioning of tissue prosthetic valves under pulmonary conditions.

Methods: Using a pulse duplicator, hydrodynamic characteristics of a 21-mm and 25-mm Magna Ease valve were evaluated. Among parameters evaluated were leakage orifice area, closing time (ie, time required to close), and leakage duration. This procedure was performed under different pulmonic pressure conditions (15/5 mm Hg, 28/11 mm Hg, 73/32 mm Hg) and normal aortic pressure (120/80 mm Hg) as a reference. Moving images were obtained using a Phantom MIRO M320S high-speed camera (Vision Research Inc, Wayne, NJ) at 600 frames per second and used to analyze valve area in closed position.

Results: Under normal pulmonic conditions (28/11 mm Hg) the leakage orifice area was 0.020 ± 0.012 mm^2 for the 21-mm valve and 0.054 ± 0.041 mm^2 for the 25-mm valve ($P = .03$). Hydrodynamic characteristics of the valves differed between pulmonary and aortic testing condition. Valve closing volumes were significantly lower under pulmonary hypotension and normal pulmonary conditions than under normal aortic conditions ($P < .05$).

Conclusions: Under normal pulmonary pressure conditions, the hydrodynamic characteristics of Magna Ease valves are significantly different compared with aortic conditions. Further research is needed to determine whether these results are associated with prosthetic valve failure. (J Thorac Cardiovasc Surg 2020;159:1051-9)



Forward flow, closing, and leakage duration compared with normal aortic conditions.

Central Message

Under normal pulmonary pressure conditions, the hydrodynamic characteristics of Magna Ease (Edwards Lifesciences, Irvine, Calif) valves are significantly different compared with aortic conditions.

Perspective

Little research has been done on the functionality of prosthetic heart valves in the pulmonary position. With this study we demonstrate that under normal pulmonary pressure conditions, the hydrodynamic characteristic of Magna Ease (Edwards Lifesciences, Irvine, Calif) valves are significantly different compared with aortic conditions. Further research is needed to determine the clinical relevance of these results.

See Commentaries on pages 1060 and 1061.

A spectrum of congenital cardiac defects require the surgical replacement of the pulmonary valve. There are several options for pulmonary valve replacement (PVR), including homografts, bovine jugular vein conduits, and biological and mechanical prosthetic valves. Homograft valves are not always available and often have limited size options,

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Received for publication Aug 10, 2018; revisions received May 14, 2019; accepted for publication May 16, 2019; available ahead of print Aug 2, 2019.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.05.084

Abbreviations and Acronyms
EOA = effective orifice area
PVR = pulmonary valve replacement

yet bovine jugular vein conduits are limited in size and appear to be associated with an increased occurrence of infective endocarditis.[1] Mechanical valves are associated with a continuous risk of valvular thrombosis and require lifelong anticoagulation therapy.[2] These circumstances make biological valvular prostheses a widely used option for PVR, especially for adults.

The most frequently used prosthetic valvular prosthesis is the Carpentier Edwards Perimount Magna Ease (Edwards Lifesciences, Irvine, Calif) heart valve, the leaflet material of which is made out of bovine pericardial tissue. In the aortic position, results for the Perimount family of valves have been excellent, both in young and elderly populations.[3] The durability of the Magna Ease valve has been shown to be promising in an in vitro test situation under aortic valvular pressure conditions.[4] However, in the pulmonary position the clinical results of biological prosthetic valves have not been uniform.[5-9]

In this context, it is pertinent to remark that all prosthetic valves that are used in the pulmonary position for adults are originally designed for the aortic position. When valvular prostheses are implanted into the right ventricle they are exposed to hemodynamic conditions that are essentially different from the left ventricle, characterized in particular by much lower pressures. We hypothesize that the behavioral characteristics of bioprosthetic valvular prostheses are related to the systolic and diastolic pressures exerted upon the valve.

MATERIALS AND METHODS

Valves

For the in vitro simulation, the Carpentier-Edwards Perimount Magna Ease aortic 3300 TFX prosthetic valve was used. Prosthetic valves were tested in the sizes 21 mm and 25 mm. These sizes were selected to represent the usual range of pulmonary prosthetic valves in adolescents and adults. Sewing ring and stiches of the valves were sealed after mounting in the test setup with silicone to prevent paravalvular leakage.

Testing Setup

Right and left ventricular conditions were simulated with the use of the Edwards Valve Analyzer (Edwards Lifesciences), a pulsatile flow system used to conduct hydrodynamic testing. The system is powered by a piston driven pump, as shown in Figure 1. The system allows for testing according to Food and Drug Administration guidelines. Aortic and pulmonary testing was performed in the same test setup under the same flow profiles. To adapt

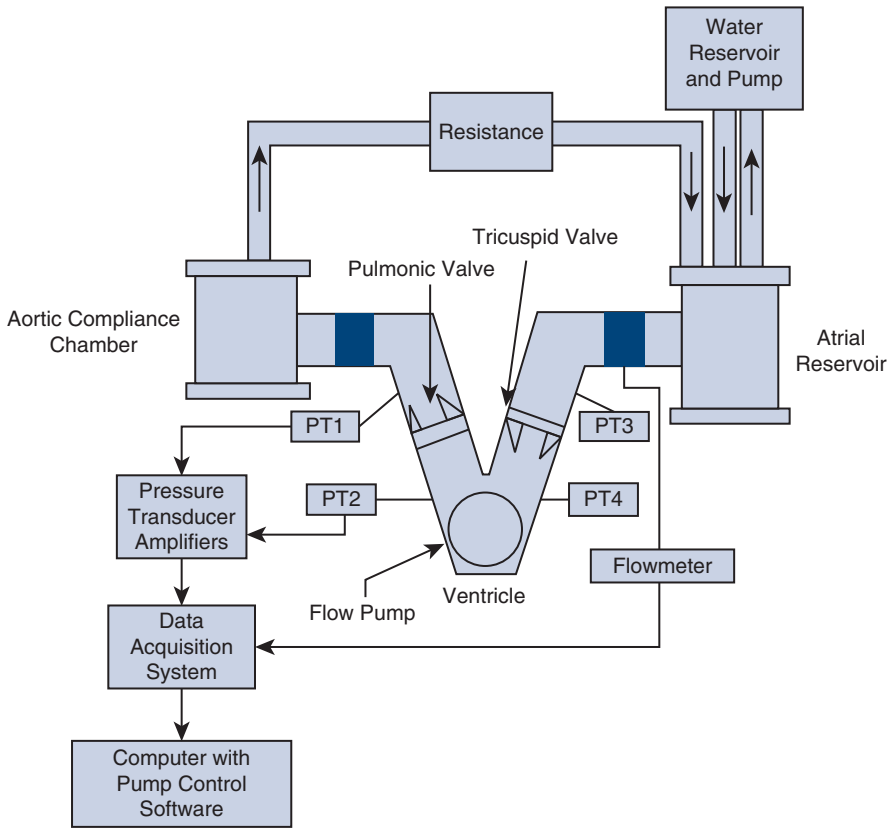


FIGURE 1. Schematic drawing of the Edwards Valve Analyzer (Edwards Lifesciences, Irvine, Calif). *PT*, Pressure transducer.

TABLE 1. Pressure conditions used for valve evaluation

Pressure condition	Peak systolic pressure (mm Hg)	End diastolic pressure (mm Hg)
Pulmonary		
Hypotension	15	5
Normotension	28	11
Severe hypertension	73	32
Aortic*		
Normotension	120	80

*Reference condition.

the test setup to right ventricular conditions for pulmonary testing, the atrial reservoir and the afterload compliance chamber were adjusted to right cardiac conditions. An additional chamber was added to create more volume in the afterload compliance chamber. To make the Edwards Valve Analyzer operable for testing of the 21-mm and 25-mm pulmonary valves, respectively, a 29-mm and 31-mm Perimount mitral valvular prosthesis was used in the tricuspid position to complete the test system. The pulmonary and tricuspid valvular prostheses were matched based on normal native pulmonary and tricuspid valve sizes.[10,11]

Images were obtained using a high-speed camera: model Phantom MIRO M320S (Vision Research Inc, Wayne, NJ) at 600 frames per second. Residual open valve areas, if any, in closed position was measured using the image processing software ImageJ (National Institutes of Health and the Laboratory for Optical and Computational Instrumentation, Washington, DC).[12] Stills were taken for 3 consecutive cycles when the valve was stable in closed position without resonances in the pressure measuring system and the forward flow was 0. Resonance is a phenomenon consisting of small repetitive pressure differences initiated by the oscillation of the valve leaflets caused by a small periodic stimulus close to the natural frequency of the leaflets.

Test Conditions

We used 3 pulmonary valve-like test conditions and 1 aortic valve reference condition (Table 1), based on the ISO 5840-1 guidelines.[13] We accepted a variance of 10% for arterial peak systolic pressure and arterial end diastolic pressure. For each valve size, 3 valves were tested and for each testing condition 10 measurements were taken from consecutive selected cycles. The following variables were evaluated:

- Mean pressure difference: Mean pressure difference (in millimeters mercury) over the prosthetic valve during forward flow;
- Forward flow volume: Flow volume (in millimeters) ejected through the prosthetic valve in a forward direction during 1 cycle (Figure 2);
- Forward flow duration: The time range (in milliseconds) within 1 cycle in which the flow through the pulmonary valve is in forward direction (Figure 2);
- Regurgitant volume: fluid volume (in milliliters) that flows through a prosthetic valve in reverse direction during 1 cycle (a combination of closing volume and leakage volume, where closing volume is defined as the volume that flows in reverse direction during the beginning of the closing period, when the leaflets start to move, until that very movement has stopped, and leakage volume is defined as the volume that flows in reverse direction after the end of the closing period until the beginning of the opening movement of the leaflets);
- Regurgitant fraction: Regurgitant volume expressed as a percentage of the forward flow volume;
- Closing volume: Proportion of the regurgitant volume (in milliliters) that is associated with the dynamics of valve closure during a single cycle (Figure 2);
- Closing time: The time interval (in milliseconds) associated with the dynamics of valve closure during a single cycle (Figure 2);

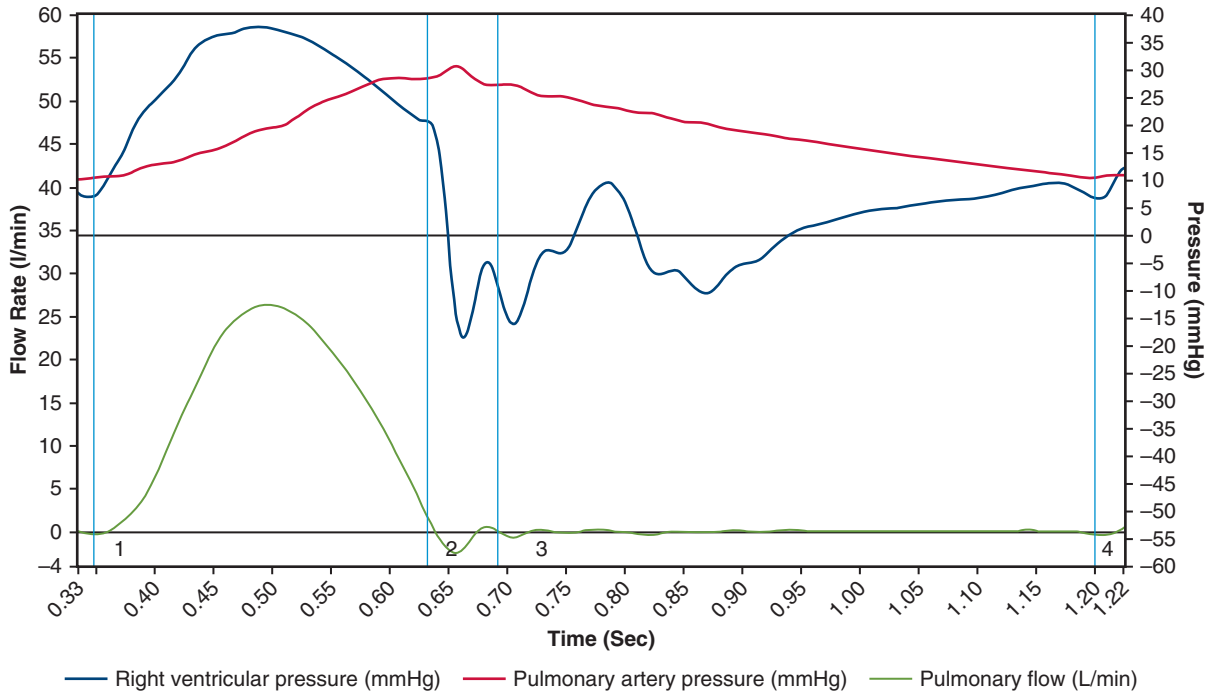


FIGURE 2. Edwards Valve Analyzer (Edwards Lifesciences, Irvine, Calif) output for pulmonic normotensive (28/11 mm Hg) condition (size 21 mm). Distance between points 1 and 2 indicate forward flow duration. Distance between points 2 and 3 indicate closing time and closing volume. Distance between points 3 and 4 indicate leakage duration and leakage volume.

- Leakage volume: Proportion of the regurgitant volume (in milliliters) associated with leakage during the closed phase of a valve in a single cycle (Figure 2);
- Leakage duration: The time (in milliseconds) between the closure of the valve and the beginning of forward flow during a single cycle (Figure 2); and
- The effective orifice area (EOA) (in centimeters^2): $EOA = \frac{Qv_{RMS}}{51.6\times\sqrt{\frac{\Delta p}{\rho}}}$

  where Qv_{RMS} is the root mean square forward flow (in milliliters per second) during the positive differential period, Δp is the mean pressure difference (in millimeters mercury), and ρ is the density of the test fluid (grams per centimeters^3).

Tests were performed using a phosphate buffered saline solution with a density of 1.006 g/cm^3, at room temperature. Heart rate was maintained at 70 bpm, cardiac output was set at 5 L/min and systolic duration was kept at 35%.[13]

Statistical Analyses

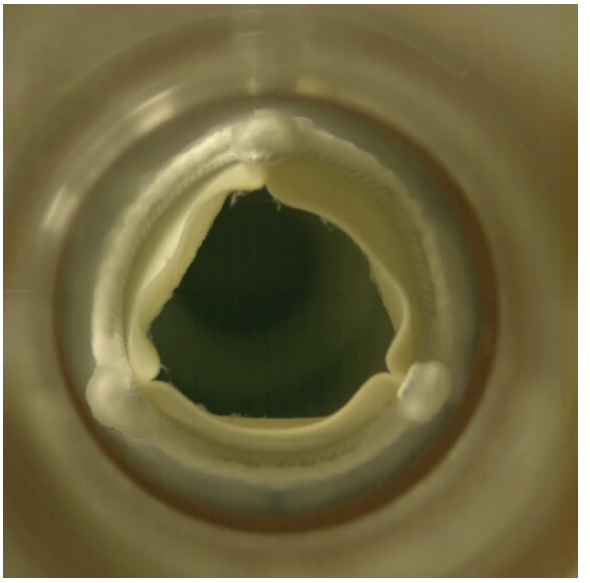
Continuous variables are presented as mean ± standard deviation. Repeated measures analysis of variance with Bonferroni testing was used to compare means between different test conditions, and analyses were stratified by valve size. Valve size was added to the unstratified model to detect differences between valve size. All statistical analyses were performed using an IBM SPSS Statistics version 23 (IBM-SPSS Inc, Armonk, NY).

RESULTS

Flow and pressure profiles generated under pulmonary condition are shown in Figure 2, and were deemed adequate for evaluation.[14] Some resonance in the flow and pressure curves under low-pressure conditions was observed.

The video images illustrate an increase in closing time with decreasing pressures. Video 1 shows the opening and closing of a 25-mm valve under normal pulmonary conditions and Video 2 under normal aorta conditions. During testing under the normal (28/11 mm Hg) and hypotensive (15/5 mm Hg) pulmonary pressure conditions, the valve did not completely close (Figure 3), thus leaving a regurgitant opening. Under normal pulmonary testing conditions (28/11 mm Hg), the area of the regurgitant opening closed position was 0.020 ± 0.012 mm^2 for the 21-mm valve and 0.054 ± 0.041 mm^2 for the 25-mm valve (P = .03). For hypotensive pulmonary testing conditions (15/5 mm Hg) the regurgitant area was 0.097 ± 0.026 mm^2 for the 21-mm valve and 0.19 ± 0.13 mm^2 for the 25-mm valve (P = .041) (Figure E1).

Closing duration was, 54.6 ± 3 ms for a 25-mm valve compared with 42.9 ± 3.2 ms (P < .001) for the 21-mm valve, leakage duration was 524 ± 3.9 ms compared with 539 ± 3.5 ms (P < .001), respectively, under 28/11 mm Hg and 120/80 mm Hg. Closing time decreased with increasing pressure conditions, whereas the leakage duration increased. Leakage duration is the period in which the valve is in closed position. Figure 4 shows the difference between the aorta reference and pulmonary testing conditions in percentages for the forward flow duration, leakage duration, and closing time. Under all pulmonary test conditions, the closing time and leakage duration differed significantly from the aortic position (P <.001). The forward flow duration was significantly longer for the pulmonary hypotension testing condition (15/5 mm Hg) compared with the aortic position (P < .001).



VIDEO 1. Opening and closing of a 25 mm Carpentier Edwards Magna Ease valve (Edwards Lifesciences, Irvine, Calif) under normal pulmonary pressure condition (28/11 mm Hg). Video available at: https://www.jtcvs.org/article/S0022-5223(19)31338-8/fulltext.

VIDEO 2. Opening and closing of a 25 mm Carpentier Edwards Magna Ease valve (Edwards Lifesciences, Irvine, Calif) under normal aortic pressure condition (120/80 mm Hg). Video available at: https://www.jtcvs.org/article/S0022-5223(19)31338-8/fulltext.

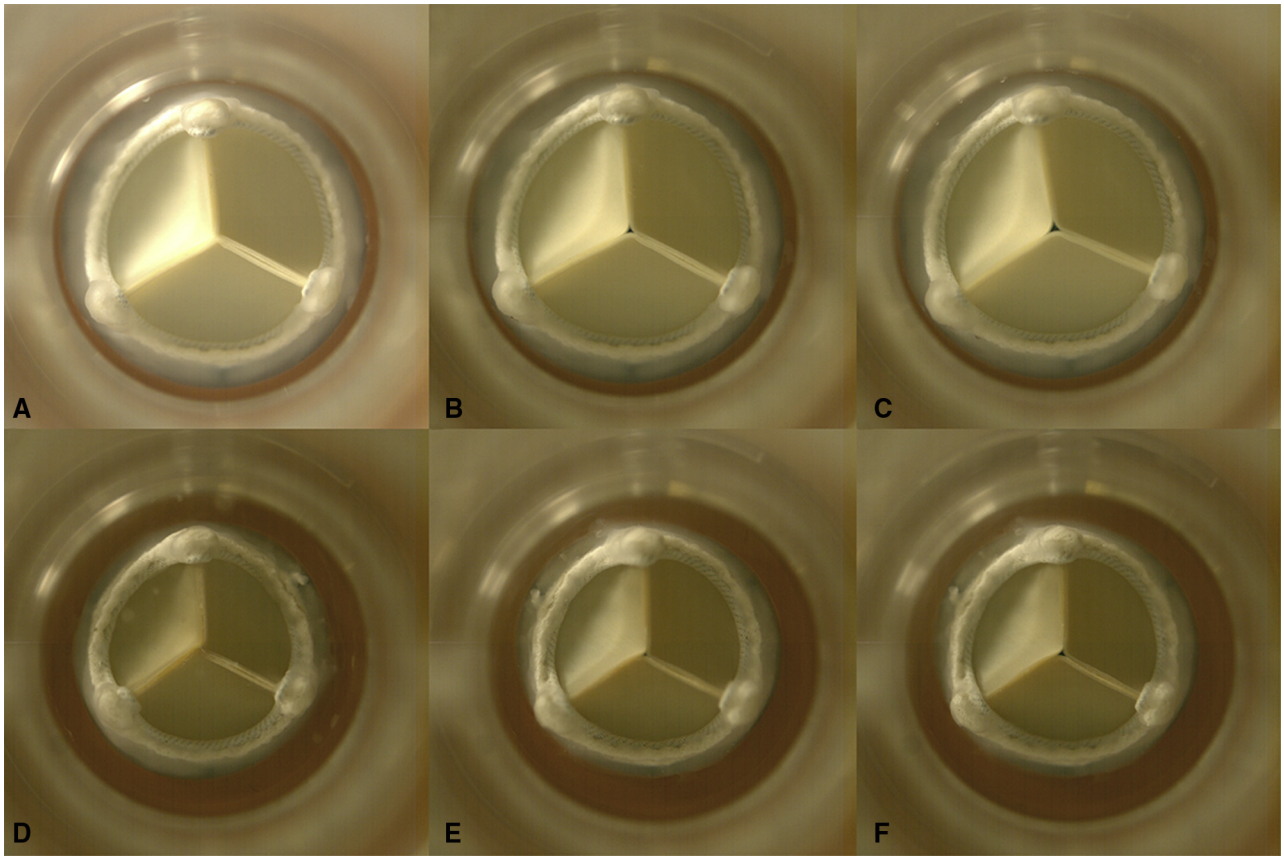


FIGURE 3. Perimount Magna Ease (Edwards Lifesciences, Irvine, Calif) valve in closed position. A, 25-mm valve under normal aortic testing conditions (120/80 mm Hg). B, 25-mm valve under normal pulmonary testing position (28/11 mm Hg). C, 25-mm valve under pulmonary hypotension testing conditions (15/5 mm Hg). D, 21-mm valve under normal aortic testing conditions (120/80 mm Hg). E, 25-mm valve under normal pulmonary testing position (28/11 mm Hg). F, 21-mm valve under pulmonary hypotension testing conditions (15/5 mm Hg).

Valvular closing volumes were significantly lower under hypotensive and normal pulmonary conditions than under normal aorta conditions ($P < .05$). Between pulmonary hypertensive conditions and aorta conditions there was no significant difference (Table 2). With increasing pressures, the total closing volume is larger, despite the decrease in closing time. The leakage volume does not show a distinctive trend with pressure (Table 2).

As could be expected, the mean systolic pressure difference over the prosthetic valve decreased with decreasing pressure conditions (Table 2). For both valves, the systolic pressure drop for the pulmonary testing conditions differed significantly ($P < .001$) from the reference aorta condition. Under all testing conditions, the mean pressure difference over the 25-mm valve was lower than over the 21-mm valve. EOA was higher for the 25-mm valve compared with the 21-mm valve, as was expected. With decreasing pressure differences, the EOA also decreases, with a significant difference between normal aortic conditions and all pulmonary conditions for both valve sizes ($P < .001$).

Regurgitant fractions were significantly decreased in normal (28/11 mm Hg) conditions for the 21-mm valve and under hypotensive (10/5 mm Hg) pulmonary conditions for both the 21-mm and 25-mm valves compared with aorta conditions (120/80 mm Hg) ($P < .001$) (Figure 5). For all valve sizes and testing conditions, the regurgitant fractions were considerably below 10%, the minimum requirement set by ISO for aortic valves.[15]

DISCUSSION

Although virtually all prosthetic cardiac valves have been designed for the aortic and mitral positions, they are also implanted, albeit off-label, in the pulmonary position. To the best of our knowledge, prosthetic valves designed specifically for use in the pulmonary position in adults do not exist yet. In this study we have shown that the Pericardial Magna Ease prosthetic cardiac valves behave differently under pulmonar conditions compared with aorta conditions in an in vitro test setup. Under pulmonary conditions compared with aorta test conditions, the pericardial Magna

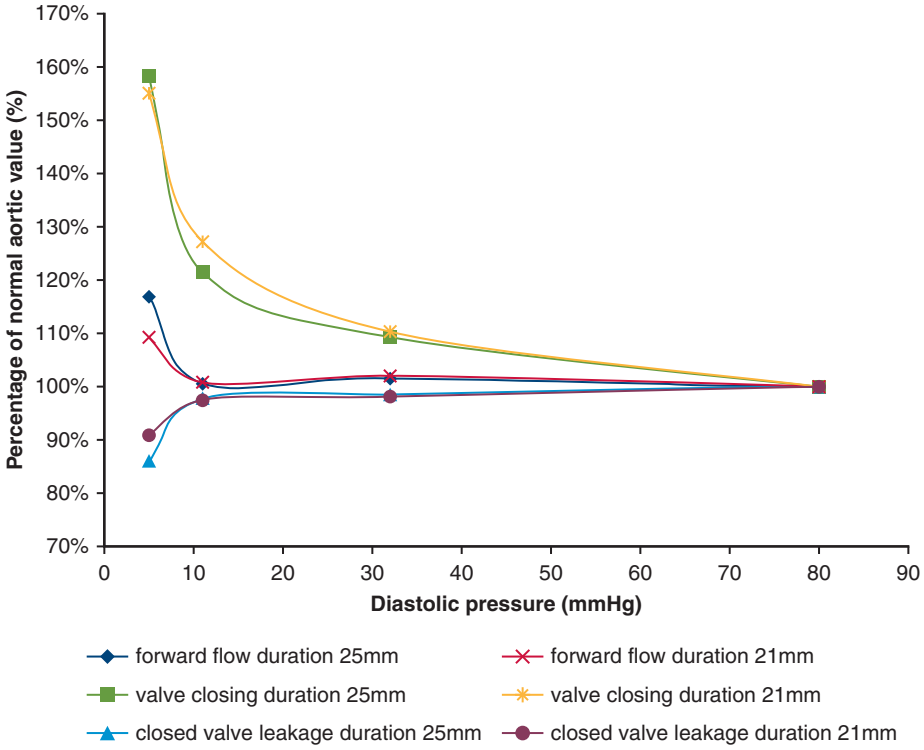


FIGURE 4. Percentage of forward flow duration, closing time, and leakage duration for the different pressure conditions compared with normal aortic conditions, for a 21-mm and 25-mm Magna Ease (Edwards Lifesciences, Irvine, Calif) prosthetic heart valve. Values for forward flow duration, closing time and leakage duration at aortic conditions (80 mm Hg) were set at 100%.

Ease valve had an increase in closing time and a reduction in leakage duration and volume, a decrease in pressure difference, and a decreased EOA. Because systolic pressure difference over a valve is in the denominator of the formula for EOA, identical valves have a lower EOA in the pulmonary position than in the aorta position. Therefore, a normal pulmonary valve is larger than an aorta valve.

Video recordings of the leaflet motion during the cardiac cycle showed that all valves do not close completely during diastole, without resonances under pulmonary testing conditions, in contrast to aorta conditions where full closure is always attained. Resonance can be caused by a rapidly decreasing oscillation of the volume because the prosthetic valve is not fully closed. A similar phenomenon can sometimes be seen within a pressure measuring setup at low pressures. Nonetheless, within the right ventricle this is likely to be not hemodynamically relevant, as far as regurgitant volume in concerned. Nonetheless, under pulmonary conditions the tension within the leaflets and the wall tension in the pulmonary artery is much lower than under aorta conditions, which may well contribute to long-term behavior.

The flow profiles created under pulmonary testing conditions and especially the hypotensive (10/5 mm Hg) testing conditions showed some resonance in both the flow and pressure curves. In the video images we observed these resonances during the closing of the valve. Most likely this is the natural behavior of the valve in a pulmonary position;

TABLE 2. Outcome variables under different testing conditions for each valve size

Condition*	Mean pressure difference (mm Hg)		Forward flow volume (mL)		Closing volume (mL)
	21 mm	25 mm	21 mm	25 mm	21 mm
Hypotension	11.89 ± 1.4†	6.74 ± 0.43†	72.23 ± 0.78†	72.24 ± 1.0†	0.63 ± 0.13†
Normotension	13.28 ± 0.73†	7.79 ± 0.15†	71.32 ± 0.38	71.04 ± 0.72	0.72 ± 0.16‡
Hypertension	14.83 ± 0.46†	8.85 ± 0.10†	70.79 ± 0.43†	70.71 ± 0.31‡	0.80 ± 0.13
Normal aortic	17.46 ± 0.65	10.54 ± 0.12	71.33 ± 0.57	70.97 ± 0.33	0.86 ± 0.16

*Conditions were defined as hypotension: 15/5 mm Hg, normotension 28/11 mm Hg, hypertension: 73/32 mm Hg, and normal aortic: 120/80 mm Hg. †$P < .001$ compared with the normal aortic reference value. ‡$P < .05$ compared with the normal aortic reference value.

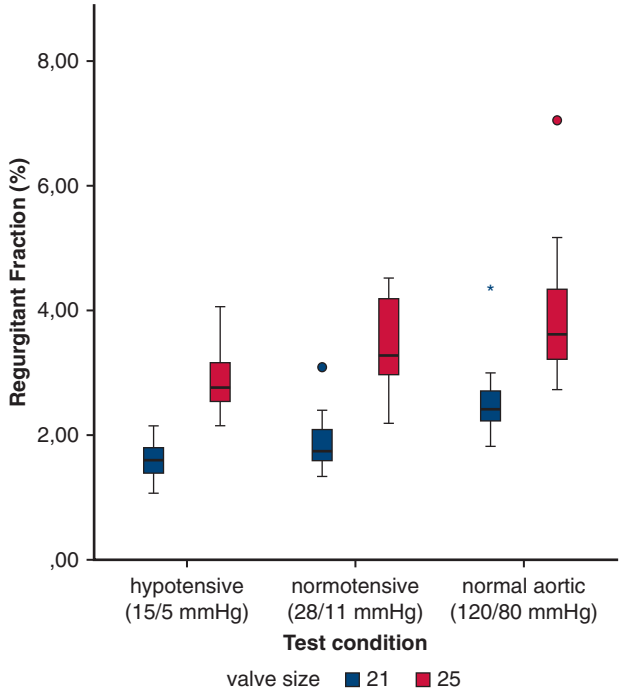


FIGURE 5. Boxplot for the regurgitant fractions of 21-mm and 25-mm Magna Ease (Edwards Lifesciences, Irvine, Calif) prosthetic heart valves under normal aortic, pulmonary hypotension, and normal pulmonary conditions. For each testing condition, 30 measurements were taken. *Upper* and *lower borders* of the *box* represent the upper and lower quartiles. The *middle horizontal line* represents the median. The *upper* and *lower whiskers* represent the maximum and minimum values of nonoutliers. Extra *dots* represent outliers.

however, we cannot be totally sure that the resonance in the testing system itself did not influence these patterns.

Although there has been no report on the opening and closing behavior of prosthetic heart valves under right ventricular conditions, some studies evaluated the opening and closing times of prosthetic heart valves under left ventricular conditions. Furthermore, there have been reports of increased opening and closing durations for pericardial valves compared with porcine valves.[16,17] In a study by Bottio and colleagues,[18] the Perimount valve showed lower closing volumes compared with other pericardial valves. In another study on the opening and closing behavior of pericardial valves by Tasca and colleagues,[19] the opening and closing behavior was not influenced by the position of the pericardial leaflets, but rather depended on the intrinsic structural characteristics of the material used for stents and leaflets. These results suggest that changes of the material could potentially adapt valves for the pulmonary position.[19]

Although the hydrodynamic characteristics of bioprosthetic valves under pulmonary conditions have not been published before, the valve has been extensively tested under aorta and mitral conditions, both in vitro and in vivo. Both in vitro and clinical results of the valves in the aortic position have shown excellent results compared with other biological prosthetic heart valves.[4,20,21] The Perimount Magna Ease series has been reported to have the best hydrodynamic properties in terms of EOA and pressure gradient compared with both porcine and other pericardial bioprosthetic valves.[16,18,20] The slight decrease we found in the EOA under pulmonary conditions will most likely have little effect on the hemodynamic functioning because pulmonary prosthetic valves are generally larger than aortic valve implants.

Previous clinical studies showed a reduced lifespan of biological valves in the pulmonary position.[9,22] However, there are many factors other than pressure differences that could influence this process. Extreme caution with translating our in vitro findings to the clinical practice is warranted. We could speculate that incomplete closure of the valve accelerates reduced motion of the leaflets, which could possibly influence pannus overgrowth onto the valve leaflets. The latter could potentially contribute to degeneration of the leaflets. It is unlikely that the incomplete closure has a direct effect on right ventricular function because the regurgitant fraction and leakage volume do not increase with decreasing pressures. In fact, regurgitant fractions decreased with decreasing pressures and stayed below 5% for all pulmonary testing conditions.

In this study we demonstrated that under similar circumstances 25-mm valves had a longer valve closing time and a larger leakage surface compared with 21-mm valves under

TABLE 2. Continued

Closing volume (mL)	Leakage volume (mL)		Regurgitant fraction (%)		Effective orifice area (cm^2)	
25 mm	21 mm	25 mm	21 mm	25 mm	21 mm	25 mm
1.04 ± 0.28†	0.54 ± 0.15†	1.06 ± 0.32	1.63 ± 0.27†	2.91 ± 0.53†	1.69 ± 0.035†	2.31 ± 0.089†
1.21 ± 0.18†	0.48 ± 0.15†	1.13 ± 0.37	1.85 ± 0.36†	3.42 ± 0.68	1.72 ± 0.033†	2.34 ± 0.029†
1.42 ± 0.30	0.69 ± 0.26‡	0.97 ± 0.32	2.20 ± 0.47‡	3.51 ± 0.80	1.75 ± 0.050†	2.38 ± 0.031†
1.53 ± 0.28	0.94 ± 0.35	1.15 ± 0.44	2.59 ± 0.66	3.87 ± 0.93	1.80 ± 0.052	2.43 ± 0.022

similar testing conditions. This could give reason to pay even more attention to the size of a prosthetic pulmonary valve. In general, surgeons are likely to oversize a prosthetic pulmonary valve. In most patients requiring PVR the right ventricular outflow tract has been surgically altered (eg, Fallot patients), in such a way that it invites for implantation of a larger valve. These results are difficult to translate directly into clinical behavior. This requires further research before making changes to the clinical practice.

The lifespan of patients with congenital heart disease has increased drastically in past decades. Currently there are more adults than children with congenital heart disease.[23] Pulmonary prosthetic valve replacements under both teenagers and adults are increasingly performed. More research of the hydrodynamic functionality and clinical results of prosthetic valves under pulmonary conditions are necessary to be able to evaluate which treatment option is most successful in these patients. We hope this research is a first step in that direction.

Limitations

Tests were performed using a saline solution and for all testing we have used the same flow profile. Although flow profiles over the aorta and pulmonary valve are quite similar, we do recognize that there are some minor differences in flow profiles that we did not take into account.[14] In our test setup we used the same ventricular simulator, not taking into account the difference in elastance between the ventricles.[24] Although it is not likely that this influences the basic principles of our results, because Dell'Italia and Santamore[25] showed that although the right ventricle is more complex, the pump properties are comparable to the high-pressure left ventricle. In this study all tests were performed using a saline solution with a density of 1.006 g/cm^3, whereas blood has a density of 1.06 g/cm^3. Although the difference in density will probably lead to different absolute numbers, the difference in proportions will likely be minimal. For demonstrating initial differences in in vitro testing, saline is an accepted fluid.

CONCLUSIONS

Under normal pulmonary pressure conditions, Perimount Magna Ease valves do not reach complete closure yet demonstrate minimal leakage. Within the right ventricle this is likely not hemodynamically relevant. Hydrodynamic characteristics of the valves were significantly different from aortic conditions. Further research is needed to evaluate whether or not these results are associated with potential increased risk of prosthetic valve failure in the pulmonary position.

Conflict of Interest Statement

Testing setup and materials were provided by Edwards Lifesciences, Irvine, Calif. Ms Pragt and Dr Ebels own rights to a patent for a mechanical valve design for the pulmonary position. Dr Mariani has been the recipient of an unrelated grant from Edwards Lifesciences. All other authors have nothing to disclose with regard to commercial support.

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Key Words: Pulomnary valve replacement, prosthetic heart valve

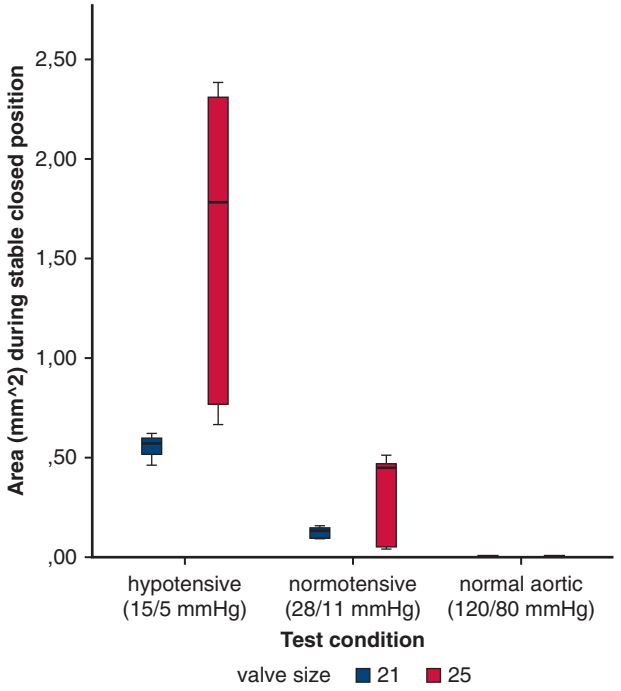

FIGURE E1. Area (mm^2) of valve opening during steady closure of the valve, showing the area that remains open when the valve is closed in steady position for a 21-mm and a 25-mm Manga Ease (Edwards Lifesciences, Irvine, Calif) prosthetic heart valve. For each testing condition 30 measurements were taken. *Upper* and *lower borders* of the *box* represent the upper and lower quartiles. The *middle horizontal line* represents the median. The *upper* and *lower whiskers* represent the maximum and minimum values of nonoutliers. Extra *dots* represent outliers.