Supplement to

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IMPORTANCE OF HEMODYNAMICS IN TAVR VALVE SELECTION

The choice for patients who can return to an active life.

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Are TAVR Hemodynamics Important in the Lower-Risk Population?

How the hemodynamic effects of TAVR and SAVR impact clinical outcomes.

BY COLIN M. BARKER, MD; MORITZ WYLER VON BALLMOOS, MD; AND MICHAEL J. REARDON, MD

Transcatheter aortic valve replacement (TAVR) has gained rapid adoption based on several trials randomized against surgery.[1-4] These trials have provided the medical community with high-quality data comparing open surgical and interventional treatments for aortic stenosis (AS). In some areas, such as survival and stroke, TAVR has done as well as or better than surgery. In other areas, such as paravalvular leak and pacemaker implantation, surgery has performed better. One area where TAVR has consistently shown better results than surgery is forward flow hemodynamics. Both the balloon-expandable and self-expanding valves that are approved in the United States have been shown to be effective treatment options, with balloon-expandable valves demonstrating equivalence and self-expanding valves demonstrating superiority in terms of effective orifice areas (EOAs) and mean gradients compared to the surgical valves.[4,5] The differences appear to be small, and both surgery and TAVR relieve AS well and show equivalent quality of life (QoL) at 6 months. This should raise the question: Are these small differences in EOA and mean gradient important now, and do they gain more importance as we move to younger, lower-risk patients?

There is no question that symptomatic severe AS is a problem associated with high mortality without correction of the stenosis. Less clear is how detrimental lesser degrees of AS are. How many of us would volunteer to have asymptomatic moderate or even mild AS rather than a normal aortic valve? Would we do this even if we could be assured that our mild or moderate AS would not progress? I suspect not. With AVR for severe AS, either with TAVR or surgery, we exchange severe AS for less severe AS, but it is still not a normal valve with normal hemodynamics. In this article, we examine whether the residual AS left after AVR is important, with a focus on the younger, lower-risk population.

SURVIVAL RATES AFTER AVR

Until the first successful TAVR in 2002,[6] our only option for treating AS was surgery. Survival after surgery was better than untreated severe symptomatic AS, but is it equal to the normal population? Although isolated articles can be found claiming that survival after AVR equals that of the normal population, it is the opinion of these authors that this would represent a statistical anomaly and publication bias because surgeons, like most physicians, tend to publish good outcomes. A source without this bias and well versed in the study of survival as it relates to the normal population is the insurance industry. Survival after surgical AVR (SAVR) has been studied and it has been found that for both mechanical and tissue valves, survival after AVR does not reach that of the normal population.[7] In fact, the younger you are at the time of AVR, the more life-years you lose compared to the normal population. Surgeons have always considered SAVR as exchanging native AS for prosthetic valve disease, which is much better but not normal functioning. Why this survival gap exists is an important question. It may exist because we are correcting AS too late and that the heart has already suffered irreversible damage. It may also be that we do not completely correct AS and that this lower-grade AS has a negative effect on long-term survival.

PROSTHESIS-PATIENT MISMATCH

The concept of prosthesis-patient mismatch (PPM) was first introduced in 1978 by Rahimtoola as an aortic valve that did not match a normal EOA for that patient.[8] By this definition, all aortic valves, short of those in the Ross procedure, would show PPM. PPM has subsequently been defined and divided by Dumesnil and colleagues into severe (EOA < 0.65 cm^2/m^2), moderate (0.65–0.85 cm^2/m^2), and absent (> 0.85 cm^2/m^2).[9] After SAVR, PPM has been associated with higher early and late mortality as well as less left ventricular mass regression.[10-13]

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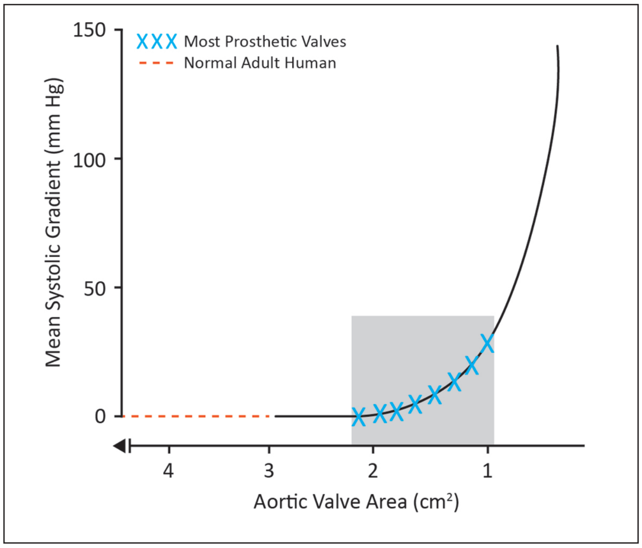

Figure 1. Mean gradient versus aortic valve area. The gray box represents the EOA of most surgical aortic valves. Reprinted with permission from Rahimtoola SH. The problem of valve prosthesis-patient mismatch. Circulation. 1978;58:20-24. http://circ.ahajournals.org.

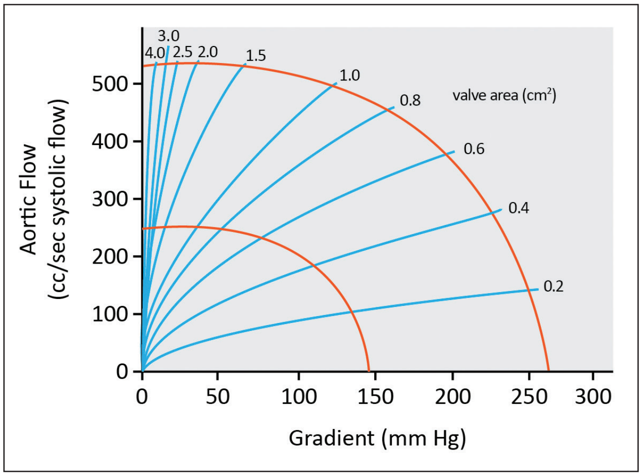

Figure 2. Aortic flow versus aortic valve gradient mapped for different EOAs. Reprinted with permission from Baim DS, Grossman W. Cardiac Catheterization, Angiography and Intervention. 5th ed. Wolters Kluwer. 1996.

A meta-analysis by Head and colleagues, which included 27,186 patients and 133.141 patient-years of follow-up, showed both moderate and severe PPM increased all-cause mortality (hazard ratio, 1.19 and 1.84, respectively).[14] This relationship was consistent over the 12-year time period. In randomized trials, SAVR has consistently shown more PPM than TAVR, and severe PPM has been associated with increased mortality.[15] Because younger, lower-risk patients will be expected to live longer, any PPM after AVR will be increasingly important.

IMPACT OF HEMODYNAMICS

Most studies of the hemodynamics of both surgery and TAVR have been performed while patients are at rest. This leaves the question open of how these valves react to the increased flow during exercise that is more likely to occur in the younger patient. In Rahimtoola's original article, he mapped out the gradient versus EOA at physiologic normal flow and showed where most surgical valves existed on that graph (Figure 1).[8] For the many older, more sedentary patients currently being treated, this is likely satisfactory. However, what happens in younger patients who are more likely to engage in physical activity requiring an increase in aortic flow with increased cardiac output?

Figure 1 shows that increased aortic flow will shift the line to the left, placing the box for surgical valves in a higher gradient area. Another way to look at this is the theoretical curves that can be generated for aortic flow versus gradient at a series of different EOAs (Figure 2).[16] If the EOA of a "normal" aortic valve is 3 cm^2, we can double the normal systolic flow of 250 mL/s to 500 mL/s without an appreciable increase in gradient. If we look at the middle of the graph in Figure 1 and take an aortic valve with an EOA of 1.5 cm^2, then a doubling of normal flow leads to a gradient of 55 mm Hg. Examination of Figure 2 shows that we need to achieve an EOA of approximately 2 cm^2 before we can substantially raise aortic flow without a large increase in transvalvular gradient. This is because the gradient is proportional to the area available for flow, which is related to the square of the EOA radius. Below 2 cm^2, the area available for flow rapidly diminishes.

Is this inability to increase flow without also increasing the transvalvular gradient related to the decreased long-term survival seen in SAVR, especially in younger patients? That is difficult to say from the available data, but achieving an EOA of 2 cm^2 or greater would seem to be a reasonable goal in younger patients to allow physical activity without a large gradient penalty. A hint at how activity may be related to PPM comes from the SURTAVI trial.[4] Using the summary Kansas City Cardiomyopathy Questionnaire (KCCQ) to measure the patients' perception of their QoL, TAVR has a faster increase than surgery, but by 6 months, both are equal and show a large improvement in QoL and remain equal at 1 year (Figure 3A). The KCCQ summary considers multiple domains for QoL and is filled out by the patient generally while sitting somewhere at rest.

A more objective evaluation of the ability to increase aortic flow would be the 6-minute walk test. In SURTAVI, a 6-minute walk distance was measured for patients undergoing either SAVR and TAVR at preprocedure,

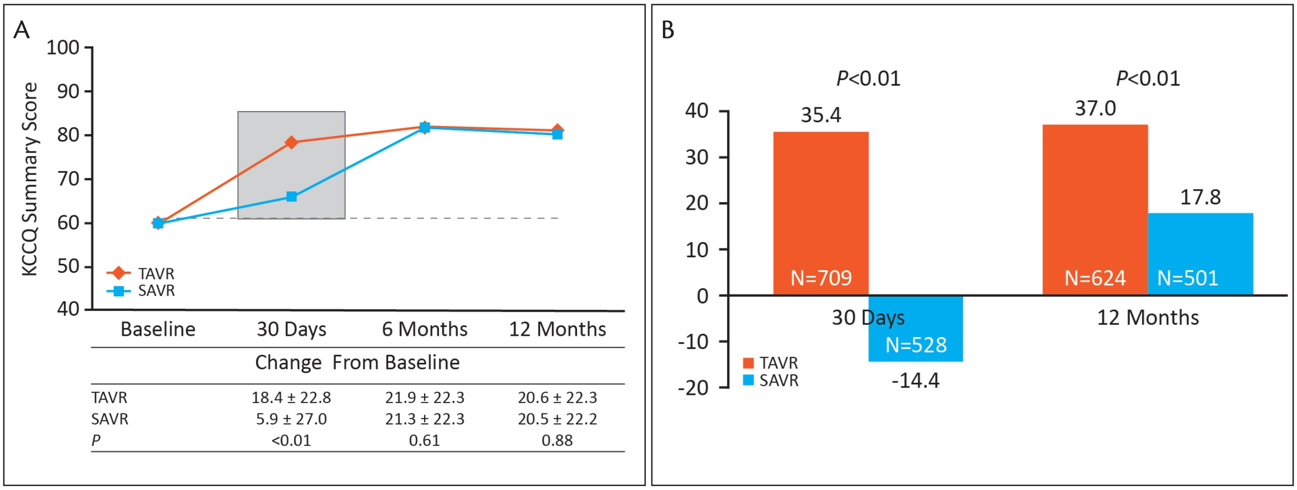

Figure 3. Summary KCCQ for SAVR and TAVR over time in SURTAVI (A). Change from baseline 6-minute walk distance over time for SAVR and TAVR in SURTAVI (B). Reprinted from Van Mieghem NM, Reardon MJ, Popma JJ, et al. Transcatheter aortic valve replacement with a self-expanding prosthesis or surgical aortic valve replacement in intermediate-risk patients: 1-year results from the SURTAVI clinical trial. Presented at 2017 Transcatheter Cardiovascular Therapeutics; October 29–November 2, 2017; Denver, CO.

1 month postprocedure, and 1 year postprocedure. The 6-minute walk distance improved from baseline to 1 month for TAVR and fell for SAVR. This should not surprise us, as these patients are recovering from open heart surgery. At 1 year, however, TAVR maintained its improved 6-minute walk distance and SAVR improved from baseline but still statistically less than the improvement seen with TAVR (Figure 3B). At the current time, we can only speculate as to why SAVR does not catch up completely to TAVR given the equal QoL by summary KCCQ, but we know from SURTAVI that the mean EOA was > 2 cm^2 for TAVR and < 2 cm^2 for SAVR (Figure 4).

DURABILITY

In both SAVR and TAVR, long-term durability and the threat of structural valve deterioration (SVD) gain in importance as we move to younger and lower-risk patients with potentially longer life spans. Durability is addressed in greater detail elsewhere in this supplement, so we will just note that evidence exists that the smaller the EOA and the higher the initial mean gradient are in SAVR, the more likely and sooner the patient will develop SVD.[17] Because this is one factor that we know hastens SVD, it would make sense to avoid this as much as possible by achieving the highest EOA and lowest gradient possible.

CONCLUSION

TAVR has seen a progressive move to lower-risk patients and is currently a class I indication in high-risk patients and a class IIA indication in intermediate-risk patients in the United States guidelines. It can be argued that the intermediate-risk indication is only a class IIA based on the fact that the SURTAVI results were unavailable when these guidelines were published, and intermediate-risk use will likely receive a class IA recommendation in the next iteration of these guidelines. Two low-risk randomized trials in the United States are now complete and data are expected in 2019. If the results of these trials are positive, then a low-risk indication will likely be available by 2020 or sooner. As we move down the risk scale, we must also consider age as well as lifestyle and activity. We believe

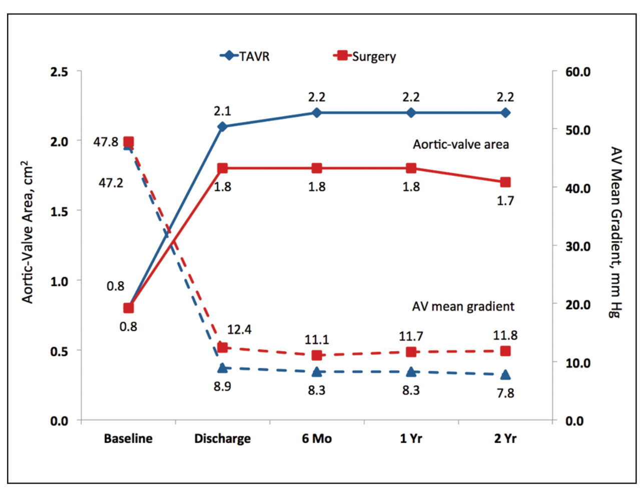

Figure 4. SURTAVI data showing that the mean EOA was > 2 cm^2 for TAVR and < 2 cm^2 for SAVR. From The New England Journal of Medicine, Reardon MJ, Van Mieghem NM, Popma JJ, et al, Surgical or transcatheter aortic-valve replacement in intermediate-risk patients., 376, 1321-1331. Copyright © 2017. Massachusetts Medical Society. Reprinted with permission.

that hemodynamics are increasingly important for both SAVR and TAVR as we move to more active patients and that an EOA of at least 2 cm^2 is a worthy goal. ■

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Aortic Valve-in-Valve Hemodynamics

Considerations for this minimally invasive approach to treating patients with failed bioprostheses.

BY DANNY DVIR, MD

An aging population and significant increase in the use of bioprosthetic tissue valves will no doubt contribute to a large population of patients with degenerated tissue valves. Patients who have failed bioprosthetic valves are usually at increased risk for open heart surgery. These patients are increasingly referred for aortic valve-in-valve (ViV) transcatheter aortic valve replacement (TAVR) procedures. Clinical data show that aortic ViV procedures are safe and effective[1]; however, there are two meaningful adverse events that still deserve careful consideration. The first is coronary obstruction, which is a life-threatening complication of ViV that occurs in approximately 2% to 3% of cases, and the second is residual stenosis, which is a relatively common adverse event that may reduce the efficacy of the procedure (Figure 1).[2,3] Furthermore, elevated postprocedural gradients are considered the Achilles heel of aortic ViV.

This article focuses on hemodynamics after ViV procedures and describes strategies that may enable optimal valve function in these increasingly performed procedures (Table 1).

TABLE 1. MAIN CORRELATES FOR ELEVATED GRADIENTS AFTER VALVE-IN-VALVE
Nonmodifiable Factors
• Baseline prosthesis-patient mismatch
• Stented surgical valve
• Small surgical valve
• Stenosis as the mechanism of failure
Modifiable Factors
• Intra-annular transcatheter heart valve device
• Low positioning of the transcatheter heart valve
• Lack of bioprosthetic valve ring fracture
• Lack of anticoagulation therapy

PROSTHESIS-PATIENT MISMATCH OF THE SURGICAL VALVE

Small label size of the surgical valve is associated with inferior results after ViV procedures. Data from the VIVID registry show that patients with bioprosthetic valves with a label size of 21 mm and smaller had higher mortality rates than those with larger surgical valves.[1] In addition, patients with small surgical valves undergoing ViV display much higher postprocedural gradients and inferior recovery after surgery. Preexisting prosthesis-patient mismatch (PPM) is a major contributor to these worse clinical outcomes. In these conditions, the implanted valve, when fully expanded, enables too small of an effective orifice area in relation to the

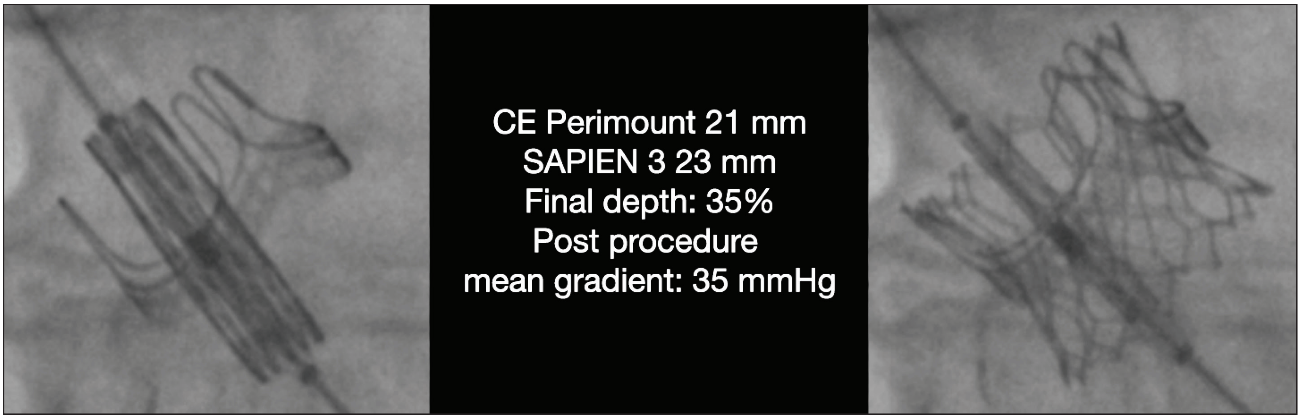

Figure 1. An example of elevated postprocedural gradients immediately after aortic ViV.

patient's body size. A more recent analysis showed that preexistent severe PPM of the surgical valve is the main correlate of elevated postprocedural gradients, as well as short- and long-term mortality after ViV.[4] This is clearly a strong argument for preventing PPM during the original implantation of bioprosthetic valves. It is also suggestive that the existence of bioprosthetic valve PPM should be part of the ViV assessment and would influence the decision to perform the ViV procedure, the type of transcatheter valve to be used, and the method of implantation.

ELEVATED POSTPROCEDURAL GRADIENTS

Residual stenosis after ViV is commonly the result of the nondistensible characteristics of bioprosthesis stent rings, often resulting in underexpansion of the transcatheter valve implants. That underexpansion is commonly revealed by the elevated postprocedural gradients. The mean gradient after aortic ViV is commonly 15 to 20 mm Hg, which is significantly higher than the common gradients seen after native aortic valve TAVR (10 mm Hg).[1,2,5] Some registries that utilized core lab echocardiographic adjudication revealed an average mean gradient of 13 to 20 mm Hg after ViV.[2,5,6] The mean gradient after aortic ViV in the VIVID registry was 15.8 ± 8.9 mm Hg.[1] Similarly, data from the TVT registry on aortic ViV procedures reveal an average mean gradient of 16 mm Hg after the procedure.[7]

The proportion of patients with high postprocedural gradients (mean gradient ≥ 20 mm Hg) was greater in the severe PPM group than in those without severe PPM (47.5% vs 29.6%; $P = .001$).[4] The risk of elevated postprocedural gradients was higher in those treated with balloon-expandable valves (35.3% vs 25.1%; $P < .001$) and was especially high when balloon-expandable transcatheter heart valves (THVs) were deployed in surgical valves that had severe PPM (78.3% vs 33.9%; $P < .001$).[4]

Data from the PARTNER trial evaluating ViV with the Sapien XT valve (Edwards Lifesciences) showed an average mean gradient of 17.6 mm Hg after the procedure, with elevated postprocedural gradients (mean ≥ 20 mm Hg) in 34.3% of patients.[2] Interestingly, patients with elevated postprocedural gradients had a higher mortality rate within 1 year after the procedure (16.7% vs 7.7%; $P = .01$). Although the pivotal study of the CoreValve device (Medtronic) showed a mean gradient of 17 mm Hg after ViV,[5] a more contemporary European registry of ViV procedures, mainly using the CoreValve Evolut device (Medtronic), included meticulous technique of high device positioning and showed better hemodynamic results, with an average mean gradient of 12.2 mm Hg.[6] A matched comparison of THV devices utilized in ViV procedures revealed that the Portico valve (Abbott Vascular) was associated with higher gradients in ViV procedures than CoreValve Evolut (17 ± 7.5 mm Hg vs 14 ± 7.5 mm Hg; $P = .02$), whereas the Sapien 3 device (Edwards Lifesciences) showed similar hemodynamics after ViV in comparison to the Sapien XT device (16.9 mm Hg vs 17.4 mm Hg; $P = .5$).[8,9] In general, clinical data show that supra-annular THV device positioning usually demonstrates better hemodynamics in comparison to devices that are deployed intra-annularly. However, it should be stressed that device characteristics are not the only contributing factor for supra-annularity, as device positioning is also an important consideration in that regard.

DEVICE POSITIONING

Underexpansion of the THV device at the level of the functional valve is commonly a result of the internal characteristics of that device that may not allow for true separation of the leaflet function position from the implanted region (ie, intra-annular devices vs supra-annular valves). However, even a device with potential supra-annular capability may be affected by the annular underexpansion effect when implanted low.

The advantage of high device implantation was discovered in the large cohort of cases analyzed in the VIVID registry when it became clear that devices that were implanted low were much more commonly associated with elevated postprocedural gradients.[10]

The higher position may allow for greater THV expansion, which is especially necessary in small bioprostheses (Figure 2). Later, the relationship of THV positioning and final device expansion has clearly been shown in bench studies as well.[11,12] It seems that for each

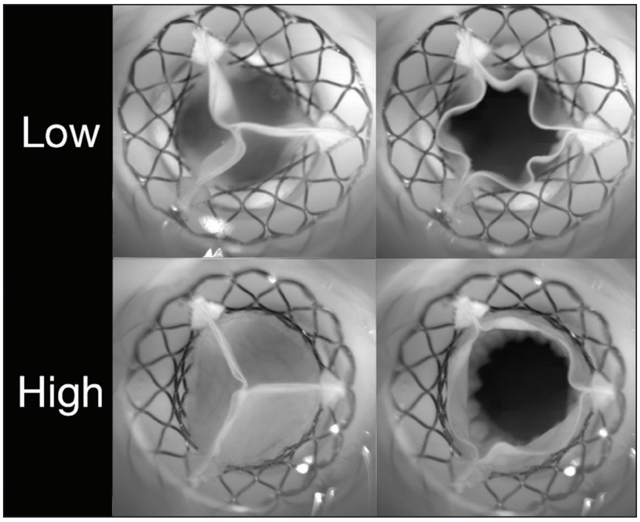

Figure 2. Bench testing of aortic ViV revealing the importance of appropriate device positioning, which can impact effective orifice area during systole and leaflet coaptation during diastole.

THV, there is a zone in which optimal hemodynamics will be enabled. Clinical data from the VIVID registry suggest that the CoreValve Evolut device should be implanted at a depth of up to 4 mm, whereas the Sapien 3 device should be implanted with no more than 15% to 20% of the frame below the ring of the surgical valve.[9,10,12,13]

BIOPROSTHETIC VALVE RING FRACTURE

The restrictive effect of the surgical valve ring is increasingly modified by a technique that is known as bioprosthetic valve ring fracture (BVF). This method utilizes inflation of a high-pressure balloon inside the surgical valve either before or immediately after the ViV procedure. Although surgical valve rings look metallic, most are made of plastic and can break. According to the few cohorts of cases in which BVF has been performed, this technique has been reported to be effective in enabling lower postprocedural gradients than in cases in which BVF is not attempted.[14-19] Bench testing and clinical data suggest that surgical valve rings differ in their ability to undergo fracture: some surgical valves can fracture at relatively low pressure while others cannot.[18,19]

Some TAVR instructions for use contain precautions against performing ViV where the surgical aortic valve is not structurally intact (eg, wireform frame fracture). In addition, the clinical data and anecdotal reports suggest that BVF is not a benign procedure. The observed risks posed by BVF have been reported to include surgical valve leaflet injury/severe regurgitation (if BVF is done first), THV leaflet injury/severe regurgitation (if ViV TAVR is done first), coronary obstruction, pericardial effusion, stroke/systemic embolism, mitral chord rupture/mitral regurgitation, and ventricular septal defect. Theoretical risks posed by BVF include aortic or annular injury, a higher risk of a conduction abnormality, and paravalvular leakage after ViV. It seems that there is still much to learn about the clinical and anatomic features that could predispose one to complications from BVF. One of the main concerns with BVF after ViV is subclinical structural damage to the implanted THV that may result in long-term durability issues. Further research is required to determine the safety, effectiveness, and viability of this technique.

FUTURE PERSPECTIVES

In the current bioprosthetic valve era, it seems that our ability to safely and effectively treat failed tissue valves is more relevant now than ever before. Technical considerations in aortic ViV procedures may improve clinical outcomes and prolong device durability. It is possible that the lessons learned in our ability to treat small surgical valves while enabling optimal hemodynamics could be translated to other subgroups of patients, such as those with small native aortic valves. An important objective for the operator is to ensure optimal hemodynamics that will enable the best possible clinical outcomes for patients with valvular heart disease. ■

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TAVR in Patients With a Small Aortic Annulus

The choice of transcatheter heart valve affects hemodynamics in patients with a small aortic annulus.

BY TOBY ROGERS, MD, PhD

As the field of transcatheter aortic valve replacement (TAVR) has evolved over the last 15 years, many of the early challenges to procedural success have been effectively addressed through advances in newer device generations/iterations and procedural technique. For example, many of the challenges of vascular access and vascular complications have been mitigated by device miniaturization, wholly percutaneous technique, and use of expandable and in-line sheath technology. Another example is the challenge of paravalvular leak, which has been mitigated by systematic use of CT sizing and device engineering to achieve better sealing between the transcatheter heart valve (THV) and the aortic annulus through the use of sealing skirts and wraps.

As a consequence, as TAVR has become safer and increasingly offered to younger patients with fewer comorbidities and longer life expectancies, our focus has shifted to different challenges: optimizing THV hemodynamics and durability.

SURGICAL APPROACH TO PATIENTS WITH A SMALL ANNULUS

Cardiothoracic surgeons aim to implant the largest possible aortic bioprosthesis to achieve optimal hemodynamics. In a patient with a small annulus, the surgeon has a number of available options to maximize the size of the implanted bioprosthesis. These options include root enlargement surgery or implantation of a stentless or sutureless valve. However, the reality is that many patients still receive a small bioprosthesis. The most recently published data of more than 78,000 surgical aortic valve replacement patients from the Society of Thoracic Surgeons database between 2007 and 2010 demonstrated that 38% of patients received a 19- or 21-mm valve.[1] The same pattern was observed in the surgical arms of the SURTAVI and PARTNER 2 trials in intermediate-risk patients, 34% and 44% of whom, respectively, received a 21-mm (or smaller) bioprosthesis.[2,3]

Many of these patients will have prosthesis-patient mismatch (PPM) with high gradients that may predispose to early bioprosthetic valve failure from increased leaflet shear stress. PPM after surgical aortic valve replacement is also associated with more frequent hospital readmissions and higher mortality.[4] Furthermore, the implantation of a small surgical bioprosthesis constrains the patient's options for valve-in-valve TAVR in the future. Even if the bioprosthetic valve ring is fractured with high-pressure balloon inflation before TAVR,[5] it may be difficult to achieve optimal valve-in-valve hemodynamics. The experience with surgical bioprosthesis fracture is still limited and the long-term impact on THV leaflet durability—if performed after TAVR—remains unknown. Data from the VIVID (Valve-in-Valve International Data) registry confirmed that 32% of patients have severe PPM immediately after valve-in-valve TAVR.[6] Furthermore, patients with a small surgical valve (≤ 21 mm) undergoing valve-in-valve TAVR had worse 1-year survival, with a hazard ratio of 2.04 (95% confidence interval, 1.14–3.67; *P* = .02).

IS TAVR THE SOLUTION FOR PATIENTS WITH A SMALL ANNULUS?

Through necessity, THVs have very low-profile metallic frames (compared to surgical bioprostheses with bulky sewing rings), which have the added benefit of maximizing effective orifice area (EOA) compared to an equivalently sized surgical bioprosthesis. This has the potential to be of particular benefit in patients with a small aortic annulus or in patients undergoing valve-in-valve TAVR for a failing surgical (or transcatheter) bioprosthesis with a small true internal diameter.

An early study of TAVR in patients with a small annulus (mean, 19 ± 1 mm by transesophageal echocardiography) using the 23-mm Sapien valve (Edwards Lifesciences), reported excellent procedural success but moderate or severe PPM (defined as indexed EOA ≤ 0.85 cm^2/m^2)

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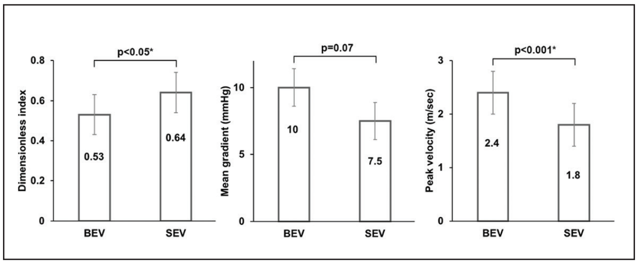

Figure 1. Valve hemodynamics according to valve type (balloon-expandable vs self-expanding) in patients with a small aortic annulus. BEV, balloon-expandable valve; SEV, self-expanding valve. * indicates statistical significance. Adapted from The American Journal of Cardiology, 119, Rogers T, Steinvil A, Gai J, et al, Choice of balloon-expandable versus self-expanding transcatheter aortic valve impacts hemodynamics differently according to aortic annular size, 900–904, Copyright 2017, with permission from Elsevier.

was observed in 38% of patients.[7] A substudy of patients with a small annulus from the Japanese TAVR registry (OCEAN-TAVI) compared hemodynamics in those who received a 20-mm versus a 23-mm Sapien XT THV (Edwards Lifesciences). Mean annulus area was 289 ± 28 mm^2 and 356 ± 38 mm^2 and mean annulus perimeter was 61 ± 3 mm versus 69 ± 4 mm in each group, respectively. Postprocedure mean gradients were 15 ± 4 mm Hg versus 11 ± 4 mm Hg, and the rate of moderate or severe PPM after TAVR was 32% versus 8% with the 20-mm versus the 23-mm THV, respectively. Neither of these studies included long-term follow-up data on valve hemodynamics or clinical outcomes.

A key feature of the self-expanding CoreValve Evolut R/PRO THV (Medtronic) is the supra-annular location of the leaflets. This offers a theoretical advantage over balloon-expandable valves in the setting of a small annulus because the supra-annular leaflets afford a larger EOA. In the PARTNER trial, 39.4% of patients with a small annulus had moderate or severe PPM after implantation of a balloon-expandable valve.[8] My colleagues and I published a comparison of valve hemodynamics and clinical outcomes according to annulus size and type of THV (balloon-expandable vs self-expanding).[9] In our study, a small annulus was defined as a < 73-mm perimeter (or approximately 23-mm diameter). Although there was no difference in valve hemodynamics in patients with a medium or large native aortic annulus, there were statistically significant differences in hemodynamics in patients with a small annulus (Figure 1). Notably, peak velocity was lower and dimensionless index was higher with self-expanding THVs.

We prefer to report the dimensionless index rather than the EOA. The dimensionless index is the ratio of the subvalvular velocity obtained by pulsed-wave Doppler and the maximum velocity obtained by continuous-wave Doppler across the aortic valve, and thus is not subject to transthoracic echocardiographic measurement error of the left ventricular outflow tract area, which typically overestimates the prevalence of PPM.[10] PPM is considered severe when the dimensionless index is < 0.25 and moderate when it is ≥ 0.25 and < 0.5. Although the hemodynamic differences observed between THV type were significant, the number of patients was too small and the follow-up duration too short to evaluate for a correlation between THV hemodynamics and long-term THV durability.

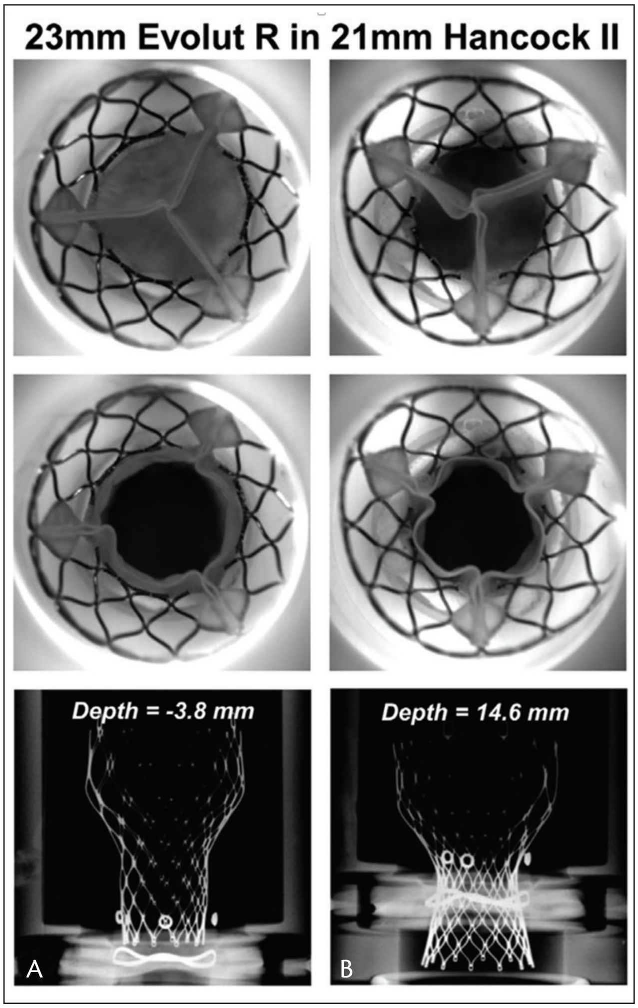

Figure 2. High (A) versus low (B) implantation of a 23-mm CoreValve Evolut R inside a 21-mm Hancock II bioprosthesis (Medtronic). Reprinted from The Journal of Thoracic and Cardiovascular Surgery, 153, Azadani AN, Reardon M, Simonato M, et al, Effect of transcatheter aortic valve size and position on valve-in-valve hemodynamics: an in vitro study, 1303–1315, Copyright 2017, with permission from Elsevier.

Mechanistically, it makes sense that leaflet durability would be reduced by higher transvalvular gradients, increased leaflet shear stress, and eccentric geometry. Therefore, the approach to patients with a small annulus is not as simple as “small annulus = TAVR.” In vitro studies, mostly focused on valve-in-valve TAVR, have demonstrated that type of THV (balloon-expandable vs self-expanding), suboptimal THV sizing, THV implantation depth, and annulus eccentricity contribute to leaflet pinwheeling and abnormal leaflet shear stress, which could affect hemodynamics and ultimately durability.[11-13] Many of the lessons from studies on valve-in-valve TAVR are applicable to patients with a small native aortic annulus. For the self-expanding CoreValve Evolut TAVR platform, optimal hemodynamics are achieved with a high implantation to maximize the benefit of the supra-annular leaflets (Figure 2).[14] Oversizing the THV is probably not advisable, as this leads to excessive leaflet redundancy, pinwheeling, and shear stress.

CONCLUSION

Patients with a small aortic annulus deserve careful consideration by a heart team. If the patient is operable but the surgeon is not prepared to perform root enlargement surgery or implant a stentless or sutureless valve, then TAVR should be the preferred treatment option. The data are clear: hemodynamics and clinical outcomes are worse in patients with small aortic bioprostheses. Available data in patients with a small native aortic annulus support the use of TAVR over surgical aortic valve replacement and favor the use of self-expanding THVs with supra-annular leaflets to achieve optimal hemodynamics. ■

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Durability and Hemodynamics: The New Frontier in TAVR

A surgeon's perspective on how device attributes can improve these factors to facilitate good outcomes as the TAVR treatment population expands.

BY DANIEL O'HAIR, MD

Surgical treatment of aortic valve disease is a well-established therapy, and nearly 60 years have passed since the first reported successful case.[1] Long ago, issues of access and reproducibility were resolved, allowing surgeons to objectively focus on hemodynamics and long-term valve performance. Standard criteria to assess valve function have been established and the importance of using objective criteria to evaluate heart valve performance cannot be overstated.[2]

STATEMENT OF THE PROBLEM

The more recent development of transcatheter aortic valve replacement (TAVR) therapy initially focused on safe delivery and reliable early performance.[3,4] Now that these issues have largely been addressed, attention must be focused on the critical issue of longer-term valve performance and durability. These key issues are becoming increasingly important as TAVR therapy moves to a younger and healthier patient population with longer life expectancy.

THE IMPORTANCE OF DESIGN

Heart valve durability is heavily influenced by design. Materials including bovine pericardium, porcine valve tissue, and bovine venous valve tissue have been extensively studied and each displays characteristics contributing to in vivo durability in the aortic, mitral, and pulmonic positions.[5-7] Beyond material application, the design of the supporting structure for the valve leaflets may also have important implications on durability. For example, bovine pericardium and porcine aortic leaflet tissue have excellent durability when the tissue is contained within the supporting architecture (ring and struts) of the valve, such as in the Magna (Edwards Lifesciences) and the Mosaic (Medtronic) valves.[5,6] On the other hand, when the design puts pericardial leaflets external to the frame of the valve, such as in the Mitroflow device (Sorin Group) and Ionescu-Shiley valve (Shiley Inc., a Pfizer subsidiary), durability appears to suffer.[8] These concepts underscore the need for careful study of the design characteristics of current transcatheter valves, as well as patient outcome data, in order to draw conclusions about TAVR durability and hemodynamic performance.

DURABILITY

Long-term durability data, traditionally considered to be 10 years or more, are currently unavailable in the TAVR treatment population. Unlike surgical aortic valve replacement (SAVR), where biologic valves have been used in all age groups for decades (although only recommended for those 60 years or older and, more recently, 50 years or older), TAVR has initially been applied in elderly inoperable patients with many comorbidities. Not surprisingly, 5-year all-cause mortality has been reported up to 71%, and therefore, most of these patients are not available for long-term follow-up.[9] As treatment moves toward lower-risk patients with increasing life expectancy, careful monitoring of ongoing valve function will provide essential insight into the durability of TAVR. Establishing standard objective criteria for ongoing evaluation of bioprosthetic valve function, including the definition of structural valve deterioration, continues to be an active point of discussion. Among the many definitions proposed, the Valve Academic Research Consortium is in the process of finalizing an update to be considered in addition to a newly published European consensus statement.[10] Once established, using objective uniform criteria, valve durability can be assessed as patients mature with their devices.

Although 10-year data are still lacking, important 6-year follow-up data have come from the NOTION trial, which was the first study to randomize lower-risk patients between SAVR and TAVR using early generation self-expanding valves.[11] Six-year follow-up of hemodynamic performance with this early generation TAVR valve showed sustained low (single-digit) gradients, unchanged from year 1 through year 6. Importantly, valve gradient was significantly lower and the effective orifice area (EOA) was significantly greater than with surgical valves at every time point. This supports the concept that supra-annular design may allow improved hemodynamics versus the

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intra-annular design in older-generation surgical valves and perhaps balloon-expandable valves. Moderate hemodynamic structural valve deterioration, defined as mean gradient of ≥ 20 mm Hg or increase in gradient of ≥ 10 mm Hg over baseline, was present in 3.6% of TAVR patients and 23.7% of surgical patients. Again, this suggests that a supra-annular TAVR design may be superior to the design of most surgical biologic valves. Valve thrombosis was not seen in either valve. Endocarditis rates were low (< 6%) and not different between surgical and TAVR treatment groups.[12]

Five-year data from the ADVANCE study show that among the 860 patients who had echocardiographic data after 30 days, 22 patients (2.6%) had aortic valve stenosis as defined by VARC-2 criteria.[13] Longer-term follow-up from the POST-TAVI registry has been reported by the group at Heart Center in Bad Segeberg, Germany.[14] Fifty-six patients with echocardiographic follow-up beyond 5 years (mean, 6.3 years; range, 5–8.9 years) had an EOA of 1.6 cm^2 and mean gradient 6.7 mm Hg, signaling good durability beyond 5 years.

DESIGN CONSIDERATIONS

Human anatomic details also play a potential role in the long-term durability of aortic devices. The aortic annulus has measurable and somewhat fixed dimensions for each individual patient. As a result, there are limits to the amount of prosthetic material that can reside within the annulus without compromising the EOA. This becomes increasingly important in cases of small native annulus or a valve-in-valve case for a failed surgical prosthesis. Balloon-expandable devices are largely intra-annular, and therefore, by definition, the frame, leaflet, and skirt material are contained within the annulus. When the goal is to obtain the largest EOA, these valves are already challenged when compared to supra-annular self-expanding devices. The supra-annular self-expanding devices are positioned with only the low-profile nitinol frame and skirt within the annulus and the actual leaflets of the functional valve well above the annulus, providing a fundamental advantage when working in the fixed dimensions of the calcified native annulus. As annular size decreases, this advantage becomes increasingly important.

Leaflet shape is also thought to contribute to long-term durability. Much like the long cables of a suspension bridge (eg, the Golden Gate Bridge) that distribute forces over a large area to gain stability, the taller leaflets of the self-expanding design are thought to distribute stress over a larger area, thereby reducing risk of failure at any given point (data on file at Medtronic). Additional evidence of the importance of proper leaflet shape and orientation has been obtained in vivo. Overexpansion, underexpansion, or irregular expansion of the balloon-expandable valve have been shown to result in either improper leaflet contact (pinwheel effect) or incomplete leaflet coaptation, both of which are thought to contribute to early valve failure.[15] This effect is not seen in the supra-annular self-expanding devices, in which the leaflets are unconstrained by the annulus and can reliably take the shape of the frame in the larger area of the sinuses of Valsalva.

At the current time, failure of TAVR valves is relatively uncommon. In general, valve failure occurs by either restenosis of the leaflets or leaflet tear. Both of these mechanisms will have profound effects on the hemodynamics. In the more common failure mode, restenosis, there is usually a slow progression of increasingly rigid leaflets, resulting in an increasing transvalvular gradient. For this reason, trends in gradient development provide a signal on durability and deserve consideration.

Strategies to enhance the performance of the leaflet tissue itself may also play an important role in durability. Recently, a four-dimensional CT radiographic finding described as hypoattenuated leaflet thickening (HALT) has gained attention. This finding, when extensive, is believed to diminish leaflet mobility and lead to subacute valve failure. Midha et al recently described how balloon-expandable valves with HALT were noted to be those that were expanded to a greater degree than those without HALT.[15] It is unclear how, if at all, this information could be used to guide procedural details, but it is notable that this relationship was not present in the self-expanding cohort. In vitro studies also suggested that supra-annular valves have significantly less stagnation of flow but may be at risk with increasing depth of implantation. If true, potential mitigation strategies might include accurate and precise deployment enabled by the recapture and repositioning features of self-expanding technology. The topic and impact of HALT continue to be widely discussed and there is debate about the clinical implications. Anticoagulation as a strategy to mitigate this finding must be cautiously approached due to heterogeneity of comorbidities among patients treated with TAVR. Patient-independent strategies to reduce leaflet degradation may offer a solution. One such strategy involves processing the leaflet tissue with alpha-amino oleic acid, a naturally occurring long-chain fatty acid shown to reduce calcification in vitro.[16,17] This strategy is currently in use in the Evolut valve (Medtronic).

Certain patient-specific factors can also pose challenges to long-term valve durability. The presence of a small previously placed bioprosthetic valve, prosthesis-patient mismatch (PPM), and altered calcium metabolism are examples of patient-specific conditions that affect durability. Patients who have previously been treated with a small (19 mm) surgical valve and have developed restenosis also represent a particular challenge. These patients are typically elderly, frail, and poor surgical candidates. Relief of gradient is an important feature because residual gradient portends a poor outcome. A supra-annular TAVR design (eg, Evolut R, Medtronic) is critical in these cases to maximize the resultant EOA. In our experience, high deployment (1–2-mm depth) has shown good results. At our institution, five patients with

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stenosis of a 19-mm prosthetic aortic valve underwent treatment with a 23-mm Evolut R or CoreValve (Medtronic), which resulted in low gradient (mean gradient, 12; EOA, 1.3) and excellent symptom relief (unpublished data). Reports from the Global Valve in Valve Registry[18] (Valve-in-Valve International Data [VIVID][19]) show that treatment of small bioprosthetic valves with CoreValve did not increase the occurrence of high gradient after TAVR, whereas the use of a Sapien valve (Edwards Lifesciences) resulted in a substantial increase in the frequency of high residual gradient. Treatment of small prosthetic valves with the Sapien device was an independent predictor of leaflet distortion and valve failure.[20]

When patients are found to have an unexpectedly high gradient across a prosthetic valve, such that the effective orifice is inadequate for the patient's size, this condition is known as *PPM*. The transvalvular gradient (TVG) is calculated by dividing the square of the flow (Q) by the square of the EOA multiplied by a constant[21]:

$$TVG = \frac{Q^2}{k \times EOA^2}$$

Because the gradient is directly related to the square of the flow and inversely related the square of the EOA, relatively small changes in either the flow or the EOA have a large impact on increasing or decreasing the gradient. Due to the fact that TAVR has been shown to have a lower gradient than SAVR,[22] TAVR should be viewed as a protective strategy in those patients at risk for PPM and as therapeutic strategy for treating prosthetic valve degeneration or PPM. The less material placed within a degenerative prosthetic valve (especially in sizes ≤ 21 mm), the lower the expected gradient. Supra-annular valves appear to have an advantage in this situation. The strategy of TAVR, in place of surgical root or annular enlargement in patients with very small native anatomy, is gaining popularity. This is particularly effective when using a supra-annular valve that has a lower gradient and larger EOA than surgical valves.[22]

Finally, the issue of accelerated calcium metabolism and secondary hyperparathyroidism is most common in patients with end-stage renal disease (ESRD). This challenging population has a high prevalence of cardiovascular disease and typically shows extensive vascular calcification. TAVR with CoreValve or Evolut can be performed with low procedural mortality (5%) despite a Society of Thoracic Surgeons Predicted Risk for Operative Mortality score of 16 ± 7. In the national trial, gradients remained low (< 10 mm Hg) throughout the 1-year follow-up period.[23] In many centers, TAVR has become the standard of care for ESRD patients because of an unexpectedly low procedural mortality and good early functional results under the most challenging metabolic conditions.

CONCLUSION

The continued application of TAVR to lower-risk patients demands careful attention to valve performance and long-term durability. Early and midterm performance look very promising but ongoing consideration of hemodynamics, structural design, and precise placement will allow us to provide effective solutions for patients with aortic valve disease. ■

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