Introduction

Conventional surgical aortic valve replacement (SAVR) remains one of the most common cardiac surgery operations performed worldwide. It has been shown to be the most effective treatment for several categories of patients affected by aortic valve disease (1). In presence of concomitant severe mitral regurgitation (MR), a double-valve operation is indicated according to international guidelines (2–4). Conversely, in case of moderate MR the choice of performing mitral valve surgery combined to SAVR should be carefully assessed, considering that a double valve operation carries increased operative mortality and morbidity (5,6). Clinical and echographic evidences showed that MR severity may decrease after isolated SAVR due to reduced systolic intraventricular pressure (7). However, in
some cases (still anatomically to be determined) MR appears to worsen, thus requiring a second surgical treatment which implies a greater risk for frail patients (8).

In recent years, this surgical problem has been translated in the scenario of transcatheter aortic valve replacement (TAVR) considering that the key pathophysiologic mechanisms are similar. Patients undergoing TAVR might have an associated significant MR that can potentially lead to left ventricular (LV) failure after procedure (9). Another factor contributing to detrimental mitral valve functioning after TAVR, not present in SAVR, relies in the anatomical features of the mitro-aortic continuity. The mitral valve may be subject to changes in both geometry and structure that can potentially cause functional MR or accentuate the problems of a pathological mitral valve (10-17). Considering the specific alterations in the mitral valve in the setting of TAVR and the widespread use of TAVR in recent years (18), it appears important to know and understand the anatomical, functional and clinical implications to develop adequate strategies for the future.

Methods

A literature search using PubMed, EMBASE and Cochrane library was performed to evaluate clinical studies, observational studies and reports on mitral valve biomechanics after TAVR from inception to November 2019. Search strategy included the following keywords and their MeSH terms, in various combinations: transcatheter aortic valve, surgical implantation, transcatheter, transapical, transfemoral, percutaneous, aortic valve replacement/implantation/insertion, MR, mitral valve mechanics. References from retrieved results were checked for potential additional sources.

Results and discussion

Anatomical, functional and biomechanical implication

The mitral valve and subvalvular apparatus are composed of annulus, leaflets, chordae, papillary muscles, and LV wall. In the anterior and posterior leaflets of the valve, scallops A1, A2, and A3 and in P1, P2, and P3 can be distinguished. The continuity between the leaflets is ensured by the anterior and posterior commissures. The chordae tendinae are connected to the free edge of the leaflets creating a connection between the valve and the subvalvular apparatus. The subvalvular apparatus is composed antero-lateral and postero-medial papillary muscles that are embedded in the wall of the left ventricle. Chordae tendinae originate from the tips of the papillary muscles, and their anatomy and function ensure continence of the mitral valve that depends on the coordinated interaction of the valve with the subvalvular apparatus. From a biomechanical point of view, the MV can be divided into: anterior and posterior cantilever beams (the leaflets), the basements (the papillary muscles) and the pillars (chordae tendinae) (11,17). During the systole, the upper part of the LV chamber moves towards the lower base rotating around the interventricular septum, and the left fibrous trigone of the heart is subjected to a high mechanical stress. The aortic valve and the mitral valve are in close contact at the level of the left trigone, so that the anterior commissure of the mitral valve is significantly affected by mechanical modifications of the aortic root (11,17).

The biomechanics of the MV differs between the leaflets and the connective support. A linear inverse finite element technique was used to measure the properties of the MV anterior leaflet in vivo. The mechanical testing was performed by Stanford group in order to assess the stiffness of anterior leaflets, but these results are not in agreement with ex-vivo studies on explanted anterior leaflets placed in heart simulators, reporting circumferential and radial strains oscillating between 15% and 40%. In-vitro studies of mechanical testing underlined inadequacy of biomodelling of numerical studies on the MV apparatus. Recent biomechanics studies suggest that all the components of the MV are responsible of active contraction thus affecting MV functionality and self-influencing each component of the mechanism (19-24).

General considerations of mitral valve regurgitation in patients with TAVR

Patients with severe MR have been generally excluded from randomized clinical trials, making poor the impact that associated MR can have on clinical outcomes after TAVR (25-31). Mitral-valve pathology is characterized predominantly by organic etiology, documented in about 70% of studied patients (32). The patients who received the transcatheter valvular therapy for severe aortic valve stenosis are predominantly older with annular and/or leaflets calcification of MV (33,34). The prolapsing mitral valve, when documented, does not have excess leaflet tissue but shows fibroelastic deficiency indicating a myxomatous processes (1,34). A functional MR in ischemic-
non ischemic cardiomyopathy may be highlighted in patients who received a TAVR (26,27,29,30). MV structure is normal and the gap in leaflet coaptation is determined only by LV remodeling. Echographic-based assessment shows normal leaflets with a restrictive movement, that is determined by tethering resulting in outward displacement of papillary muscles and worsening in sphericity of LV wall. Although these patients can have a regional LV wall motion abnormality with a preserved overall LV function; however various degrees of LV systolic dysfunction, geometric changes, or annular dilation can be revealed. Moreover, many elderly patients have severe target coronary lesion or clinical evidence of ischemic cardiomyopathy. The presence of LV remodeling in the population of patients with isolated compensated aortic stenosis is not generally linked to functional MR. However, several factors must be considered whose presence influences the grade of functional MR in these subjects. For example, the high prevalence of CAD with consequent ischemic MR may account for LV dilation observed in the late phase of aortic stenosis. Another factor that contributes to increased driving force through the regurgitation area is the marked increase in LV-to-left atrial pressure gradient observed in case of severe AS. Thus, the possibility of mixed etiologies must be taken into account in assessing the severity of the MR and its potential regression or worsening after TAVR. Patients with AS and concomitant MR may evidence an ERO that is less variable than in case of isolated AS, and this parameter should be systematically measured. Similarly, volume overload on the left ventricle imposes rigorous echographic detection as LV volume abnormalities have a role in MR etiology. Results from studies showing an EROA $\geq 0.2$ cm$^2$ and a regurgitant volume $\geq 30$ mL/beat have been associated with poorer outcomes in case of functional MR. When the range of regurgitant orifice area is between 0.2 and 0.4 cm$^2$ a more thorough echocardiographic evaluation of regurgitation severity is required with the use of additional parameters (2,3,7,35,36).

Clinical evidence

We are not aware of any randomized trials that have evaluated the outcomes of TAVR procedure in patients with significant MR, either treated percutaneously or with medical therapy alone. However, evidence from the RCT Partner and TAVR registries strongly suggests that the proportion of concomitant moderate-to-severe MR oscillates between 2% and 33% (27,29,30,37-45). In the Partner 3 study (30), moderate-to-severe MR was present in 1.3% (6 out of 477 patients) in TAVR group and in 3.2% (14 out of 437 patients) of SAVR group (P=0.045, data not shown), and this statistically significant baseline difference may account for worse results in the SAVR group. Worth noting, studies did not report systematically the grade of regurgitant volume and ERO for the assessment of MR and the effect on early and mid-term outcomes. One study, SOURCE (SAPIEN Aortic Bioprosthesis European Outcome) registry evaluated the rate of MR which reached 25.2%, but no data were reported about the severity of concomitant mitral valve disease. Incongruences are noticed concerning the rate and the grade of MR. Hence, some study reports the rate of grade $\geq 3/4$ or severe MR that was estimated at 10% of all cohort. When the rate was grade $\geq 2/4$ or moderate the incidence of MR increased up to 20% (37,39-42,44,45).

Data from the PARTNER trial showed an incidence of moderate-to-severe MR that range between 19.8% in the cohort A and 22.2% in the cohort B (39,40). One meta-analysis from PARTNER 1 cohorts A and B showed that 3.8% of patients had severe MR, although severe MR was an a priori exclusion criterion for enrollment (46). In a recent meta-analysis performing that included 8 studies involving 8,927 patients, none-mild MR was present in 77.8% and moderate-severe MR in 22.2% of the patients (47).

The number of studies that provided details on the etiology of MR in patients undergoing TAVR are poor (45,48-54). Although a vast majority of patients have an organic mitral valve disease a range between 30% and 50% among recipients of TAVR shows a functional MR that is likely to improve after mechanical intervention (33).

We had found a discrepancy in the studies that evaluate the impact of significant MR in early mortality (30-day mortality) after TAVR (46). To our knowledge, some studies reported an increase in early mortality (37) after TAVR whereas others do not notice this complication (44-46). Again, however, data from studies suggest for a discordance concerning severity of MR, highlighting both severe MR (37,44) or moderate to severe (43,46,53,55,56), that might partially account for the clinical differences.

A global weighted analysis of 8 studies showed that patients with moderate-to-severe MR had higher early mortality [odds ratio (OR) 1.49; 95% CI, 1.12 to 2.00, P=0.004]. However, the studies lack information regarding the nature of diseased mitral valve, functional or organic, not indicating which of it can affect early mortality.

Patients with moderate to severe MR may have
hemodynamic frailty with clinical deterioration during mechanical intervention. However, increasing severity of hemodynamic status inflicts a volume overload on the LV that results in HF if sustained over time (57). In addition, pulmonary congestion and the resulting pulmonary hypertension can determine cardiogenic shock leading to poorer outcomes both in patients who received SAVR than in those who had TAVR (37,38,45,58,59). The high risk of decompensated heart failure may imply more hospitalization due to HF within the first months (45).

Evidence from several series strongly suggests that concomitant moderate-to-severe MR independently predicts mid-term mortality after TAVR. One study evaluated the effect of moderate to severe MR on mortality in 1,391 patients undergoing TAVR within 1 month; after excluding 30-day events, patients with significant MR undergoing TAVR had a worse survival rate [adjusted risk ratio 1.70; 95% confidence interval (CI), 1.19 to 2.42; P=0.003] (42).

In another study, 1,007 patients with moderate to severe MR and aortic stenosis were studied. During the follow-up period of 1 year, the MR was independently associated with a higher risk of death (HR 1.7; 95% CI, 1.2 to 3.4; P=0.01) (45).

In German and Italian registries, a significant increase of MR in patients who underwent TAVR was shown, similarly to other cardiac diseases (60). In contrast, in a report from the PARTNER trial (TAVR cohort) with 499 patients who received TAVR, there was no statistically significant difference in survival at 30 days between patients with moderate-to-severe MR (20.6% of the cohort) and those who had no or mild MR (3.9% vs. 6.1%, P=0.41) (46). A pooled analysis of 10 studies showed that patients with moderate-to-severe MR had higher late cumulative mortality (OR 1.44; 95% CI: 1.23 to 1.68, P<0.001).

The SWEDEHEART registry (61) included all TAVR patients in Sweden. Mild MR was observed in 82% of patients and moderate-to-severe MR in 18%. Baseline moderate-to-severe MR carried a higher mortality risk after 5 years (HR 1.29; 95% CI, 1.01–1.65, P=0.04). Notably, if pre-procedural moderate-to-severe MR improved to mild MR after TAVR, no excess mortality was observed (HR 1.09; 95% CI, 0.75–1.58, P=0.67). On the other hand, in case of persistence or worsening of MR after TAVR, 5-year mortality rates were increased (HR 1.97; 95% CI, 1.29–3.00, P=0.002). Factors associated with MR worsening were atrial fibrillation (OR 2.1; P=0.004), self-expanding valve (OR 3.8; P<0.001) and paravalvular leak (OR 4.3; P<0.001) (61).

Other studies indicate that post-procedural, but not pre-procedural moderate-to-severe MR was associated with mortality and adverse effects (62), and significant MR post TAVR resulted in adverse LV and right ventricular remodeling and poor hemodynamic suggesting an early treatment to reduce the clinical impact of MR after TAVR (62). Those results are supported by other studies (32,63-66) suggesting that intervention to treat persistent severe MR after TAVR should be discussed by the heart team. In fact, after stratification for MR after 30 days from TAVR, the 5-year cumulative incidence of adverse cardiac events (cardiovascular mortality and HF hospitalization) was 37.5%, 40.0%, and 58.2% in patients with mild, moderate, and severe MR, respectively (P<0.001). Compared to mild MR, severe HR carries a 5-fold increase in complications during mid-term follow-up (HR 4.83; 95% CI, 2.49–9.38, P=0.001).

The most recent analyses indicate that baseline MR grade ≥2 was connected with both early and late increased mortality rate (67). Patients who receive TAVR procedure are older with several comorbidities and a high-risk for frailty, hence severe MR with symptoms or with LV dysfunction or both should be observed until the resolution of the hemodynamic overload (57).

TAVR is associated with insignificant improvement in quality of life or functional capacity in one-fourth of patients (59,68,69). These results are not confirmed in others several studies in which an improvement in functional status was noticed (45,46,55,56). However, baseline differences such as the incidence of moderate-to-severe MR, as in the Partner 3 study, may account for different results.

One of the most common cause for poor functional response after TAVR is the severe baseline MR and organic nature is a worse condition (57). In patient with moderate to severe MR the poorer New York Heart Association class is not an accurate parameter for functional for the evaluation of functional improvement and it should not consider in combined end point of mortality and poor functional response (70,71). Clearly a further evaluation with the use of more objective and reliable tools is necessary to assess the real impact of MR after TAVR.

**Clinical implication**

Patients with significant MR should undergo transthoracic or transesophageal echocardiography (TTE/TEE) or computed tomography (CT) to evaluate the mechanism and severity of MR, LV size and function (32). Quantitative
doppler assessments are advocated to establish the severity of MR mitral more accurately; parameters that indicate severe MR include a regurgitant volume >60 mL, a regurgitant fraction >50%, and an effective regurgitant orifice >40 mm. When severe aortic stenosis is combined to significant MR, we can observe various physiological change after aortic flow restoration resulting with a decreased MR severity (72). First, LV cavity pressure decreases dramatically after SAVR and, consequently, the trans-mitral pressure gradient may decrease, resulting in a reduction in MR in a large number of recipients of mechanical intervention. In patients who have functional MR this mechanism is not visible, and the reduction of the closing forces may determine a persistence of MR. Second, we can observe a decline of concentric myocardial hypertrophy related to a reduction in ventricular afterload that is frequent in patients who received mechanical intervention causing an improvement of mitral valve hemodynamics (73,74). Finally, a better improvement of reverse remodeling leads to restore an adequate geometry of LV causing an amelioration of functional MR related to a decrease of LV end-diastolic volume and mitral tethering forces (75). Clinical and echographic evidence might suggest a MR improvement after TAVR in case of functional etiology (45,51,53), but the identification of factors for potential improved LV reverse remodeling have a primary role in the evaluation of the likelihood of MR improvement after TAVR.

The use of CoreValve (Medtronic, Minneapolis, Minnesota) system, as documented in registries of TAVR, revealed that moderate-to-severe MR was an independent and effective predictor of late mortality (38,42,45). In patients in which the use of the CoreValve system was preferred (41,44), multivariable analysis failed to replicate the results of univariable analysis but an incidence of 50% was observed.

Data from registries reporting the use of balloon-expandable valves evidenced no impact on late mortality with a 100% of incidence (37,43,53,76). Conversely when evaluating the data from several report describing the use of self-expandable system, we found a higher rate of moderate-to-severe aortic regurgitation after TAVR (41,77-81), that could have a detrimental effect on LV remodeling and increase the exposure of patients with moderate to severe MR to adverse outcomes. Although difference in survival was detected when compare two systems of implant; however, a final word about which type of transcatheter heart valve therapy is optimal remains an objective for future studies.

Recently, a report that evaluate 1,110 patients has confirmed that significant MR is not uncommon in TAVR recipients and it was coupled with greater mortality both in hospital than 6-month follow-up clinical outcomes. By mean of a predictive model using multidetector CT that can evaluate the features of valvular and subvalvular mitral valve apparatus, the authors showed that in more than one-half of patients the degree of MR improves after TAVR. According to standardized imaging criteria, the authors concluded that at least 1 in 10 patients MR persists after TAVR and that they could benefit from percutaneous mitral procedures. The extreme solution considers the use of MitraClip after a dedicated pre-imaging evaluation (32).

**Adverse effects**

The most common cause of mechanic dysfunction of mitral valve is the altered post implant MV configuration. Predictors of mechanic dysfunction include associated MV abnormalities contributing to left ventricular outflow tract (LVOT) obstruction. Also, the role of a mechanic dysfunction of MV can be significant in case of anterior leaflet and chordae tendineae elongation with papillary muscles displacement (82-86). Each mechanism might individually or conjunctly contribute to the development of chordal slack, systolic anterior motion (SAM), or dynamic LVOT obstruction, eventually resulting in MR.

The role of mitral annular calcifications (MAC) has been recently evaluated by Okuno et al. (87). Authors concluded that isolated MAC has no effect on clinical outcomes following TAVR in patients with preserved MV function (adjusted HR 0.52; 95% CI, 0.21–1.33, P=0.173). However, patients with MV disease had an increased risk of death at 1 year irrespective of MAC (adjusted HR 1.97; 95% CI, 1.12–3.44, P=0.018 in case of MAC and significant MR). The role of MAC in patients undergoing TAVR with concomitant significant MR should be further investigated.

The experimental data from porcine biomechanical model of mitral valve were used in finite element studies of human MV to investigate the dynamic changes on the MV mechanical response during systole. Authors found that during systole the diseased MV bulged into the left atrium with the shape of a balloon, while the anterior leaflet of a normal MV remained in the LV. This phenomenon could be exacerbated significant MR post TAVR implant (21,22).

**Areas of uncertainty**

We are not aware of any RCT that have compared TAVR
combined to Mitraclip procedure with TAVR alone for significant mitral-valve regurgitation and aortic stenosis, and it is not likely that this trial will be held before to determine with certainty safety and effectiveness of transcatheter mitral valve treatment using edge to edge procedure. Therefore, the current recommendation for percutaneous MV repair in the treatment of severe organic and functional MR is confined to handling of one valve (2).

It is unclear whether predictive biomodelling using 3D CT through finite element analysis (FEA) may give a contribute to the identification of patients who should undergo to double transcatheter valve therapy (10,11,17,88-92). Some investigators found evidences that a wrinkle process can induced tear in the mitral valve leaflet tissue leading for a progression of diseased MV in presence of degenerative MV disease (93,94) or the EROA may not change after successful TAVR (95).

The growing experience in the use of FEA research is required to develop predictive modelling performed through 3D imaging (10,11,17,96,97). Single and multi-center series involving a large number of patients may be useful to assess the indication to handling two valves by mean of transcatheter valve treatment using one of the validated risk-scoring algorithms (10,11,17,96,97). Intraoperative transesophageal echocardiography coupled with FEA investigation should be performed to provide anatomical and functional details for biomodelling assessment that would tailor the details of the operative procedure (10,11,17). This specific approach requires further evaluation for generalizability and cost-effectiveness and it is currently performed only in few specialized centers (10,11,17,96-99).

Conclusions

In recent years, the change in paradigm from surgical treatment to percutaneous options revealed the importance of comprehensively addressing all functionally and prognostically relevant factors in order to optimize treatment and improve long-term prognosis. The incidence and the prognostic impact of concomitant MR in patients undergoing TAVR requires specific attention as might trigger adjunctive strategy treatment which should be carefully evaluated in clinical trials.

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Footnote

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