Long-term durability of a new surgical aortic valve: A 1 billion cycle in vitro study

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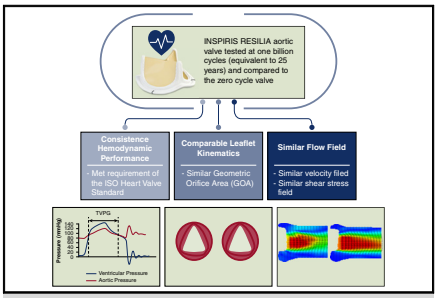
ABSTRACT

Background: This study assessed the long-term hemodynamic functional performance of the new Inspiris Resilia aortic valve after accelerated wear testing (AWT).

Methods: Three 21-mm and 23-mm Inspiris valves were used for the AWT procedure. After 1 billion cycles (equivalent to 25 years), the valves' hemodynamic performance was compared with that of the corresponding zero-cycled condition. Next, 1 AWT cycled valve of each valve size was selected at random for particle image velocimetry (PIV) and leaflet kinematic tests, and the data were compared with data for an uncycled Inspiris Resilia aortic valve of the same size. PIV was used to quantitatively evaluate flow fields downstream of the valve. Valves were tested according to International Standards Organization 5840-2:2015 protocols.

Results: The 21-mm and 23-mm valves met the International Organization for Standardization (ISO) durability performance requirements to 1 billion cycles. The mean effective orifice areas for the 21-mm and 23-mm zero-cycled and 1 billion–cycled valves were 1.89 ± 0.02 cm^2 and 1.94 ± 0.01 cm^2, respectively ($P < .05$) and 2.3 ± 0.13 cm^2 and 2.40 ± 0.11 cm^2, respectively ($P < .05$). Flow characterization of the control valves and the study valves demonstrated similar flow characteristics. The velocity and shear stress fields were also similar in the control and study valves.

Conclusions: The Inspiris Resilia aortic valve demonstrated very good durability and hemodynamic performance after an equivalent of 25 years of simulated in vitro accelerated wear. The study valves exceeded 1 billion cycles of simulated wear, 5 times longer than the standard requirement for a tissue valve as stipulated in ISO 5840-2:2015. (JTCVS Open 2022;9:59-69)



The 1 billion-cycled valve exhibits similar flow characteristics as a zero-cycled valve.

CENTRAL MESSAGE

The Inspiris Resilia aortic valve has demonstrated very good durability and hemodynamic performance after an equivalent of 25 years of simulated in vitro accelerated wear testing.

PERSPECTIVE

Surgical aortic valves must have long-term durability. The Inspiris Resilia valve performed well after in vitro testing simulating 25 years of wear, suggesting that it may be a viable option for patients. Other factors, such as leaflet thrombosis and calcification, may contribute to structural valve degeneration but are not studied here.

See Commentaries on pages 70 and 72.

More than 200,000 surgical aortic valve replacement (SAVR) procedures are performed annually worldwide.[1] Currently, bioprosthetic heart valves (BHVs) represent approximately 60% of the valves used in SAVR procedures globally. With the extension of BHV to younger patients,[2] valve durability and hemodynamic performance have emerged as more important issues in SAVR. Structural valve degeneration (SVD) as a result of fracture, leaflet tear, mechanical wear, and calcification[3] may result in valve dysfunction and necessitate reintervention. Histologic evaluation of explanted valves has demonstrated that leaflet tears and disrupted collagen fiber bundles are found in areas of high leaflet strain, even in the absence of associated calcification.[4] This suggests that mechanical stress plays a significant role in the development of SVD.[5]

Forcillo and colleagues[6] evaluated the Carpentier-Edwards Perimount aortic valve and reported a freedom

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Abbreviations and Acronyms

AWT = accelerated wear testing
BHV = bioprosthetic heart valve
EOA = effective orifice area
GOA = geometric orifice area
PIV = particle image velocimetry
SAVR = surgical aortic valve replacement
SVD = structural valve degeneration
RSS = Reynolds shear stress
TVPG = transvalvular pressure gradient

from reoperation due to prosthesis dysfunction and other causes of 98% at 5 years, 96% at 10 years, and 67% at 15 years.[6] In another study, Bourguignon and colleagues[7] reported a freedom from SVD with this same valve model of 78.6% at 15 years and 48.5% at 20 years.[7] Thus, the available data suggest that clinically significant SVD is unusual within the first 10 years and develops progressively. Currently, the International Organization for Standardization (ISO) has mandated durability testing of BHVs in an in vitro setting up to 200 million cycles (equivalent to 5 years in vivo), as specified in the ISO 5840-2:2015 International Heart Valve Standard.[8]

The Inspiris Resilia aortic valve (Edwards Lifesciences), based on the Perimount valve design, has been recently approved for use throughout most of the world for patients requiring SAVR. This valve features tissue leaflets that have undergone a proprietary preservation technology designed to reduce calcification,[9] as well as an expandable stent frame designed to optimize potential future valve-in-valve replacement. Because this valve is relatively new to the marketplace, understanding its long-term performance and durability is important to clinicians. Therefore, the aim of this study was to assess the long-term durability, kinematics, and hemodynamic performance of the Inspiris Resilia aortic valve in an in vitro setting.

METHODS

General Methodology

This study evaluated Inspiris Resilia aortic valves through 1 billion cycles of simulated use, which is equivalent to approximately 25 years of in vivo wear. To determine how the performance of the valves may change over time, 3 tests were conducted: (1) accelerated wear testing (AWT), which enabled the simulation of in vivo mechanical wear (excluding calcification and other biological processes) within a relatively short time by accelerating the beat rate; (2) hemodynamic and leaflet kinematic evaluation; and (3) particle image velocimetry (PIV), to characterize the fluid flow characteristics of the valves. PIV is an instantaneous, nonintrusive, whole-field, optical flow diagnostic technique for measuring the global velocity field.

The study met the requirements for test equipment, setup, and test intervals as specified for hemodynamic, durability, and flow visualization testing specified in the ISO 5840-2:2015 International Heart Valve Standard.[8] No patient data was used in this study, and thus Institutional Review Board approval was not required.

Valve Selection

Three 21-mm and three 23-mm Inspiris Resilia aortic valves (the most common valve sizes implanted in patients) were used for the AWT and hemodynamic tests. Hemodynamic parameters were measured for each valve at both zero cycles (pre-AWT) and 1 billion (1B) cycles (post-AWT). One AWT cycled valve from each valve size was then selected at random for PIV and leaflet kinematic tests. PIV and leaflet kinematic tests were not performed on these valves before AWT because of logistic shortcomings; therefore, a "true" control (pre-AWT) was not available for the PIV and leaflet kinematic measurements. Although not ideal, a separate uncycled valve of each size served as a "control" for PIV and leaflet kinematic measurements.

AWT

A Biomedical Device Consultants and Laboratories accelerated wear tester was used in this study to simulate valve wear within a relatively short time by accelerating the beat rate. According to Food and Drug Administration–approved guidelines,[8] all non-nitinol valves can undergo AWT at room temperature. The tested valves' cobalt-chromium metal stent and cloth are not temperature-dependent, and thus the AWT testing was performed in saline solution at room temperature. The peak differential closing pressure was maintained at >100 mm Hg for at least 5% of each pressure cycle throughout the duration of testing. This required an average peak closing pressure for each valve of ~120 mm Hg over the duration of the test. The AWT tester was tuned to achieve complete valve opening and closing during each cycle similar to or greater than the valve opening and closing observed in a pulse duplicator at a flow rate of 5 L/minute, a heart rate of 70 bpm, and a mean arterial pressure of 100 mm Hg. The study valves were removed from the tester and subjected to detailed macroscopic inspection, radiographic evaluation, high-speed video documentation, photo documentation, and hemodynamic evaluation at the start of the test and at every 250 million cycles thereafter.

The valves' hemodynamic performance was evaluated using the transvalvular pressure gradient (TVPG) and effective orifice area (EOA). TVPG was calculated as the mean pressure gradient (ΔP_{mean}) across the valve during systole, and EOA was calculated as the root mean square of the measured flow (Q_{rms}) using the following equation[10]:

$$EOA = \frac{Q_{rms}}{51.6\sqrt{\frac{\Delta P_{mean}}{\rho}}}$$

Ten consecutive cardiac cycles of hemodynamic data (ie, aortic pressure, ventricular pressure, and flow rate) were collected for each test condition at a 2-kHz data sampling rate and used to calculate the hemodynamic variables; therefore, all hemodynamic results presented in this study represent the average of 10 cardiac cycles.

In Vitro Pulsatile Flow Loop Left Heart Simulator

The leaflet kinematic and PIV evaluations were conducted in the Georgia Tech Left Heart Simulator, a validated pulsatile flow loop that simulates physiologic and pathophysiologic conditions of the heart.[11] The valves were mounted in an aortic chamber, an idealized rigid acrylic chamber designed to simulate the aortic sinus and ascending aorta. This experimental setup has been described in detail previously.[11]

The flow conditions used for these experiments were a nominal physiologic cardiac output and stroke volume of 5.0 L/minute and 70 mL per

beat at a mean arterial pressure of 100 mm Hg. A water-glycerin solution containing 36% glycerin by volume was used as a blood analog fluid to match the density and viscosity of blood (kinematic viscosity of 3.51 cP). This solution is optically transparent, which is necessary for quantifying the velocity field with PIV.

PIV

Planar PIV was used to quantitatively assess flow field characteristics downstream of the valves at the acceleration (75 ms), peak systole (175 ms), and deceleration (225 ms) phases of the cardiac cycle (856 ms); these time points are in relation to the beginning of systole. The flow was seeded with fluorescent particles, and a pulsed Nd:YAG laser source was used to create a thin laser sheet using appropriate optics along the centerline of the valve assembly such that one commissure post and line of leaflet coaptation was aligned with the imaging plane and the opposing leaflet was aligned perpendicular to the same plane (Figure 1). A total of 200 image pairs were acquired at each acquisition time point. All flow field results presented in this study represent the average of 200 cardiac cycles. These techniques have been described in detail previously.[12,13]

To predict the potential areas where platelet activation or blood damage may occur, principal Reynolds shear stress (RSS), derived from PIV data, was calculated and analyzed. RSS is a measure of the average momentum flux in a flow field due to temporal variations in the velocity field arising from cycle-to-cycle variations as well as fluctuations in turbulent flow. The principal RSS has been well correlated to blood cell damage and is used to predict potential regions of hemolysis.[14,15] The principal RSS is defined as follows[16]:

$$Principal\ RSS\left(N/m^2\right)=\rho\sqrt{\left(\frac{\overline{u'u'}-\overline{v'v'}}{2}\right)^2+\left(\overline{u'v'}\right)^2},$$

where u' and v' are defined as the deviations of instantaneous velocities from their average values over 200 cycles.

Leaflet Kinematics

For describing general leaflet kinematics, the valves' geometric orifice area (GOA) was calculated during the PIV experiments. The GOA was determined over each beat cycle through en face high-speed imaging (Phantom VEO-340L; Vision Research). Three cardiac cycles of data at 1800 Hz were collected for each condition. The images were segmented manually to determine peak systolic GOA. In addition, the GOA integral was obtained from en face videos of the valves' leaflet motion. The GOA integral was computed by determining the time-varying projected orifice area as seen en face and integrating it over the systolic period (when the GOA is nonzero).

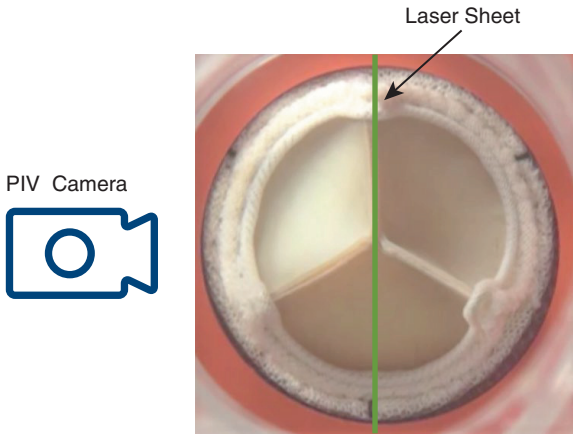

FIGURE 1. Orientation of the particle image velocimetry plane relative to the aortic valve tested. *PIV*, Particle image velocimetry.

Statistical Analysis

The normality of data was assessed using the Shapiro–Wilk test. The paired-samples t test or Mann–Whitney U test was used to compare values with normally distributed and non-normally distributed data, respectively. A P value <.05 was considered statistically significant. Normally distributed data are presented as average ± SD, and non-normally distributed data are presented as median (interquartile range [IQR]). All statistical analyses were performed using SPSS version 25 (IBM).

RESULTS

AWT and Hemodynamic Performance

Representative images of a fully open and fully closed 23-mm study valve in the AWT and pulsatile flow tester before after 1B cycles are shown in Figure E1. After 1B cycles, 1 of the 23-mm valves developed a minor tear in the wire form cloth near the top of the stent post (Figure 2, *A*). In addition, 2 of the 23-mm valves developed a slight abrasion at the base of the leaflets after 1B cycles (Figure 2, *B*). However, no tears or abrasions were observed in the 21-mm valves. X-ray evaluation of the study valves showed that all structural components of all valves remained intact over the 1B cycle testing, with no fractures in the cobalt-chromium wire form or band.

The hemodynamic data for the study valves are provided in Table 1. The study valves displayed EOA values well above the minimum EOA requirement of 0.85 cm^2 for the 21- mm valves and 1 cm^2 for the 23 mm valves, based on ISO 5840-2:2015.[10] Thus, the aortic test valves exceeded the minimum EOA acceptance criteria after enduring 1B cycles of AWT. Moreover, the average regurgitant fraction for the 1B cycle valves was below the ISO 5840-2:2015 regurgitant fraction performance requirement of 10%. The higher regurgitant fraction value for the zero-cycled valve is normal, whereas the new valve cuff was not sealed at the start of the test, which led to leaking through the cuff until it became sealed (from clogging by fluid particles). Although the P values shown in Table 1 indicate statistically significant differences in the hemodynamic parameters between zero and 1B cycles, the magnitude of these differences are very small, and therefore these hemodynamic results are clinically and functionally equivalent.

Flow Field Results

Figures 3 and 4 compare average velocity fields at a cardiac output 5 L/minute during systolic acceleration, peak systole, and deceleration phases downstream between the zero-cycled and 1B-cycled valves. For the 21-mm valves, during the acceleration phase, the maximum velocity of the zero-cycled valves was lower than that of the 1B control valves (2.06 m/s vs 2.52 m/s) (Figure 3). At peak systole, the maximum velocity observed was 3.07 m/s for the zero-cycled valves and 3.45 m/s for the 1B-cycled valves. During

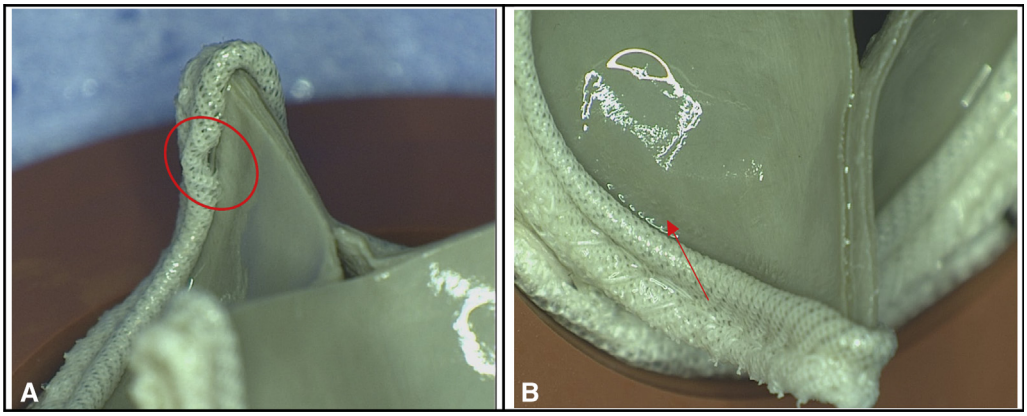

FIGURE 2. Two 23-mm zero-cycled valves with (A) a cloth tear near the commissure (*red circle*) and (B) leaflet abrasion (*red arrow*) near the valve cloth.

the deceleration phase, a higher velocity was observed in the zero-cycled valves (1.95 m/s vs 1.82 m/s).

For the 23-mm valve (Figure 4), the maximum velocities observed were 1.75 m/s for the zero-cycled valves and 2.21 m/s for the 1B-cycled valves during the acceleration phase, 2.26 m/s and 2.8 m/s, respectively, at peak systole, and 1.59 m/s and 1.74 m/s, respectively, during the deceleration phase.

Figure 5 illustrates the principal RSS fields for the 21-mm and 23-mm valves at peak systole ($t = 175$ ms). For both the 21-mm and 23-mm valves, the peak magnitudes of the principal RSS were comparable for the zero-cycled and 1B-cycled valves ($\sim$350 N/m^2 for 21-mm valves), whereas the spatial distributions differed between the zero-cycled and 1B- cycled valves (for both the 21-mm and 23-mm valves).

Leaflet Kinematics Studies

The GOA results are summarized in Figure 6. At 5 L/minute, during acceleration, the 21-mm zero-cycled valve leaflets opened more fully than the 1B-cycled valve leaflets, leading to a slightly greater GOA and slower closing during deceleration. For the 23-mm valves, the leaflets opened more fully at acceleration and peak systole in the zero-cycled valves, leading to higher GOA values.

Figure 7 shows the GOA integral, a measure of the openness of valve leaflets over the systolic period. The 21-mm zero-cycled valves had a similar but statistically significant increase in GOA integral compared with the 21-mm 1B-cycled valves (median, 0.42 [IQR, 0.06] vs 0.38 [IQR, 0.03]; $P = .028$). Similarly, the 23-mm zero-cycled valves had a slightly greater GOA integral than the 23-mm 1B-cycled valves (0.47 [IQR, 0.01] vs 0.46 [IQR, 0.02]; $P = .047$).

DISCUSSION

Experimental and clinical studies have shown that BHVs maintain structural integrity and hemodynamic stability for up to 20 years in patients.[7,17] Therefore, it is important that these valves be tested for mechanical wear for longer than 20 years. In this study, the in vitro flow characteristics of the Inspiris Resilia aortic valve were investigated to quantify its performance through 1 billion cycles ($\sim$25 years) of simulated wear, under an average transvalvular pressure of approximately 120 mm Hg; these settings represent an approximately 5-fold longer time and 25% higher pressure than the standard requirements for a tissue valve according to ISO 5840-2:2015. The Inspiris Resilia aortic valve's hemodynamic, kinematics, and velocity flow field were functionally equivalent to those of the zero-cycled control valve after 1 billion cycles of testing (Figure 8).

The Inspiris Resilia aortic valve showed good structural integrity through the 1 billion cycles of AWT testing. It is worth mentioning that the tear seen on 1 of the valves after 1 billion cycles (Figure 2, *A*) might have been caused by the relative motion between the wire form and the wire form cloth as the commissures bend inward and outward during pressure cycling. Cloth tears are a known test artifact observed in vitro with other Perimount models,[18] but to

TABLE 1. Hemodynamic results

	Mean TVPG, mm Hg			EOA, cm^2			Total regurgitant fraction, %		
Valve size	Zero-cycled valve	1B-cycled valve	*P* value	Zero-cycled valve	1B-cycled valve	*P* value	Zero-cycled valve	1B-cycled valve	*P* value
21 mm (n = 3)	16.25 ± 0.62	15.79 ± 0.43	<.05	1.89 ± 0.02	1.94 ± 0.01	<.05	15.76 ± 2.67	4.86 ± 1.36	<.05
23 mm (n = 3)	12 ± 1.29	10.96 ± 0.86	<.05	2.3 ± 0.13	2.40 ± 0.11	<.05	21.38 ± 1.37	7.75 ± 3.24	<.05

Data are mean ± SD. *TVPG*, Transvalvular pressure gradient; *EOA*, effective orifice area.

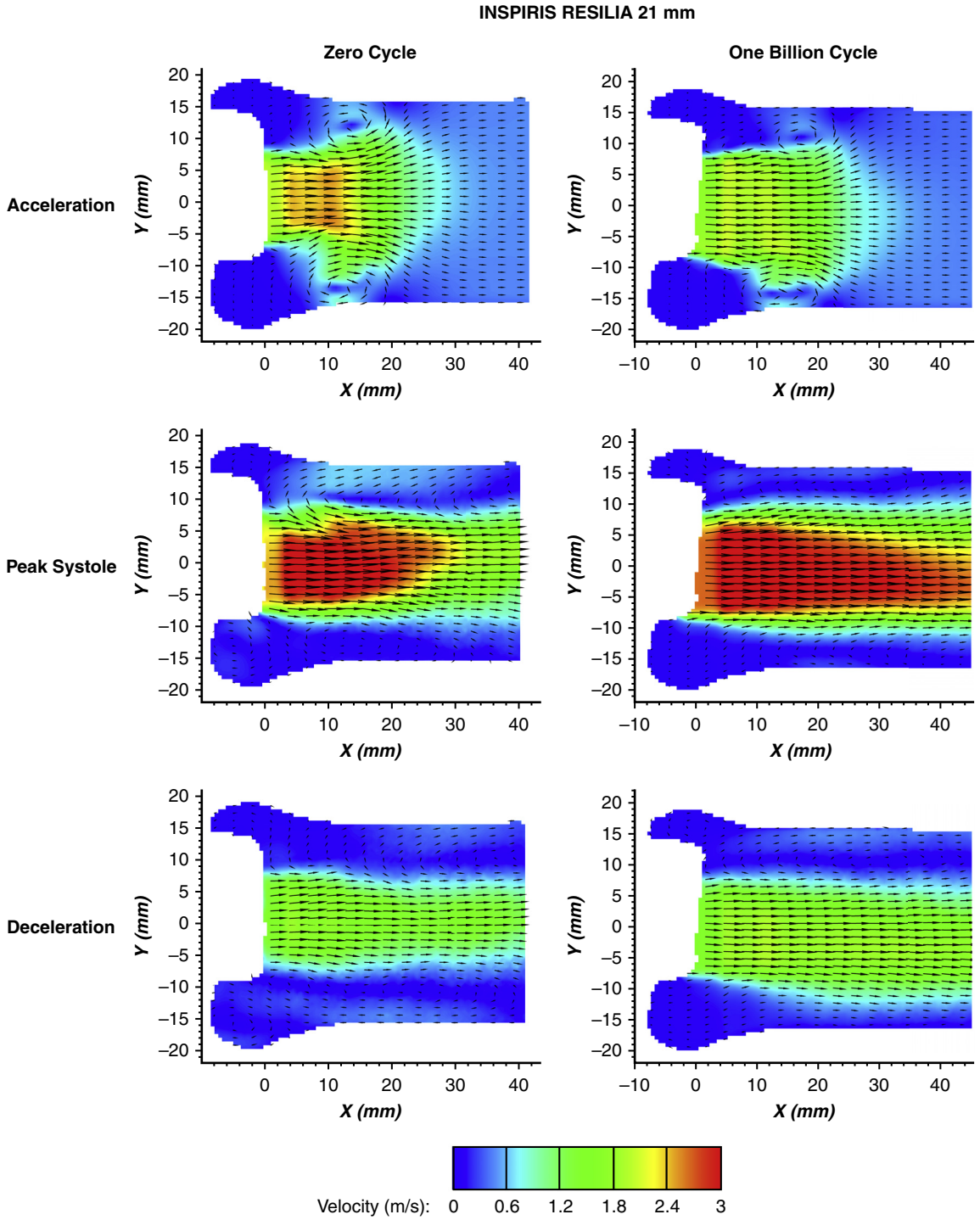

FIGURE 3. Ensemble averaged velocity fields acquired from particle image velocimetry under a cardiac output of 5 L/minute for the zero-cycled and 1B-cycled 21-mm Inspiris Resilia valve during the acceleration, peak systolic, and deceleration phases of cardiac cycle. The *black vectors* indicate the direction of flow. All panels use the same color scale for velocity magnitude.

our knowledge, this type of tear has not been reported clinically. Deposition of blood proteins and eventual ingrowth of host tissue reduces the direct contact between the wire form cloth and tissue. Moreover, the slight abrasion observed in 2 study valves (Figure 2, *B*) usually occurred when the leaflet was in a fully open position and rubbed against the wire form cloth and appears to have a minimal effect on the hemodynamic performance of the valve.

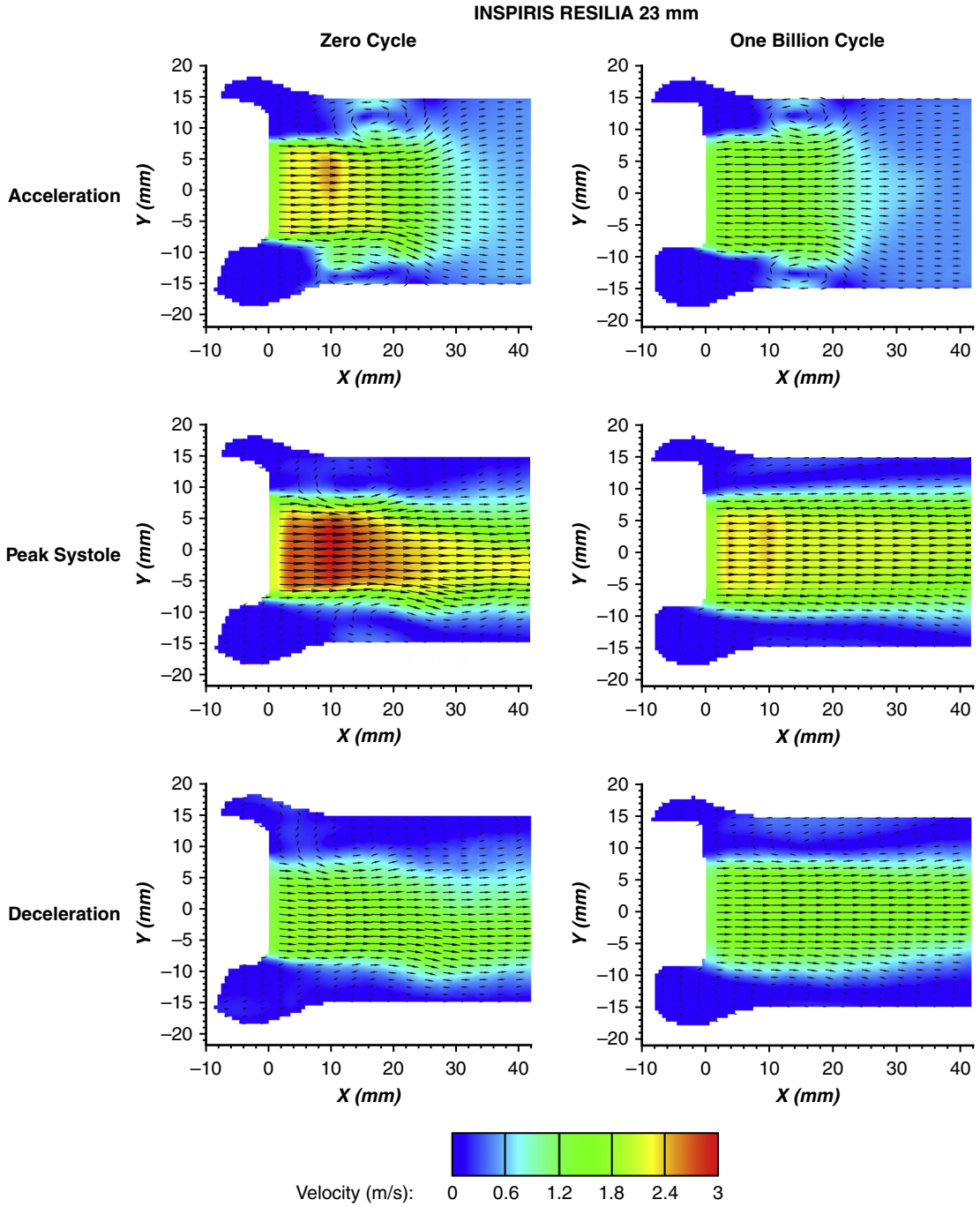

FIGURE 4. Ensemble averaged velocity fields acquired from particle image velocimetry under a cardiac output of 5 L/minute for the zero-cycled and 1B-cycled 23-mm Inspiris Resilia valve during the acceleration, peak systolic, and deceleration phases of the cardiac cycle. The *black vectors* indicate the direction of flow. All panels use the same color scale for velocity magnitude.

Both the zero-cycled and 1B-cycled valves showed excellent pressure gradients and EOA values for both valve sizes. The slight increases in EOA of the study valves may be due to leaflets becoming more flexible from the repeated pressure loading in the accelerated wear tester over time.[19] It is important to emphasize that even after 1 billion cycles, the hemodynamic results for the study valves were functionally equivalent to those for the zero-cycled control valves, suggesting that the valves are able to withstand the mechanical environment of aortic valves for approximately 25 years.

Moreover, our PIV results show that the zero-cycled valves exhibited similar flow field characteristics overall as the 1B-cycled valves; however, at peak systole, the velocity fields

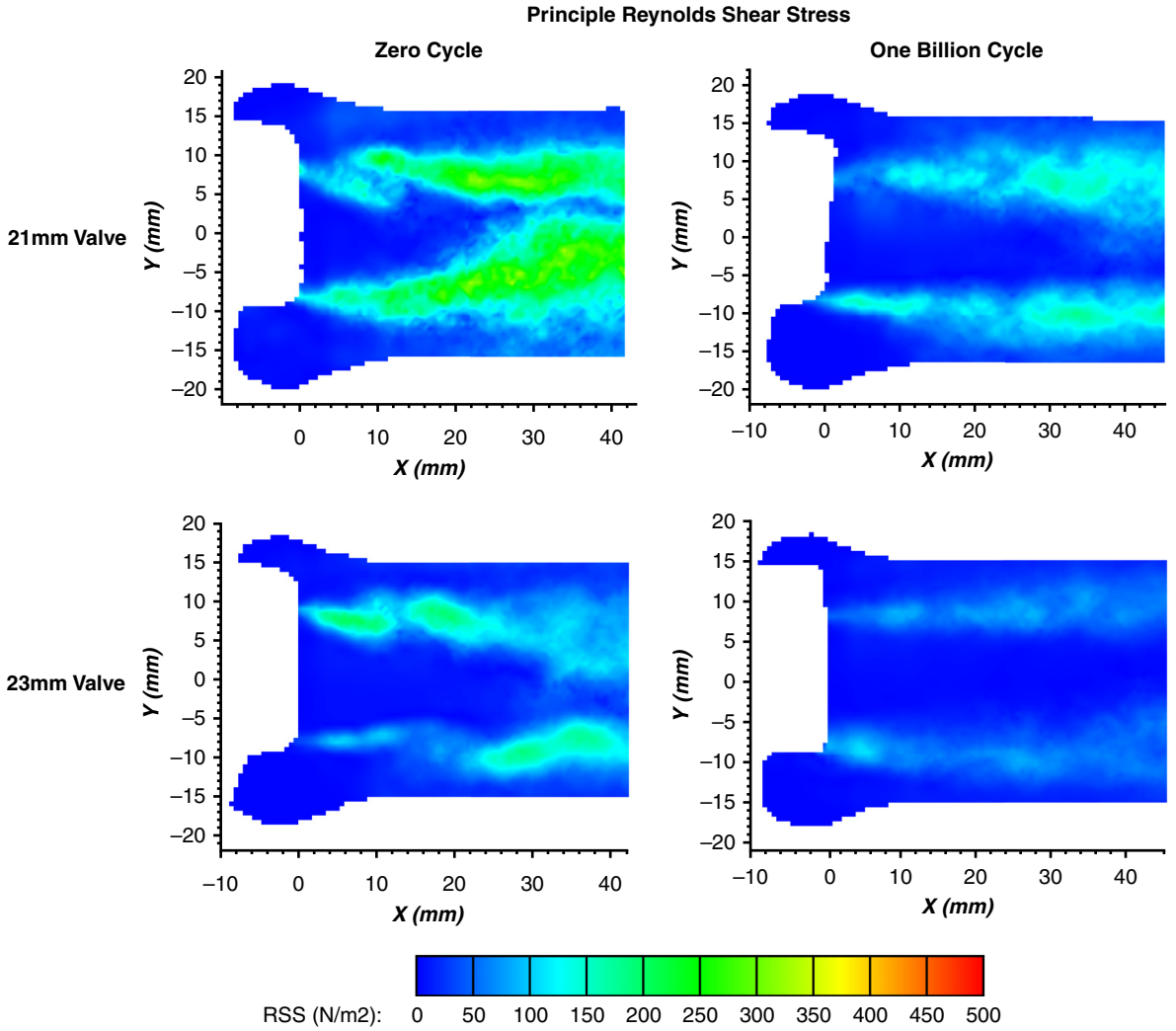

FIGURE 5. Principal Reynolds shear stress (*RSS*) at peak systole for the 21-mm and 23-mm zero-cycled (*left*) and 1B-cycled (*right*) valves at the center plane.

downstream of the zero and billion cycled valves differed (Figures 3 and 4). The larger opening of the 1B-cycled valves (Figure 6) resulted in smaller maximum velocities than seen the zero-cycled valves, to maintain a constant volumetric flow rate. This reduction in maximum velocity reduced the shear stresses and ultimately led to less dissipation, lower TVPG, and reduced principal RSS (Figure 5). These fluid dynamic results are consistent with the high-speed imaging of the leaflets confirming a wider opening and correspondingly higher GOA of the zero-cycled valves compared with the 1B-cycled valves.

Principal RSS is a well-known metric that has been experimentally correlated to the shear-induced damage to platelets.[20] As shown in Figure 5, all principal RSS values for the 1B-cycled valves were below the threshold for platelet damage, which ranges between 600 N/m^2 for exposure times of 5 ms and 200 N/m^2 for exposures times of 15 ms,[15] demonstrating no significant difference between the zero-cycled and 1B-cycled valves with respect to blood cell damage potential. In addition, the maximum principal RSS from this study is in agreement with previous in vitro studies that reported similar values in the range of 250 to 500 N/m^2.[18,21] Therefore, the blood damage potential of the valves observed in this study are within the standard reported and accepted ranges. Overall, our data show that in the absence of thrombosis and calcification, the Inspiris Resilia aortic valve is durable through 25 years.

Study Limitations

Rigid, idealized flow chambers were used in this study. Similarly, the AWT system used for this study is idealized; however, the hemodynamic environment in which the valves were tested matches the worst-case scenarios of in vivo conditions. Furthermore, planar PIV measurements do not provide the third velocity component; however, in the bulk jet flow from the aortic valve, this third component should be

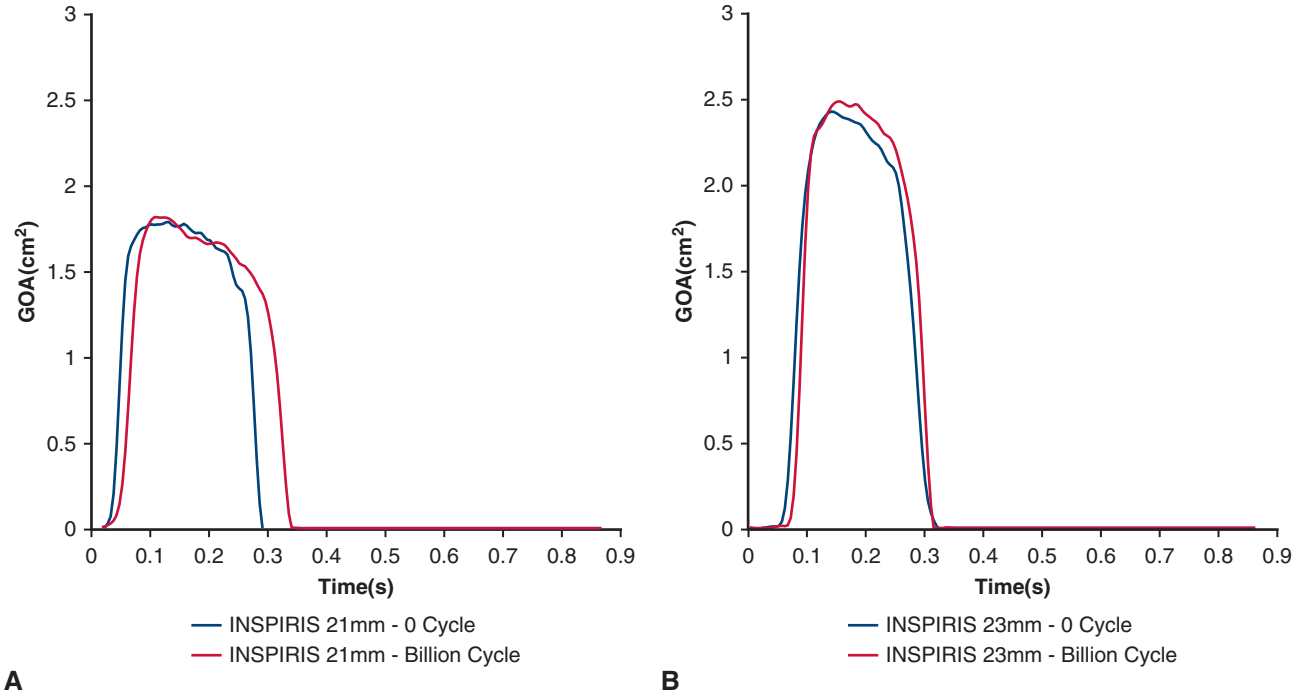

FIGURE 6. Geometric orifice area (*GOA*) at a cardiac output of 5 L/minute for the 21-mm (A) and 23-mm (B) Inspiris Resilia valves.

minimal. In addition, at the moment, it is not feasible to test the durability of the valves with blood or blood components. This shortcoming of AWT testing needs to be addressed in the future to allow more realistic evaluation of valve durability. Finally, a small sample size of each valve size was tested; however, these valves are expected to be reproducible, and thus these results should be representative.

CONCLUSIONS

In summary, this in vitro study shows that the Inspiris Resilia aortic valve performed well through 1 billion cycles of testing (the equivalent of approximately 25 years of use). All the structural components of the study valves remained intact, and the hemodynamic results were functionally equivalent to those for the zero-cycled control valves.

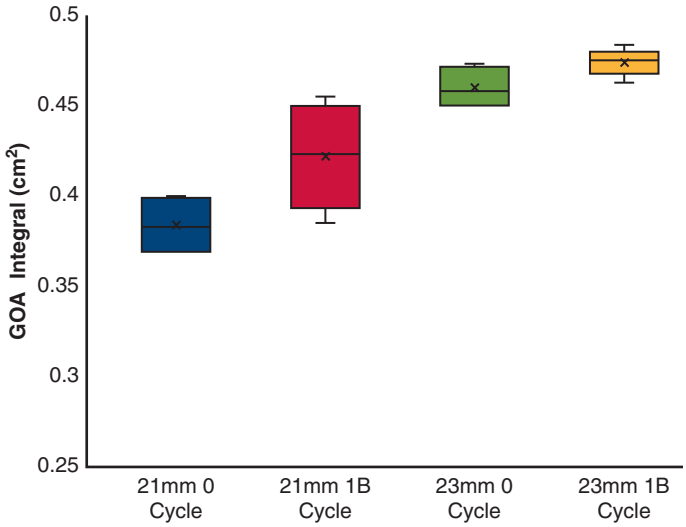

FIGURE 7. Geometric orifice area (*GOA*) integrals for the 21-mm and 23-mm Inspiris Resilia valves at zero and 1 billion cycles. The *box* represents quartile bounds of data for all experiments, with the middle horizontal line representing the median of the data. The *bar lines* above and below the box represent the maximum and minimum values for each valve.

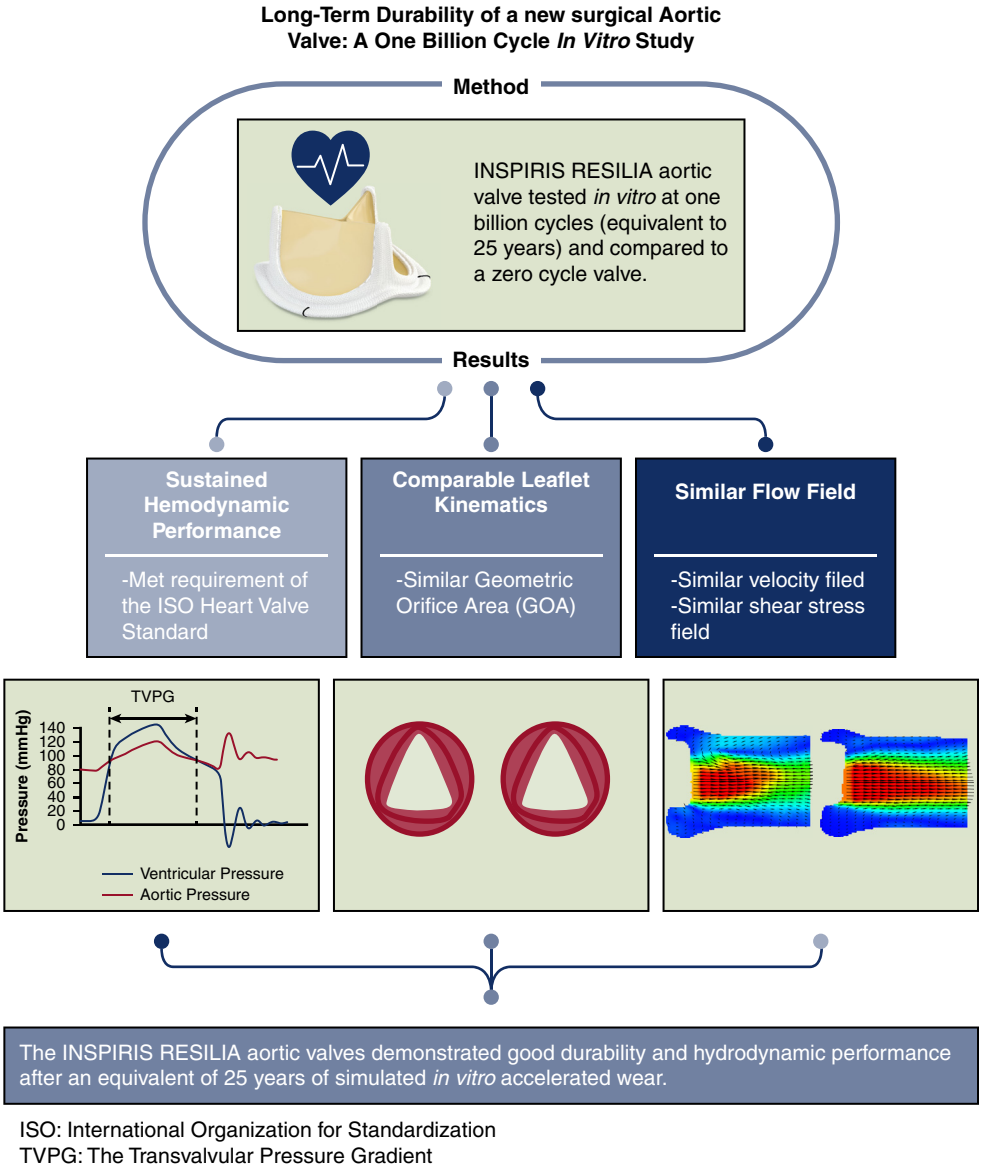

FIGURE 8. In vitro testing showed that the 1B-cycled Inspiris Resilia aortic valve's hemodynamic, kinematics, and velocity field values were functionally equivalent to those of the zero-cycled control valve.

Furthermore, the 1B-cycled valves exhibited similar flow field characteristics as the zero-cycled valves.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: valve durability, aortic valve, surgical heart valve, structural valve degeneration

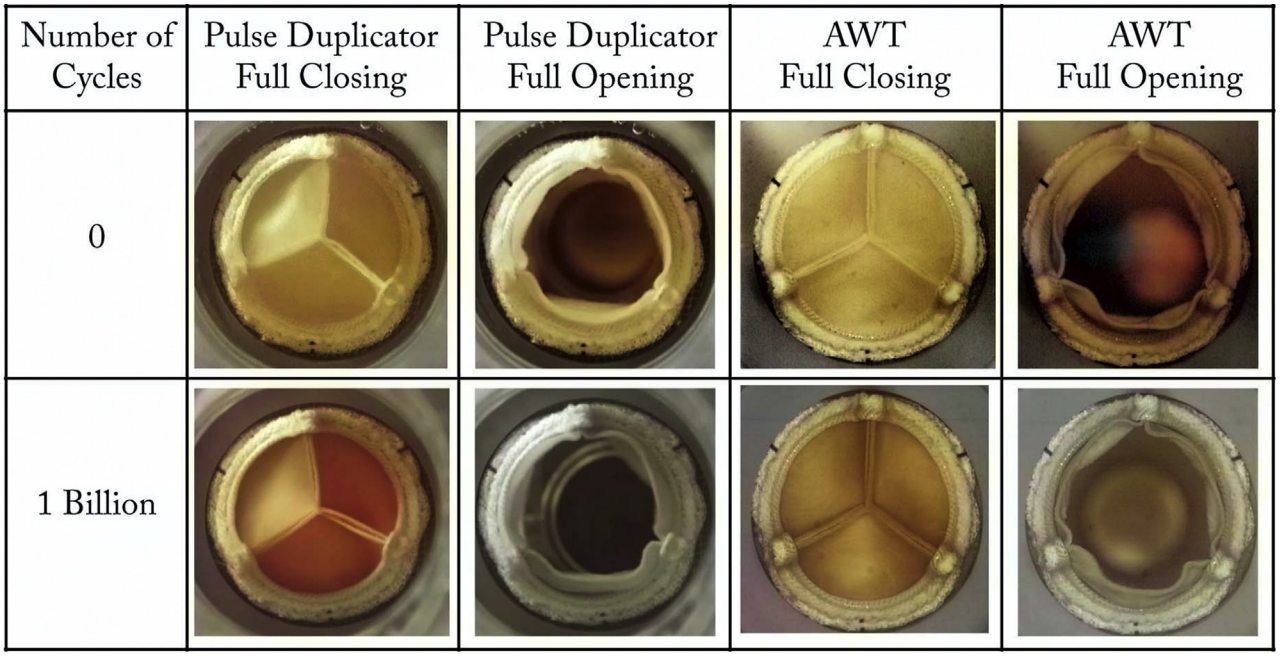

FIGURE E1. Representative photos of the 23-mm valve in the open and closed states before and after 1 billion cycles in both the left heart simulator and accelerated wear testing (*AWT*) testers.