Effect of Right Ventricular Function and Tricuspid Regurgitation on Outcomes After Transcatheter Aortic Valve Implantation

Forgotten Side of the Heart

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Transcatheter aortic valve implantation (TAVI) has rapidly evolved during the past decade and is now well established for the treatment of patients with severe, symptomatic stenosis at increased surgical risk. Results from randomized clinical trials reported long-term outcomes, which were comparable or superior to surgical aortic valve replacement (SAVR) among patients at intermediate to high surgical risk.[1,2] Over the years, technological advancement in valve design and delivery, optimized peri-interventional medical management, and, not least, improved patient selection have led to breathtaking improvements in periprocedural outcomes. This development has been recently highlighted by the report of the 30-day results of the Placement of Aortic Transcatheter Valve (PARTNER) II S3 trial performed in high (Society of Thoracic Surgeons [STS] score, 8.6%) and intermediate risk (mean STS score, 5.3%) patients. Using the Edwards Sapien 3 system (Edwards Lifesciences, Irvine, CA), the investigators reported exceedingly low rates of mortality (2.2% and 1.1% in the high- and intermediate-risk cohort, respectively), with an observed to estimated (STS score based) ratio of mortality of 0.26 in the high-risk cohort and 0.21 in the intermediate-risk cohort. For the purpose of comparison, the 30-day mortality in the transcatheter group of the PARTNER A trial amounted to 5.2% with an observed to estimated mortality ratio of 0.44.[3] Notwithstanding, despite the indisputable benefits of TAVI, the recently published long-term data from the PARTNER B trial highlighted the high mortality (72%) and readmission rates (48%) within 5 years of follow-up among inoperable TAVI patients.[4] Ideally, improvements in clinical outcomes after TAVI should go beyond a reduction in mortality and also address improvements in quality of life. Therefore, it is of pivotal importance for the Heart Team to identify patients and lesions who benefit most from this intervention.

See Article by Lindman et al

Several independent predictors of mortality related to TAVI have been established including various comorbidities and procedural factors. In a recent study, the analysis of the outcomes of >3700 TAVI patients identified moderate or severe aortic regurgitation (hazard ratio [HR], 2.79; 95% confidence interval [CI], 1.82–4.27; $P<0.001$), atrial fibrillation (HR, 2.33; 95% CI, 1.62–3.35; $P<0.001$), new-onset left bundle branch block (HR, 2.26; 95% CI, 1.23–4.14; $P=0.009$), chronic obstructive pulmonary disease (HR, 1.59; 95% CI, 1.11–2.29; $P=0.012$), elevated systolic pulmonary artery pressure (>60 mm Hg; HR, 1.99; 95% CI, 1.21–3.28; $P=0.007$), reduced left ventricular ejection fraction (<40%; HR, 1.68; 95% CI, 1.10–2.56; $P=0.017$), lower mean transaortic gradient (HR, 1.11; 95% CI, 1.02–1.22; $P=0.04$), and transapical access (HR, 2.38; 95% CI, 1.60–3.54; $P<0.001$) as predictors of cardiac deaths.[5]

Concomitant valvular heart disease represents another prevalent condition that may influence the outcomes of patients undergoing TAVI. Pooling the data of large-scale TAVI registries, coexisting moderate to severe mitral regurgitation (MR) is encountered in 19% to 34% of the patients.[6] Despite limited data, relevant tricuspid regurgitation (TR) seems equally frequent, affecting 15% to 25% of patients undergoing TAVI.[7,8] In the past, both MR and TR have been associated with an increased risk of mortality after SAVR.[9,10] More recently, moderate to severe MR has also been related to worse clinical outcomes after TAVI,[6] whereas the association is less well established among patients with relevant TR.[7]

Although the prognostic effect of left-sided heart disease has been well investigated, far less attention has been paid to the right side of the heart, in particular, right ventricular (RV) function and tricuspid valve regurgitation. The study published in this issue of *Circulation: Cardiovascular Interventions* by Lindman et al[11] intends to fill this gap in our knowledge.

The PARTNER II trial was designed to compare the balloon-expandable Sapien XT prosthesis with the first-generation Edwards SAPIEN bioprosthesis among 542 patients with severe aortic stenosis deemed inoperable. Using data from this study (cohort B), the authors investigated the effect of RV dysfunction and TR on prognosis and 1-year mortality. For this purpose, RV fractional area change and dimensions of the RV along with TR severity were assessed by transthoracic echocardiography at baseline and analyzed by an independent core laboratory. In addition, invasive hemodynamic measurements were obtained at the time of the procedure. After multivariable adjustment, moderate to severe TR as well as RV and right atrial enlargement were found to be independently associated with increased 1-year mortality. However, this did not apply for RV dysfunction. Of note, moderate to severe TR was associated

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with increased mortality among patients without coexisting MR, whereas this was not the case in patients with moderate to severe MR. In contrast to previous studies, increased pulmonary artery pressure did not result in adverse prognosis. At 1-year follow-up, TR improved from moderate-severe to trace-mild in ≈30% of the patients, and RV dysfunction resolved in all patients in whom follow-up data were available.

Although these findings provide important insights into the poorly explored effect of right heart disease and TR, some limitations inherent to the study design deserve considerations. First, because of the selection of high-risk patients (mean age, >84 years; mean STS, >10%), the results may not be applicable to younger lower risk patients increasingly evaluated for TAVI. Second, the retrospective nature of the study may have been associated with imperfect echocardiographic assessment of MR, TR, and RV function because the initial protocol did not focus on the influence of multivalvular disease. Third, information on the frequency and intensity of medical treatment, in particular diuretics, is lacking.

TAVI and TR

TR is most frequently the result of secondary causes, including left heart failure, concomitant MR, and pulmonary hypertension, eventually leading to RV volume overload with subsequent RV hypertrophy and enlargement. As a consequence of increased pericardial constraint, relative RV ischemia, and modified left ventricular geometry, reduction of cardiac output may occur late in the disease course, resulting in congestive heart failure. Vague echocardiographic definition, high dependence from preload and afterload conditions, as well as frequent association with interfering comorbidities render TR assessment, and the determination of its prognostic value particularly challenging.

Although the effect of isolated TR is well established,[12] the true clinical consequences of TR after left-sided valve surgery still remain a subject of controversy. Outcome studies focusing on the prognostic value of TR occurring late after surgery produced contradictory results.[13,14] Only a recently published report investigated the effect of baseline TR and its evolution after SAVR. In this study, relevant TR was identified in 15% of 354 surgical patients and improvement after SAVR occurred in only half of the patients.[10] After TAVI, TR improvement has been reported to occur in 15% to 50% of the patients. However, TR severity was not associated with mortality after multivariable adjustments in these studies.[7,15] Although conflicting with the results of Lindman et al,[11] these findings challenge the widespread notion that successful treatment of left-sided valve disease effectively resolves secondary manifestations, including TR. Thus, improvement of TR requires not only reversal of its primary underlying cause, such as pulmonary hypertension, MR, or left ventricular dysfunction, but also normalization of the tricuspid annular abnormalities. In case of long-standing disease with profound changes in RV geometry and pronounced leaflet tethering, this may no longer be possible. The same principles may apply to patients presenting with comorbidities invariantly associated with pulmonary hypertension, such as chronic obstructive pulmonary disease and thromboembolic disease. Furthermore, the frequent need for permanent pacemaker insertion after TAVI may also act as a factor facilitating TR.[16]

Another important finding of this study concerns the complex interaction between TR and MR. First, moderate to severe MR has emerged as a predictor of impaired prognosis among patients undergoing TAVI, and concomitant left ventricular dysfunction in the context of relevant MR of degenerative cause seems particularly harmful.[17] It is conceivable that coexisting untreated moderate to severe MR may prevent improvement of TR after TAVI because of the maintenance of increased pulmonary pressures. In this particular hemodynamic situation, TR is only a bystander and the clinical outcome is directly related to relevant MR. In this context, it is important to note that the prevalence of MR was rather high (40.1%) in the study by Barbanti et al,[7] which may explain at least in part the lack of effect of TR after multivariable adjustment.[7]

TAVI and RV Function

Baseline impaired RV function has been linked with poor short-term outcome in surgical candidates.[18] After SAVR, further deterioration of RV function has been reported, most likely explained by the loss of the pericardial support and impaired myocardial blood flow during surgery.[19] In contrast, previous studies have provided inconsistent results on the evolution of RV function after TAVI (ranging from no change to significantly improved RV function),[19,20] and the prognostic effect of RV dysfunction among TAVI patients has not been investigated before.

Lindman et al[11] used RV fractional area change performed in a limited number of patients as a quantitative indicator of RV function. However, because of the complex geometric shape of the RV, accurate appreciation of its function requires considerable experience and sufficient image quality of the right cavity (present in a minority of patients). In general, multimodal assessment with measurement of >1 variable is required to reach sufficient accuracy. As an example, peak systolic velocity of the lateral tricuspid annulus obtained by tissue Doppler imaging has shown particularly good correlation with cardiac magnetic resonance imaging, which is considered the gold standard.[21] In contrast, RV fractional area change did not emerge as the best-performing variable for determination of RV function in another comparative study.[22] Because of these limitations, the data on RV function should be interpreted with caution and serve as the basis for further investigations and extension to RV dysfunction.

In summary, the work by Lindman et al[11] provides important information that should be carefully implemented in the routine evaluation of patients considered candidates for TAVI presenting with multivalvular disease. According to these data, patients with moderate or severe TR undergoing successful TAVI have to be considered at increased risk of morbidity and mortality as long as TR persists and remains untreated. Depending on the cause of TR, alternative treatment options, including surgical management and optimal medical therapy, addressing pulmonary hypertension should be evaluated. In case of coexisting MR, the risk of mortality is even higher. As a result, combined or staged minimal invasive treatment of MR needs to be taken into consideration in inoperable or high-risk patients deemed eligible for TAVI. A thorough diagnostic work-up and all therapeutic options should be carefully weighed by the Heart Team and guide the discussions with the

patient. In the near future, the already ongoing development of transcatheter solutions for the treatment of the native tricuspid valve[23] may further refine therapeutic strategies for TAVI patients with concomitant multiple valvular heart disease.

Disclosures

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