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Paravalvular Regurgitation Following Transcutaneous Aortic Valve Replacement: Predictors and Clinical Significance

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Abstract Despite the higher incidence of paravalvular regurgitation (PVR) with transcatheter aortic valve replacement (TAVR), this novel treatment modality has rapidly emerged as a reasonable alternative to surgical aortic valve replacement (SAVR) in high risk and inoperable patients. This review will discuss the current literature with respect to assessment, outcomes, predictors, and intraprocedural treatment options of PVR following TAVR. Understanding the predictors may help reduce the incidence of PVR and improving the outcome of this procedure.

Keywords Paravalvular regurgitation · Transcutaneous aortic valve replacement · TAVR · TAVI · Aortic stenosis

Introduction

Untreated severe, symptomatic aortic stenosis (AS) is associated with high mortality [1–3] yet studies suggest that up to 38 % of these patients remain untreated [4–7]. Transcatheter aortic valve replacement (TAVR) has rapidly emerged as a reasonable alternative to surgical aortic valve replacement (SAVR) in high risk and inoperable patients [8•, 9•, 10–13]. Multiple studies, however, have shown a higher incidence of paravalvular regurgitation (PVR) in the TAVR population compared with the SAVR population with moderate or severe PVR seen in 0 % to 24 % [8•, 9•, 14–26]. Studies also suggest that aortic regurgitation (AR) is an important predictor of mortality [14, 19, 27, 28]. This review will discuss the current literature with respect to incidence, outcomes, predictors, and intraprocedural treatment options of PVR following TAVR.

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Quantifying Paravalvular Regurgitation

The inconsistency of reported incidences of PVR may in part be due to differences in the method of assessing regurgitation (fluoroscopy vs magnetic resonance imaging [MRI] vs echocardiography) as well as the difficulties inherent in quantifying prosthetic valve regurgitation. Fluoroscopic assessment of regurgitation relies on the relative density of contrast media in various structures [29] and is highly subjective and dependent on observer's experience as well as the numerous technical factors (ie, the intensity of fluoroscopy, the use of 1 or 2 planes for obtaining the images, the volume of the contrast medium used, the position of the catheter tip and its type) resulting in significant variability in grading [30]. Although cardiac MRI may further add to a detailed analysis of regurgitation after TAVR [31], echocardiography remains the method of choice in the assessment of valvular regurgitation after TAVR [32, 33•].

The American Society of Echocardiography (ASE) has suggested semiquantitative schemes for assessing prosthetic PVR [34], however, a number of limitations of these grading criteria exist. First, the qualitative grading scheme is intended for surgical prosthetic valves. The intact calcified cusps and annulus following TAVR create atypical and irregular paravalvular jets, which may be difficult to quantify by standard methods. In addition, PVR may need to be assessed differently for each type of transcatheter valve. Finally,

discrepancies exist among the published guidelines for assessment of prosthetic AR. The updated Valve Academic Research Consortium (VARC-2) consensus document [35•], as well as methodology used for the PARTNER trial [36] differ slightly from the recommendations of the American Society of Echocardiography [37]. The grading of PVR for the PARTNER trial relied heavily on circumferential extent of the regurgitant jet but used different criteria from the ASE guidelines: no PVR (no regurgitant color flow), a trace (pinpoint jet in aortic valve [AV] short axis view), mild (jet arc length is <10 % of the AV annulus short axis view circumference), moderate (jet arc length is 10 %–30 % of the AV annulus short axis view circumference), and severe (jet arc length is >30 % of the AV annulus short axis view circumference) [36].

Hemodynamic measurements may provide additional information on the severity of PVR immediately following TAVR. Sinning et al. [38•] used a dimensionless AR index defined as the difference between the diastolic blood pressure and left ventricular end-diastolic pressure, divided by the systolic blood pressure × 100. The AR index was significantly related to qualitative echocardiographic grades of PVR (P= 0.001), however, there was significant overlap between grades and the index clearly does not differentiate between central or PVR. In addition, an AR index of <25 was predictive of increased 1-year mortality in both none/mild and moderate/severe PAR patients suggesting that the severity of regurgitation may not be the only determinant of the "AR" index; ventricular compliance for instance, may play a large role in determining end-diastolic pressures. This as well as other pitfalls make the AR index a poor discriminator of PVR severity while being a useful prognostic tool. This hemodynamic tool may be useful for intraprocedural decision-making when integrated with other imaging modalities such as echocardiography.

Although a comprehensive quantitative echocardiographic evaluation of AR in prosthetic valves could be performed, these techniques require significant expertise particularly immediately following TAVR. Quantitation of prosthetic regurgitant volume, effective regurgitant orifice area, and regurgitant fraction should be performed using ASE methods [34, 37] with the regurgitant volume calculated as the difference between the stroke volume across any nonregurgitant orifice (RVOT or mitral valve) and the stroke volume across the LVOT. Three-dimensional echocardiography may overcome the limitations of 2-dimensional and standard Doppler measurements for quantifying regurgitation [39–41].

Incidence of PVR

Significant attention has been paid to the differences in PVR incidence with valve type. A single site, core-lab comparison between these valves, matched for annular size, ejection fraction, and patient characteristics, confirmed the incidence of paravalvular aortic regurgitation was greater with the CoreValve (≥ grade 1 in 85.4 %, ≥ grade 2 in 39 %) than with the Edwards SAPIEN (≥ grade 1 in 58.5 %, ≥ grade 2 in 22 %; P=0.001). The number and extent of PVR were also greater in the CoreValve group (P <0.01 for both comparisons) [42]. A multicenter study from France compared patients who underwent transfemoral TAVR with either the SAPIEN (n= 96) or CoreValve (n=96) valves propensity matched for baseline clinical and echocardiographic characteristics, including annular size [43].The incidence of moderate or severe PVR was significantly greater for the CoreValve (14.3 % vs 35.5 %, P<0.01). The meta-analysis by Athappan et al. [44•] suggests that the incidence of moderate or severe AR after CoreValve TAVR was 16.0 % (95 % confidence interval (CI): 13.4, 19.0) and the incidence of moderate or severe AR after Edwards valve TAVR was only 9.1 % (95 % CI: 6.2, 13.1). Analysis of variance proved that moderate or severe AR was seen more often with the self-expanding CoreValve (P=0.005). A separate meta-analysis by O'Sullivan et al. [45] confirmed that the proportion of significant PVR was higher for the CoreValve, with a rate of 15.8 % (95 % CI: 12.48, 19.3), than the Edward SAPIEN valve, with a rate of 3.9 % (95 % CI: 1.1 %, 8.4 %) and that valve type was a predictor of PVR.

Interdevice differences may account for differences in reported PVR incidences. Device recoil [46] or further expansion may differ between types or iterations of current devices, which may also influence the incidence of PVR between valve types. The LVOT-Aortic angle has been implicated as an important determinant of PVR with the CoreValve [31]. Studies suggest that the overall incidence of PVR does not change over time, however, multiple studies suggest that some individual changes in PVR may occur. In the PARTNER trial, 31.9 % improved their PVR grade at 2 years whereas 22.7 % worsened [26]. Similarly for the CoreValve, both improvement and worsening of PVR may be seen in individuals over time [28, 47]. Recent unpublished work of the CoreValve US Pivotal Trial of Extreme Risk (presented at TCT 2013) suggested that the incidence of moderate or severe PVR was only 11.5 % at 30 days and when evaluating paired data for this cohort, the majority of 1-year survivors showed some reduction in PVR over time.

Outcomes with PVR

Numerous studies have shown an association between postprocedural PVR and all-cause and cardiovascular mortality [13, 14, 19, 28, 38•, 44•, 48–50]. In the 2-year follow-up of the Placement of AoRTic TraNscathetER Valve Trial (PARTNER) trial, the effect of AR on mortality was proportional to the severity of the regurgitation [13].Actually, a recently published meta-analysis demonstrated that, after

multivariable analysis including baseline characteristics, mild PVR was associated with an increased hazard ratio for mortality, (HR=1.829 [95 % CI: 1.005 to 3.329]) but was overturned by sensitivity analysis [44•]. On the other hand, some studies suggest that only moderate or severe PVR are determinants of outcome [14, 28]. The causal relationship between mild AR and increased mortality after TAVR as well as the pathophysiological mechanisms underlying this observation remain unanswered questions. Nonetheless, understanding the predictors and reducing the incidence of PVR are important to improving the outcome of this procedure.

Predictors of PVR

In the aforementioned meta-analysis of 25 studies reporting predictors of PVR, 3 primary etiologies were identified: multislice computed tomography (MSCT) mean Agatston calcium score, valve undersizing, and depth of implantation [44•]. For the balloon-expandable transcatheter heart valve (THV), significant PVR most commonly results from incomplete prosthesis apposition to the native annulus due to retained biologic material of the native valve, ridges of calcium [16, 51–53]. The extent of calcification, asymmetric distribution, as well as location of calcium on the aortic wall, valve commissure, or THV landing zone have all been implicated as etiologies of PVR [16, 48, 51, 54–58]. Haensig et al. [52] found that specific locations of heavy calcification predicted the location of subsequent PVR with the balloon-expandable valve; only the calcium in the noncoronary cusp and non-right coronary commissures failed to reach significance between patients with and without PVR. Gripari et al. [57], on the other hand, showed that by transesophageal echocardiography (TEE), commissural calcification particularly calcium within the commissure between the right and noncoronary cusps, was predictive of PVR. More recently, Feuchtner et al. [59] found that increasing amount of calcium, as well as protruding calcium (>4 mm) particularly in the left and noncoronary location, were predictive of PVR. Ewe et al. [16] similarly found aortic wall calcification near the annulus was more important than leaflet or commissural calcification in predicting PVR. In our own study of 150 TAVR patients, we found that calcification anywhere in the aortic valve complex predicts ≥ mild PVR immediately post-TAVR and the need for postdilatation. Independent predictors of PVR and postdilatation were leaflet and LVOT calcification (submitted for publication). Finally, calcium may be a predictor of outcomes following TAVR [60].

Annular shape and inaccurate annular sizing have also been implicated as an etiology of PVR. The oval shape of the annulus has been well-documented [61–66] and annular eccentricity has been implicated as a predictor of PVR [15, 48]. However, for the balloon-expandable valve, studies suggest that the annulus remodels following THV implantation [62], which may explain why other studies have shown eccentricity of the annulus plays no significant role in PVR [59, 67]. Although shape of the annulus may be irrelevant, multiple studies have suggested that undersizing of the THV is directly related to the severity of PVR [15, 22, 38•, 52, 67–69]. Three-dimensional reconstruction of the aortic root by MSCT [63–65, 70–72] or 3D TEE [57, 73–76] allow more accurate measurements of annular area or perimeter and can be used to predict PVR [77, 78•].

Malpositioning of the valve has also been identified as the cause of PVR for both the balloon-expandable and self-expanding valves [21, 22, 79, 80]. An understanding of the shortening and superior motion of the balloon-expandable valve should help reduce mal-positioning [81]. With shortening of the first generation valve occurring primarily from the proximal (apical) end, ensuring the lower edge of the skirt is positioned at or just below the annulus should reduce PVR. With very low valve implantation, valve regurgitation through the stent and above the skirt can occur [82].Higher implantation depths more frequently achieved with transapical placement of the balloon-expandable valve, is thought to be the reason this approach has a lower incidence of PVR [48]. Low CoreValve prosthesis position has also been implicated as the cause of more significant PVR [22, 83].

TAVR access may also influence the incidence of PVR. According to both the France 2 investigators [71] and the UK TAVI registry [19] transapical TAVI may be associated with a lower incidence of PVR. Moat et al. showed that the incidence of moderate or severe AR was 15.6 % with the transfemoral approach, and 9.1 % for "other" approaches (primarily transapical) (P=0.01). Similar numbers were found in the France 2 study.

Importantly, no correlation with regurgitation severity has yet been reported for baseline left ventricular outflow tract and aortic root dimensions, mean transvalvular pressure gradients, preprocedural aortic, or mitral regurgitation, and prosthesis size [14, 84].

Intraprocedural Treatment of PVR

Reballooning or postdilatation (PD) of balloon expandable valves after implantation has been proposed as an effective method to reduce post-TAVR PVR [22, 48, 54, 85, 86]. Potential risks of PD include: THV migration or injury, trauma to the conduction system, rupture of the membranous septum or aorta and cerebrovascular embolism [54, 85, 87]. Studies have shown that the severity of regurgitation can be significantly reduced with postdilatation [54, 88]. Postdilatation rates for the Edwards SAPIEN valve ranges from 10 %–40 %. Nombela-Franco et al. showed that the severity of calcium was related to the need for as well as the response

to postdilatation [54]. There was also a higher incidence of cerebrovascular events at 30 days in the postdilatation group (11.9 % vs 2.0 %, P=0.006), however, the relationship of these events to baseline characteristics such as calcium, could not be determined. An increase in mortality has not been shown with this procedure, however, and so it remains an important tool for the intraprocedural treatment of significant PVR.

A transcatheter valve-in-valve procedure may be necessary in some cases, in which PD or other techniques do not improve the degree of PVR [20, 80, 89]. In the PARTNER study of 2554 patients, valve-in-valve therapy was performed in 63 (2.5 %) of patients most commonly for severe central AR due to malpositioning of the THV or leaflet dysfunction (50.8 % of cases) but also for PVR (36.1 %). Compared with patients that were implanted with a single valve, those who underwent rescue valve-in-valve had higher 1-year cardiovascular mortality (hazard ratio [HR]: 1.86, 95 % CI: 1.03 to 3.38, P= 0.041) [80]. The reason for this association is likely multifactorial since rescue valve-in-valve in this study was associated with more frequent requirement for hemodynamic support, increased contrast use, larger total CK enzyme leakage, higher incidence of cardiac conduction abnormalities, and permanent pacemaker implantation, and longer hospital stays.

Conclusions

PVR following TAVR is a common complication associated with poor outcomes. Numerous predictors of PVR have been identified including calcification of the THV landing zone, undersizing of the valve, and device position. In addition, valve type and implantation approach may also be important factors. Improved methods for assessing and quantifying post-TAVR PVR should be developed in order to better understand the impact of PVR on outcomes.

Compliance with Ethics Guidelines

Conflict of Interest R. T. Hahn has received speaker honoraria and research grant from Edwards Lifesciences and research grant from Philips Healthcare. She has also received travel/accommodations expenses covered or reimbursed from Edwards Lifesciences, St. Jude Medical, and Mitralign for meetings, speaking engagements, and unpaid research. S. Kodali has received consulting fees from Edwards Lifesciences, St-Jude, and Claret Medical. He has received stock options from VS Medtech and Thubrikar Aortic Valve, Inc. P. Généreux has received speaker honoraria, consulting fees, and research grant from Edwards Lifesciences. M. B. Leon is a nonpaid member of the Scientific Advisory Board of Edwards Lifesciences.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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