Energy Loss Due to Paravalvular Leak With Transcatheter Aortic Valve Implantation

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Background. **Mild to moderate paravalvular leaks commonly occur after transcatheter aortic valve (TAV) implantation. Current TAVs match and may exceed hemodynamic performance of surgically implanted bioprostheses based on pressure gradient and effective orifice area. However, these hemodynamic criteria do not account for paravalvular leaks. We recently demonstrated that TAV implantation within 23 mm Perimount bioprostheses (Edwards Lifesciences, Irvine, CA) yields similar hemodynamics to the 23 mm Perimount valve. However, mild paravalvular leakage was seen after TAV implantation. The present study quantifies energy loss during the entire cardiac cycle to assess the impact of TAV paravalvular leaks on the ventricle.**

Methods. **Four TAVs designed to mimic the 23 mm SAPIEN valve (Edwards Lifesciences) were created. Transvalvular energy loss of 19, 21, and 23 mm Carpentier-Edwards bioprostheses were obtained in vitro within a pulse duplicator as a hemodynamic baseline (n = 4). The 23 mm TAVs were subsequently implanted within the 23 mm bioprostheses to assess energy loss due to paravalvular leak.**

Results. **The 23 mm bioprosthesis demonstrated the least energy loss (213.25 ± 31.35 mJ) compared with the 19 mm (330.00 ± 36.97 mJ, $p = 0.003$) and 21 mm bioprostheses (298.00 ± 37.25 mJ, $p = 0.008$). The TAV controls had similar energy loss (241.00 ± 30.55 mJ, $p = 0.17$) as the 23 mm bioprostheses. However, after TAV implantation, total energy loss increased to 365.33 ± 8.02 mJ significantly exceeding the energy loss of the 23 mm bioprosthesis ($p < 0.001$). Due to mild TAV paravalvular leakage, 39% of energy loss occurred during diastole.**

Conclusions. **Substantial energy loss during diastole occurs due to TAV paravalvular leakage. In the presence of mild paravalvular leakage, TAV implantation imposes a significantly higher workload on the left ventricle than an equivalently sized surgically implanted bioprosthesis.**

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Transcatheter aortic valve (TAV) implantation has emerged as a new clinical intervention for patients with severe symptomatic aortic stenosis at high risk for open heart surgery [1]. The TAVs allow patients who had previously been left untreated because their operative risk outweighed the benefits of surgical valve replacement [2–4] to receive therapy. Outcomes of early experiences have been promising and this modality of treatment is becoming a feasible option for selected patients [2–7]. However, one nearly unavoidable phenomenon that has been seen in early experiences with TAV implantation is paravalvular leak. Paravalvular leaks occur frequently, over 50% of the time, and are most commonly mild to moderate in severity [2–5, 7–9]. In contrast, paravalvular leaks occur rarely (6%) with surgical aortic valve replacements; they consist of very small jets, are not associated with subclinical hemolysis, and are often clinically benign [10]. While mild to moderate aortic insufficiency after TAV implantation may have little clinical impact in high risk elderly patients whose life span is expected to be limited, this degree of paravalvular leakage may have significant clinical consequences long-term if TAVs are implanted in younger patients. Though many patients have been followed long term with native central aortic regurgitation prior to clinical deterioration, the impact of mild to moderate paraprosthetic leakage long-term on hemolysis and endocarditis risk is unknown. Significant paravalvular leakage may trigger hemolysis, promote endocarditis, and eventually result in ventricular dysfunction [11, 12].

Evaluation of the quality of aortic valve prostheses based upon hemodynamic performance has typically relied upon blood flow velocity, pressure gradients, and effective orifice area. Based on these criteria, current TAVs match and may even exceed the hemodynamic performance of surgically implanted bioprostheses [13, 14]. However, none of these criteria take into account valvular regurgitation. In this study, TAV hemodynamic performance was evaluated based on transvalvular energy loss. Energy loss allows assessment of valvular hemodynamics during forward flow as well as accounts for any regurgitation [15]. By this means, we shift the focus from TAV systolic function to the effect of TAV performance on the ventricle during the entire cardiac cycle. The objective of this study was to determine TAV

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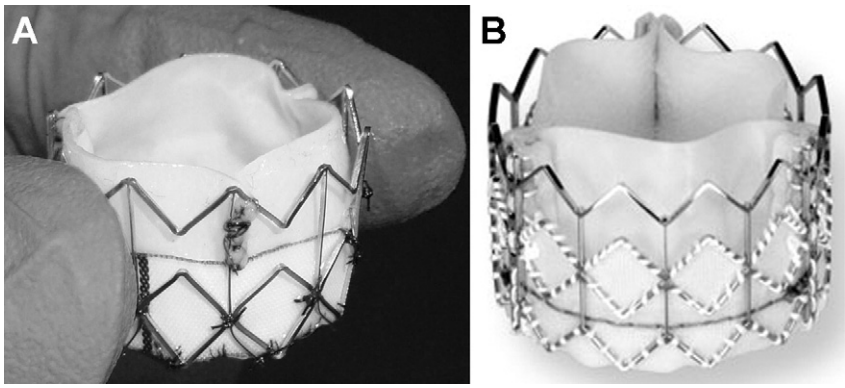

Fig 1. (A) Homemade 23 mm transcatheter aortic valve. (B) Edwards SAPIEN valve.

energy loss during the entire cardiac cycle and compare the efficacy of TAV implantation to standard surgical valve replacement from an energy standpoint. Because native aortic stenosis results in variable pressure gradients and valve areas as well as irregularity of stenosed leaflet anatomy, we implanted TAVs in vitro within normal bioprostheses to provide a consistent reproducible environment to quantify the impact of paravalvular leak. We have previously demonstrated [16] that 23 mm TAVs provide acceptable valve-in-valve mean pressure gradients and effective orifice areas when implanted within the 23 mm Perimount bioprosthesis (Edwards Lifesciences, Irvine, CA) comparable with that of standard 23 mm Perimount surgical valve replacement; however, regurgitation volume was significantly higher than with surgical valve replacement. This study examines the impact of TAV paravalvular leakage on energy loss as a measure of hemodynamic performance.

Material and Methods

Transcatheter Aortic Valves

Four TAVs (Fig 1A) were created based on the Edwards SAPIEN valve design (Fig 1B), currently being investigated in the US PARTNER trial [7, 17]. Edwards Lifesciences, Inc is restricted from providing the SAPIEN for independent testing by US Food and Drug Administration (FDA) regulations until FDA approval; however, they did provide us with bovine pericardium to create TAV leaflets. A detailed description of our TAV has been previously described [16]. Briefly, three trapezoidal shaped leaflets were cut from a flat piece of bovine pericardium (Edwards Bovine Pericardial Patch, Edwards Lifesciences). The lateral sides of the leaflets were sutured together and the leaflets were then sutured at the base to a Dacron sheet. A customized cylindrical stainless-steel stent (Cook Medical Inc, Bloomington, IN), 15 mm in height, was dilated to an external diameter of 23 mm to anchor the leaflets and Dacron sheet. Interrupted stitches were used at each intersection of the metal stent to attach the Dacron sheet to the stent.

Pulse Duplicator System

Valves were tested at room temperature in a custom-built pulse duplicator system, developed for TAV implantation (Vivitro Systems Inc, Victoria, Canada). Figure 2 depicts a schematic representation of the pulsatile flow. A recirculating fluid of 36% by volume glycerin solution in normal saline solution was used as a blood analogue fluid which mimics blood viscosity at 37°C when tested at room temperature. Physiologic circulation was simulated through viscoelastic ventricular contraction, blood-

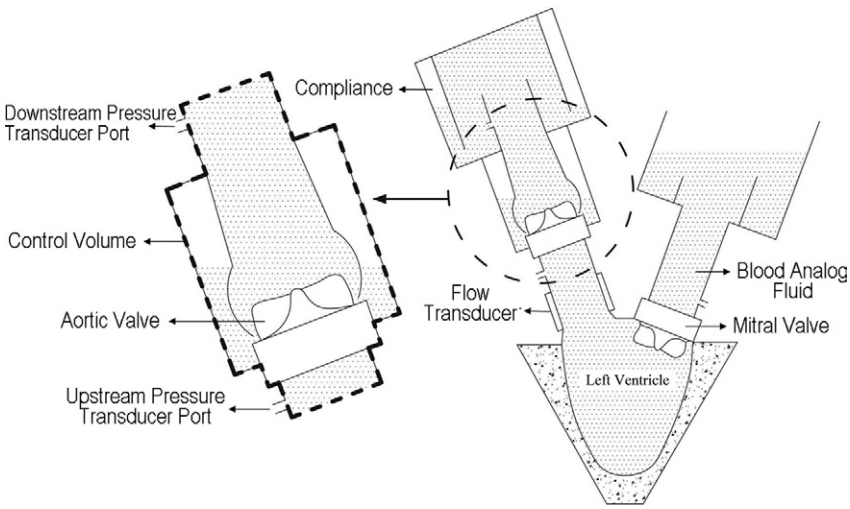

Fig 2. Diagram of pulsatile-flow testing system. Control volume is defined by the dashed line.

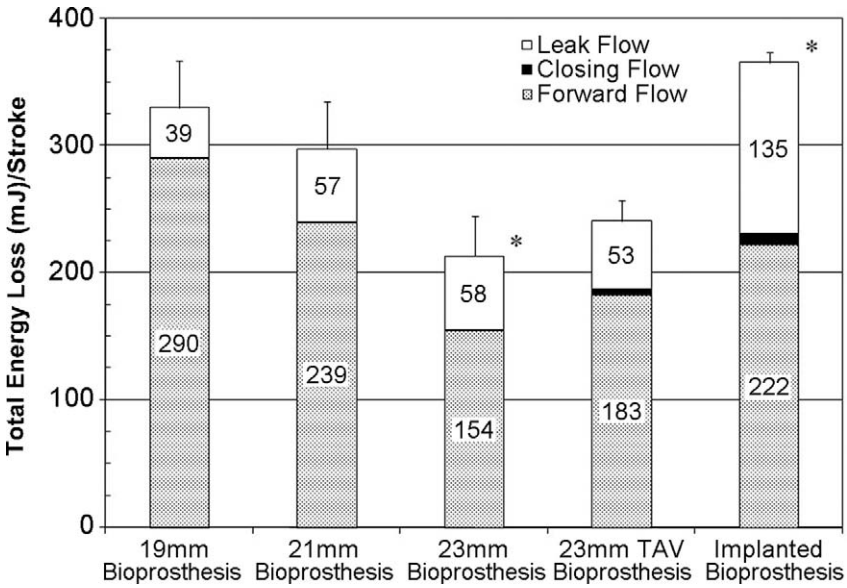

*Fig 3. Total energy loss of three Carpentier-Edwards Perimount bioprostheses, and the TAV before and after implantation within the 23mm bioprosthesis. (□ = leak flow; ■ = closing flow; ⬚ = forward flow; * is $p < 0.001$.)*

simulating fluid, and control of local compliance and peripheral resistance [16]. Pulse duplicator input parameters were used to match International Organization for Standardization (ISO) 5840 and FDA standards for testing heart valves: heart rate of 70 beats per minute, 35% systolic duration of cycle period, mean atrial and aortic pressures of 10 and 100 mm Hg, and cardiac output 5 L per minute [18, 19]. These hemodynamic parameters were maintained constant throughout the study. Pressure was measured in several locations (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, East Bend, NC) was used to measure aortic valve flow rate and regurgitation volume by determining flows during systole and diastole. Lack of paravalvular leak was demonstrated by lack of flow during diastole in contrast to paravalvular leakage, which demonstrated negative flows during diastole. Location of leakage was determined by two-dimensional echocardiography. Quantification of leakage was classified as mild, moderate, or severe based on regurgitation volume. A regurgitation fraction of less than 20% was considered mild, 20% to 40% moderate, and greater than 50% severe regurgitation.

Data Analyses

To evaluate TAV energy loss in the presence of paravalvular leak, we examined measurements from previous experiments conducted of TAV implantation within normal bioprostheses [16]. Normal bioprostheses yield highly reproducible hemodynamics in vitro in contrast to native stenosed aortic valves within the aortic root which are the following: (1) difficult to obtain by autopsy specimens; (2) highly variable with respect to flow velocities, pressure gradients, and valve areas; and (3) highly variable with respect to stenosed leaflet geometry, which in turn results in variable TAV regurgitation. Thus, the normal bioprosthesis was the ideal candidate to assess the impact of TAV regurgitation on energy loss by providing a reproducible consistent environment for TAV implantation.

Carpentier-Edwards Perimount aortic bioprosthetic valves (19, 21, and 23 mm) were tested in the pulse duplicator to obtain a hemodynamic baseline (n = 4 each). The pulse duplicator provided a well-controlled and consistent test environment to assess TAV performance. Subsequently, each TAV was tested alone in the pulse duplicator to determine its baseline hemodynamics before implantation. Then, 23 mm TAVs were implanted only within the 23 mm bioprostheses (n = 4). Data acquisition over 10 consecutive cardiac cycles yielded transvalvular pressure gradients, effective orifice area, and regurgitant volume.

In this study, we calculated energy loss of three sizes of normal bioprostheses and TAV energy loss before and after implantation within the 23 mm bioprosthesis over the entire cardiac cycle. Energy loss was calculated using control volume analysis based on the principle of conservation of energy. Control volume was identified as a

Table 1. Hemodynamics of Carpentier-Edwards Perimount Bioprostheses and the 23 mm TAV Before and After Implantation Within the 23 mm Bioprosthesis [16]

	Mean Pressure Gradient (mm Hg)	Effective Orifice Area (cm^2)	Regurgitation Fraction (%)
19 mm bioprosthesis	16.2 ± 2.2	1.3 ± 0.1	6.1 ± 1.0
21 mm bioprosthesis	11.8 ± 1.9	1.5 ± 0.2	8.2 ± 2.0
23 mm bioprosthesis	5.9 ± 0.9	2.1 ± 0.2	8.4 ± 1.8
23 mm TAV (control)	6.8 ± 1.0	2.0 ± 0.1	10.6 ± 1.4
Implanted TAV	8.3 ± 1.2	1.8 ± 0.2	19.1 ± 0.9

TAV = transcatheter aortic valve.

region in space where energies crossing the boundaries of the region were studied. Control volume was defined by the dashed line in Figure 2 and spanned the left ventricular outflow tract through the aortic root. Energy loss was assessed by the difference in the energy flux entering and leaving the control volume during one cardiac cycle. Detailed description of energy loss calculation using control volume was described by Heinrich and colleagues [20]. Changes in gravitational and kinetic energy were negligible with respect to changes in pressure energy. Energy loss (Φ) during forward flow, closing flow, and leakage flow was calculated separately by integrating instantaneous flow (Q_{valve}) through the valve and instantaneous pressure gradient (ΔP) during each time period:

$$\Phi_{Forward \cdot flow} = \int_{t_0}^{t_1} Q_{valve} \cdot \Delta P \cdot dt,$$

$$\Phi_{Closing \cdot flow} = \int_{t_1}^{t_2} Q_{valve} \cdot \Delta P \cdot dt,$$

$$\Phi_{Leakage \cdot flow} = \int_{t_2}^{t_3} Q_{valve} \cdot \Delta P \cdot dt,$$

where t_0 is the beginning of forward flow through the valve, t_1 is the end of forward flow through the valve, t_2 is the time of valve closure, and t_3 is the end of one cardiac cycle. Total energy loss was the sum of energy loss during forward, closing, and leakage flow periods. Hemodynamic measurements were compared using a one way analysis of variance (ANOVA) on average values of 10 cardiac cycles. Reported values are quoted as mean ± standard deviation and statistical analyses were performed using MATLAB (v 7.0; Natick, MA).

Results

Three sizes (19 mm, 21 mm, and 23 mm) of normal Carpentier-Edwards Perimount bioprostheses were tested in the pulse duplicator. As expected, the 23 mm bioprosthesis had less energy loss during forward flow (154.25 ± 17.04 mJ) than 19 mm (289.75 ± 29.74 mJ, $p < 0.001$) and 21 mm (239.20 ± 28.28 mJ, $p = 0.001$) bioprostheses (Fig 3). Forward flow energy loss was also statistically significant between 19 and 21 mm bioprostheses ($p = 0.035$). As previously reported, normal 23 mm bioprostheses had a larger regurgitant volume than their 19 and 21 mm counterparts (Table 1) [16]. Due to regurgitation volume, the 23 mm bioprosthesis demonstrated a trend toward greater energy loss (58.25 ± 14.80 mJ) during the leak period as compared with the 19 mm (39.25 ± 7.04 mJ, $p = 0.059$) but not the 21 mm bioprosthesis (57.20 ± 16.53 mJ, $p = 0.924$). On the other hand, during the closing period, energy loss was relatively small compared with that for the forward flow and leakage periods in all valve sizes (1.00 ± 0.00, 1.00 ± 1.22, 1.25 ± 1.5 mJ in 23, 21, and 19 mm bioprostheses, respectively) and there were no significant differences among them. Overall, the 23 mm bioprosthesis demonstrated the least total energy loss during the entire cardiac cycle (213.25 ± 31.35 mJ) as compared with the two other bioprostheses (330.00 ± 36.97 mJ in 19 mm, $p = 0.003$ and 298.00 ± 37.25 mJ in 21 mm bioprosthesis, $p = 0.008$). Total energy loss was not significantly different between the 19 and 21 mm bioprostheses ($p = 0.240$).

The 23 mm TAVs tested before valve-in-valve implantation demonstrated comparable energy loss with the 23 mm bioprosthesis (Fig 3). Energy loss was 182.67 ± 13.05 mJ ($p = 0.062$) during forward flow, 5.00 ± 1.00 mJ ($p < 0.001$) during closing flow, and 53.33 ± 16.50 mJ ($p = 0.695$) during leakage flow. Energy loss during forward and

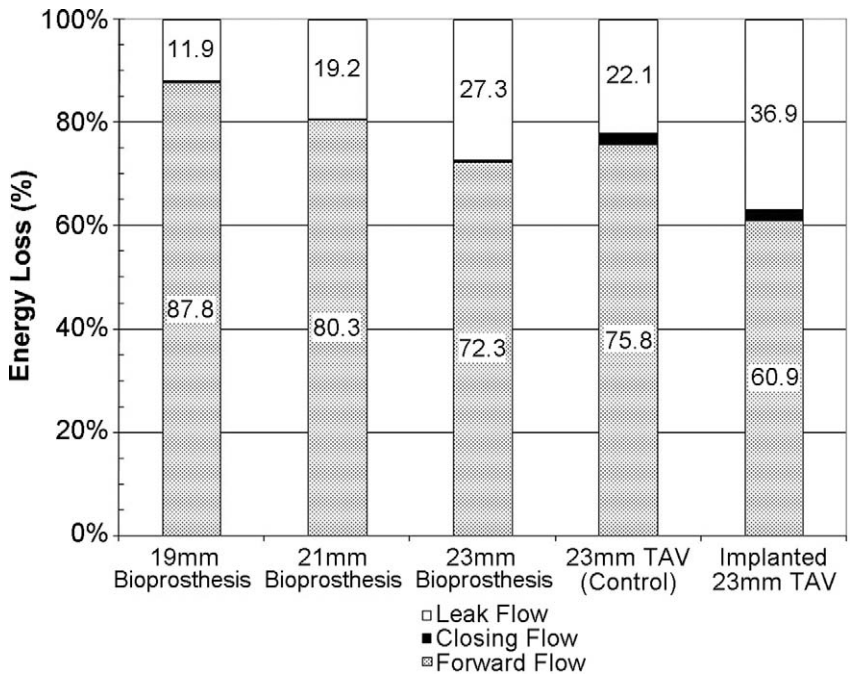

Fig 4. Percentage of energy loss during forward, closing, and leak flow. (□ = leak flow; ■ = closing flow; ⬚ = forward flow.)

leakage flow periods were not significantly different than the 23 mm bioprosthesis. However, after TAV implantation within the 23 mm bioprosthesis, energy loss increased significantly. Forward flow energy loss significantly increased to 222.33 ± 16.17 mJ when compared with preimplantation ($p = 0.029$) and when compared with the 23 mm bioprosthesis ($p = 0.003$). Furthermore, closing and leakage flow energy loss (8.67 ± 1.53 and 134.62 ± 16.86 mJ, respectively) were also significantly greater than the normal 23 mm bioprosthesis owing to larger paravalvular leak ($p < 0.001$ and $p = 0.001$, respectively). Overall, total energy loss of a 23 mm TAV implanted within a 23 mm bioprosthesis was 365.33 ± 8.02 mJ, which was significantly higher than both the 23 mm ($p < 0.001$) and 21 mm bioprostheses ($p = 0.024$) tested alone in the pulse duplicator. Based on total energy loss, the 23 mm TAV implanted within a 23 mm bioprosthesis was equivalent to reimplantation of a 19 mm bioprosthesis alone ($p = 0.172$).

The percentage of energy loss comprised of forward, closing, and leakage flow for each valve is presented in Figure 4. In 19, 21, and 23 mm bioprostheses, only 12%, 20%, and 28% of the total energy loss, respectively, was due to aortic regurgitation. Similarly, in the 23 mm TAV, 24% of total energy loss resulted from aortic regurgitation. However, after 23 mm TAV implantation within the 23 mm bioprosthesis, 39% of valve energy loss occurred during closing and leakage flow primarily due to mild paravalvular leakage.

Comment

We have previously shown that 23 mm TAV implantation within 23 mm bioprostheses yields comparable hemodynamics to surgical rereplacement with a 23 mm bioprosthesis based on the forward flow hemodynamic criteria of pressure gradient and effective orifice area [16]. We also demonstrated that this valve-in-valve implantation resulted in greater regurgitant volume than the 23 mm bioprosthesis alone [16]. This valve-in-valve regurgitation would be classified as mild based on volume [21]. The regurgitation volume was mainly paravalvular and most likely from gaps between the TAV stent and bioprosthesis or from the suturing line between the leaflets and Dacron sheet. In this study we examined the effect of paravalvular leaks on total energy loss to provide a more comprehensive understanding of bioprosthetic hemodynamics. We evaluated TAV performance based on energy loss during the entire cardiac cycle, not limited to forward flow. We found that before implantation, TAVs had energy loss comparable with their same size Perimount counterparts. However, TAVs are not surgically implanted with sutures to prevent paravalvular leak, but instead are implanted as a valve-in-valve within a stenosed native aortic valve with an understanding that paravalvular leakage will occur. As such, paravalvular leak has been quantified as aortic regurgitation with gross measurements of mild, moderate, and severe, and TAVs have typically resulted in mild to moderate paravalvular leakage. We used a normal bioprosthetic valve within a pulse duplicator as a consistent reproducible environment for TAV valve-in-valve implantation. We demonstrated that paravalvular leakage after TAV valve-in-valve increases total energy loss significantly compared with the TAV alone, but more importantly compared with the normal 23 mm bioprosthesis used for surgical replacement. Total energy loss of the 23 mm valve-in-valve combination was comparable with that of surgical valve replacement with a 19 mm bioprosthesis. Total energy loss of the implanted 23 mm TAV was 71% more than the 23 mm bioprosthesis.

Significance of Paravalvular Leak

In recent years, TAV implantation has emerged as an alternative treatment for severe aortic stenosis in patients with high or prohibitive surgical risks [1–4, 8, 9, 13]. Early and midterm hemodynamic results obtained with TAVs have been promising, with low transvalvular pressure gradients and large effective orifice area in most patients [2, 3, 7, 8]. However, aortic regurgitation, usually paravalvular, occurs frequently after TAV implantation 65% to 85% of the time; the majority being trivial to mild, with 0% to 26% moderate, and 0% to 10% severe [3, 4, 7, 8, 13, 22, 23]. Severe leaks are uncommon and TAV oversizing has been proposed to decrease aortic regurgitation [8]. However, recently it has been shown that no significant relationship exists between TAV oversizing and the occurrence and degree of aortic regurgitation [13].

Energy Loss Concept

Evaluation of heart valve performance based on energy loss allows consideration of paravalvular leak and provides more detailed information than pressure gradient and effective orifice area by studying the entire cardiac cycle. Pressure gradient is highly dependent on flow rate across the valve; thus, using isolated pressure gradients to evaluate valve performance under different cardiac output conditions particularly low output states can be misleading. On the other hand, effective orifice area is a parameter independent of the patient's cardiac output. However, the variables in the Gorlin and continuity equations used to calculate effective orifice area are based on temporal averages during systole and if temporal averages during the entire cardiac cycle are used in the presence of aortic regurgitation, these equations underestimate effective orifice area [24].

While the commonly used transvalvular pressure gradients and valve effective orifice area evaluate prosthetic valve performance during forward flow, none of these parameters account for valvular regurgitation. Energy loss is a well-established engineering concept which not only allows assessment of prosthetic valve performance during forward flow, but also accounts for the impact of leakage during diastole [15]. In this manner, the ventricle becomes the focus of evaluation rather than systolic valve function. It is the ventricle that must raise its systolic pressure and (or) volumetric capacity to overcome the added energy loss and supply blood flow at the necessary rate. Paravalvular leak causes volume overload on the ventricle, which results in higher diastolic stresses in the

myocardium. Increased myocardial stresses can then trigger eccentric hypertrophy. Quantifying energy loss is an excellent way to represent the increase in workload on the left ventricle. However, energy loss has not been routinely used clinically because direct calculation of energy loss requires complex and invasive measurements of simultaneous temporal pressures and velocities [15].

Pressure gradient and effective orifice area can correlate well with energy loss during forward flow. However, other parameters, including stroke-work loss, energy loss index, and left ventricular longitudinal shortening, may correlate better with forward flow energy loss while measured easily and noninvasively by Doppler echocardiography [24–26]. Nevertheless, energy loss due to regurgitant flow must be considered in patients with paravalvular leak. Studies have assessed energy loss due to mitral regurgitation, but few clinical studies of energy loss from bioprosthetic aortic valve insufficiency have been performed [27–31]. Energy loss assessment due to regurgitant flow can be made by integrating the instantaneous transvalvular pressure gradient and the regurgitant volume during diastole. Care must be taken in interpreting energy loss calculations. If energy loss is calculated based on the work required to move the equivalent volume of blood forward through the valve to compensate for the regurgitation, the value would be much greater.

Study Limitations

The primary limitation of the study was the inability to acquire and use stenosed native aortic roots in which to implant TAVs. Given this limitation, we are not able to predict the expected energy loss in the clinical setting of TAVs within aortic stenosis. However, our objective was to demonstrate the significance of TAV paravalvular leak on valve hemodynamics and ventricular work from the perspective of energy loss. From that standpoint, normal bioprostheses provided a consistent reproducible environment to study TAV performance in the presence of paravalvular leak. The second limitation was the inability to use the Edwards SAPIEN valve. Our custom-made TAVs mimicked SAPIEN in size and shape. However, precise leaflet geometry and dimensions are proprietary to Edwards Lifesciences, Inc, which may affect valve function. Our TAVs provided comparable pressure gradient and effective orifice area, but regurgitant volume was slightly higher. Because the blood analog fluid does not have any coagulation properties, regurgitant fraction may be expected to be greater in our in vitro experiments than in vivo. Nonetheless, the SAPIEN valve does result in mild to moderate paravalvular leakage clinically, which was similar to the mild regurgitation seen here, and thus our concerns regarding increased energy loss with paravalvular leak remain valid.

Conclusions

While the commonly used transvalvular pressure gradients and effective valve orifice area evaluate prosthetic valve performance during systole, none of these parameters account for valvular regurgitation. Energy loss is a well-established engineering concept that allows assessment of prosthetic valve performance during forward flow and accounts for regurgitation. The TAVs have emerged as an alternative treatment for severe aortic stenosis in patients with high or prohibitive surgical risks. However, mild to moderate paravalvular leak frequently occurs after TAV implantation. In this study, we demonstrated that a substantial portion of TAV energy loss is due to the paravalvular leak and in the presence of mild prosthetic regurgitation, energy loss during diastole is comparable to energy loss during systole. The TAV implantation with mild regurgitation imposes a significantly higher workload on the left ventricle than surgical aortic valve replacement of equivalent bioprosthetic size. Paravalvular leak is expected to remain the major issue to be addressed in the next generation of TAVs, if TAV indications are expanded to younger and healthier patients.

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