

# Structural Heart

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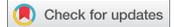
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## Post-TAVR Heart Failure

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Functional mitral regurgitation (MR) is one of the most common concomitant valvular lesions in the setting of aortic stenosis (AS), in particular with patients with an enlarged left ventricular chamber.<sup>1</sup> The combination of AS and MR raises important challenges with regard to the therapeutic management of both AS and MR. Readmission for heart failure (HF) occurs in as many as 25% of patients within the first year following transcatheter aortic valve replacement (TAVR).<sup>2,3</sup> A recent analysis of data from the PARTNER-1 trial, which included 2467 patients successfully treated and followed for 5 years, reported an incidence of first readmission for HF of 15% at 1 year and 23% at 5 years.<sup>4</sup> This study identified: (1) lower transaortic pressure gradient at baseline; and (2) higher residual transaortic pressure gradient, MR grade, and paravalvular aortic regurgitation grade at discharge as being among the most significant risk factors associated with the occurrence of acute decompensated HF after TAVR.<sup>4</sup> This commentary will discuss the pathophysiology and hemodynamic underpinnings of these risk factors.

### Hemodynamic utility versus futility of TAVR

The first important message of the study by Petersen and colleagues<sup>4</sup> is that lower transaortic gradient at baseline and higher residual gradient at discharge were associated with increased risk of HF after TAVR. In the presence of these factors, the magnitude of the drop in the aortic valve pressure gradient (i.e. the difference between baseline and discharge gradients) is smaller and the TAVR may eventually be futile from the standpoint of aortic valve hemodynamics and left ventricular (LV) function. These findings are consistent with previous studies that reported higher risk of mortality and HF rehospitalization in patients with low-gradient AS, and especially those with low LV ejection fraction (EF). However, these findings do not necessarily imply that TAVR or SAVR is not beneficial in patients with low-gradient AS. The outcome of the patients with low-gradient AS is indeed much worse with conservative management than with surgical or transcatheter AVR<sup>5,6</sup> and a meta-analysis concluded that AVR is associated with significant survival benefit in these patients.<sup>7</sup>

The occurrence of high residual gradient at discharge post-TAVR is likely related to prosthesis-patient mismatch.

A prior analysis of data from the PARTNER-1A trial reported an association between severe prosthesis-patient mismatch and mortality in patients randomized to SAVR as well as in those who underwent TAVR (randomized arm and continued access registry) and had no paravalvular leak at discharge.<sup>8</sup>

The magnitude of the hemodynamic benefit achieved by AVR essentially depends on the difference between the pre-procedural versus post-procedural gradients. So the best case scenario is a patient with a very high gradient at baseline and no residual gradient at discharge, whereas the worst scenario is a patient with low gradient AS at baseline and severe prosthesis-patient mismatch with high residual gradient at discharge. In the latter, TAVR is more likely to be futile from a hemodynamic standpoint. Future work should focus on identifying the pre-procedural factors associated with “hemodynamic futility” of TAVR in patients with severe AS, which could be defined as a decrease in mean gradient from baseline to discharge < 10 mmHg.

Secondly, as reported in several previous studies,<sup>3,9,10</sup> the presence of significant paravalvular regurgitation at discharge was strongly associated with increased risk of HF especially in the early peaking hazard phase. The LV of patients with severe AS is adapted to pressure overload but not to volume overload and, in these patients, the onset of acute aortic regurgitation, even if mild, may have a detrimental impact on LV function and therefore precipitate HF.<sup>9,11</sup>

Overall, these findings are consistent with those of Urena and co-authors who reported that low transaortic gradient at baseline and presence of  $\geq$  moderate aortic regurgitation at discharge was independently associated with the risk of death from HF in a large multicenter registry.<sup>3</sup>

In the past years, the design and sizing of new generations of transcatheter valves have been improved to reduce the risk of paravalvular regurgitation but this evolution has led to devices with somewhat smaller valve effective orifice areas and thus higher gradients, compared to previous generations. Further studies are needed to determine which factor—high residual gradient or paravalvular regurgitation—has the greatest impact on outcomes and should thus be prioritized in terms of valve design improvement.

## AS and MR: partners in crime

A second important message from the study of Petersen and colleagues is that the persistence of significant MR at discharge is a strong predictor of subsequent readmission for HF. Interestingly, neither pre- nor post-procedure LVEFs have emerged as risk factors for HF in the PARTNER-1 cohort. This is contrary to almost every study of HF since worse ventricular function correlates with worse clinical outcome, even in cohorts that include patients with HF with preserved EF (HFpEF). However, being load dependent, EF defined in the traditional way may not be an appropriate means of indexing left ventricular contractility, in particular in the setting of AS and MR.

Herein, we review the hemodynamic principles of combined AS and MR in the framework of pressure-volume analysis to explain why combined AS and MR may predispose to post-TAVR HF. Such understanding may lead to better means of risk stratification and perhaps to means of identifying patients who might benefit from multi-valve simultaneous or sequential interventions. Indeed, one of the main challenges in patients with severe AS and concomitant MR is to determine whether MR should be: (1) treated concomitantly at the time of aortic valve replacement (AVR); or (2) treated after TAVR in a staged approach if the MR, symptoms, and/or HF persist or recur after TAVR.

We use the case of prototypical patients to illustrate the key principles. In practice, patients present with highly variable degrees of lesions and range of ventricular dilation and dysfunction. However, the understanding of basic principles may ultimately allow for decision making on a patient-by-patient basis.

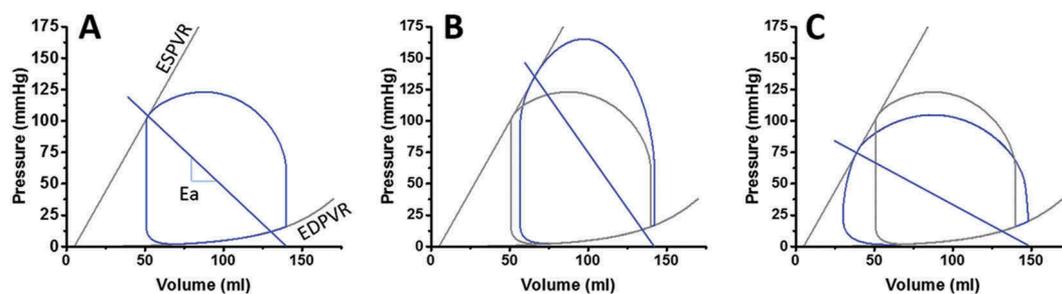
### Overview of pressure-volume analysis

We frame this problem within the context of pressure-volume analysis,<sup>12</sup> which can provide a comprehensive profile of ventricular systolic and diastolic properties, as well as quantitative insights into ventricular-vascular coupling (Figure 1A). Within this framework, the pressure-volume loop, representing the contraction sequence during a single cardiac cycle, is constrained within the boundaries of the end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively), which define systolic and diastolic

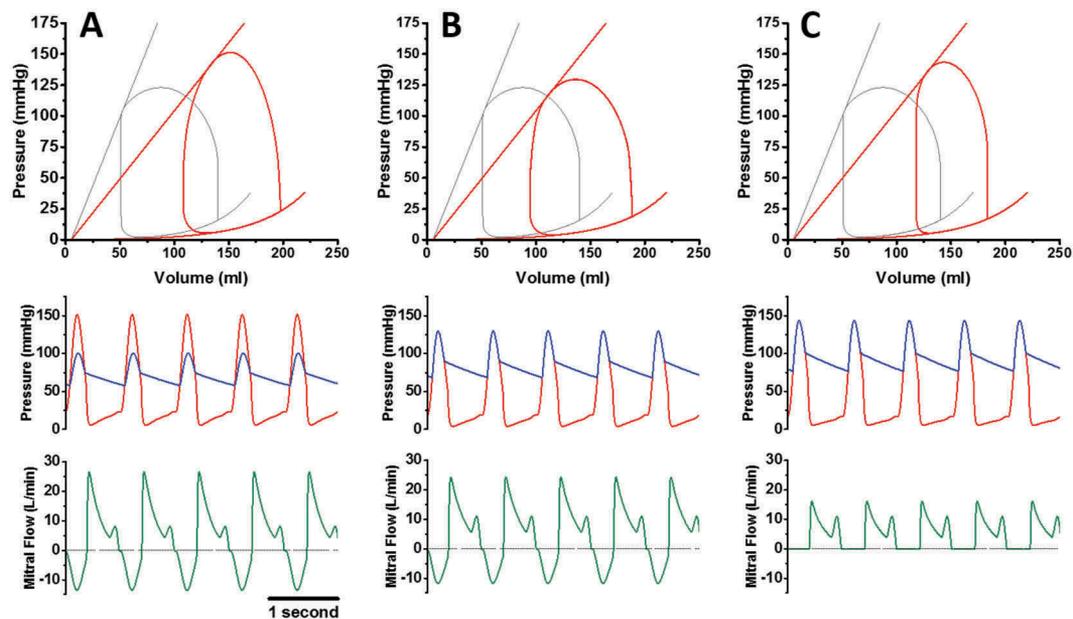
ventricular mechanical properties. Where the loop falls within these boundaries is determined by the preload (end-diastolic pressure or volume) and the afterload. Under normal conditions, the afterload is determined by the resistance and compliance of the arterial system and can be represented by the effective arterial elastance ( $E_a \approx TPR/HR$ ), which is the slope of the line connecting the point on the volume axis at the end-diastolic volume to the end-systolic pressure-volume point on the ESPVR. In the presence of AS and/or MR, the total afterload on the heart is determined not only by vascular properties but by the added resistance to ejection in AS and ejection of blood into the low pressure, compliant left atrium. The presence of these lesions also changes the shape of the pressure-volume loop. With AS (Figure 1B), the loops become tall with an exaggerated domed shape and increased  $E_a$ . With MR (Figure 1C), there is loss of isovolumic periods, with volume decreasing during both contraction and relaxation phases, and reduced  $E_a$ .

### Hemodynamics of combined AS and MR

We can use these concepts to describe the hemodynamics of a hypothetical patient with long-standing combined AS and MR and LV dilation (Figure 2A, upper panel) in comparison to those of a normal individual. These loops are generated using a previously described and validated comprehensive cardiovascular simulation.<sup>13–16</sup> This prototypical patient has an aortic valve area (AVA) of 0.8 cm<sup>2</sup> with a mean aortic pressure gradient of 32 mmHg (Figure 2A, middle panel) and cardiac output (CO) of 3.6 L/min. The mitral regurgitant fraction in this example is set at 46% (Figure 2A lower panel), indicative of moderate MR.<sup>17</sup> However, in comparison to normal (in green), the end-systolic and end-diastolic pressure-volume relations of the valve patient (in red) are shifted rightward towards larger volumes indicating LV dilatation and decreased intrinsic LV function characteristic of a remodeled heart. End-diastolic volume is ~200 ml in comparison to the ~140 ml in the normal case and LV end-diastolic pressure (EDP, related closely to pulmonary capillary wedge pressure, PCWP) is 23 mmHg. Yet, the LVEF is 45%; total stroke volume (SV, the difference between end-diastolic and end-systolic volumes as would be assessed by 2D or 3D imaging



**Figure 1.** (A) Normal pressure-volume loop constrained within the end-systolic and end-diastolic pressure-volume relations (ESPVR and EDPVR) showing two isovolumic phases, isovolumic contraction and isovolumic relaxation.  $E_a$ , the effective arterial elastance, provides a measure of the afterload imposed on the ventricle. (B) With aortic stenosis, the afterload is increased (increased  $E_a$ ) which increases pressure generation and decreases stroke volume. (C) With mitral regurgitation, afterload ( $E_a$ ) is decreased; pressure generation decreases and total stroke volume increases despite constant contractility. The forward stroke volume is a fraction of the total ventricular stroke since part of the flow goes back to the left atrium.



**Figure 2.** Pressure-volume loops and hemodynamic tracings: (A) in the presence of both AS and MR; (B) following removal of AS with MR remaining; and (C) removal of MR.

modalities) is 90 mL, while the forward SV (as measured by Doppler echo or by phased contrast CMR) is only 48 mL. These features highlight the limitations of EF as an index of ventricular contractility, mainly due to the presence of moderate MR which markedly reduces the effective afterload on the LV.

The anticipated immediate effects of TAVR are summarized in **Figure 2B**. Assuming that TAVR eliminates aortic valve gradient, peak LV pressure decreases (**Figure 2B**, upper and middle panels) and CO increases by almost 1 L/min. The mitral regurgitant fraction decreases to 39% (**Figure 2B** lower panel). End-diastolic volume and pressure decrease relatively minimally. LVEF increases in response to the decreased afterload to 50%; while the total SV is 94 mL and the forward SV has increased to 58 mL. Thus, the TAVR-induced decrease in LV afterload increases the forward SV, reduces the regurgitant fraction and EF increases. Yet, end-diastolic pressure is still relatively elevated and forward cardiac output is still compromised.

With elimination of MR (**Figure 2C**), there are more significant changes in the pressure-volume loop. Total SV decreases to 65 mL which, now, following elimination of MR, is the same as the forward SV. Accordingly, CO increases to 4.9 L/min. Since the net afterload on the LV is increased, the LVEF decreases markedly to 35%. Importantly, this reduction of EF does not reflect a reduction of LV contractility; indeed, the most important indexes of cardiovascular performance, CO, blood pressure and LV EDP have all improved with elimination of MR. The reduction of EF only reflects the influence of the increased afterload on this index of contractility.

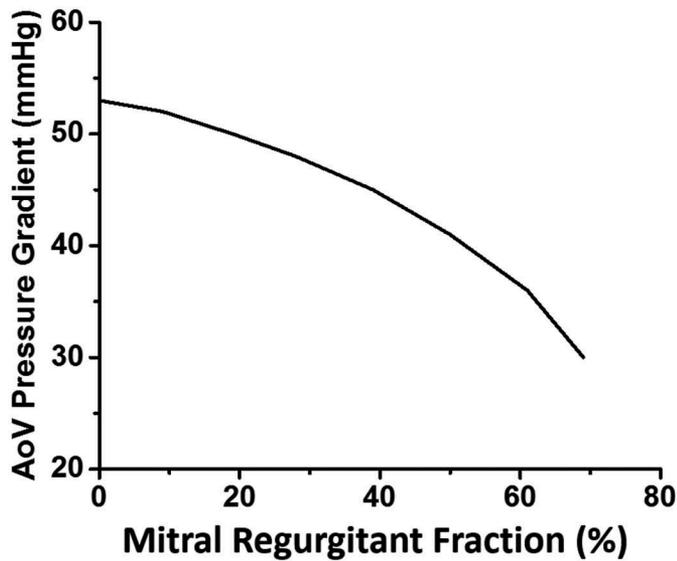
The above explanations illustrate and emphasize several important points. In the presence of significant MR, LVEF overestimates LV contractility, even in the presence of severe AS. Despite a 50% EF following TAVR, LV function in this

example was significantly compromised, forward SV and CO was limited and LV EDP (and therefore PCWP) remained elevated. Following mitral replacement/repair, hemodynamics improve, but EF drops to reveal the true measure of LV function. Thus, with combined AS and MR, a normal or mildly reduced EF does not, in general, indicate preserved LV function. Based on these physiological principles it is readily understood why the degree of MR, not EF, will correlate with post-TAVR heart failure events in the presence of significant MR.

Another important principle concerning the combination of AS and MR is that the presence of MR reduces the aortic valve pressure gradient; this phenomenon is also explained using the same simulation and varying the degree of MR with a fixed aortic valve area (**Figure 3**). With increasing degrees of mitral regurgitant fraction, forward SV and CO decrease, thus resulting in a decrease of pressure gradient. This effect can be quite substantial. Accordingly, MR can be a cause of “paradoxical” low-flow, low-gradient AS.<sup>1</sup> Furthermore, the presence of low gradient at baseline and persistence of high residual gradient at discharge may result in lesser regression of MR following TAVR.<sup>18,19</sup> There is thus a complex interaction between transaortic gradients and MR pre- and post-TAVR.

### **Alternative approaches to assessing LV function with combined AS and MR**

It has previously been proposed that a parameter referred to as “forward” or “effective EF” (eEF) may serve as a more representative and clinically applicable index of LV function in the setting of patients with primary MR.<sup>20</sup> We define eEF as the ratio of (forward SV)/EDV. In the absence of MR, eEF and traditional EF are the same. In the example of combined AS and MR above (**Figure 2A**), eEF equals 24% which



**Figure 3.** Aortic valve pressure gradient with a fixed degree of aortic stenosis with varying degrees of mitral regurgitation, indexed by the regurgitant fraction in a patient with a left ventricular ejection fraction of 35% in the absence of either AS or MR.

contrasts with 45% when EF is defined in the traditional way. Following TAVR (Figure 2B), eEF increases to 31%, which contrasts with the 50% traditional EF. These values of eEF, though clearly not completely afterload independent, are closer to the 35% EF observed in the absence of either AR and MR (Figure 2C) and are more representative as an index of true ventricular contractility. Hence, the eEF could allow a more accurate assessment of the baseline state of LV systolic function and of the benefit of aortic valve and/or mitral valve interventions on LV function.<sup>20</sup> This simple parameter could be used to enhance risk stratification prior to intervention and to guide decision making with regard to the type and timing of interventions on the aortic and mitral valves.

A more rigorous approach would be to employ real-time pressure-volume analysis with measurements made invasively by a conductance catheter. Such an approach has been used in a limited manner to study the impact of MitraClip on LV function in patients with MR.<sup>21</sup> The limitation of this technique includes the need to cross the aortic valve with the conductance catheter prior to and after the procedure, and the issues of volume signal calibration that may change pre- and post-procedure. An alternative approach would be the use of noninvasive estimations of pressure-volume relations and loops as have been employed in studies of HF.<sup>22,23</sup> Given the nature of the assumptions required for such estimates, this approach would need validation before application in research or clinical settings.

Finally, we have developed techniques for patient-specific hemodynamic simulation that include the ability to specify degrees of MR and AS<sup>13</sup> by combining standard measurements from echocardiographic studies and right heart catheterization. Custom algorithms have been developed to use these routinely available clinical data to back-calculate a host of ventricular and vascular parameters based on pressure-volume analysis. Such simulations, if specifically validated in patients with MR, AS and

combined lesions spanning a wide range of severities has the potential to help predict the hemodynamic and clinical impact of TAVR and mitral repair/replacement individually or together.

## Conclusions

The combination of low gradient AS at baseline and high residual gradient at discharge is more likely to be associated with hemodynamic futility of TAVR, with less regression of coexisting MR and therefore with increased risk of HF readmission. These findings further emphasize the importance of avoiding prosthesis-patient mismatch, particularly in patients with low gradient and/or concomitant MR.

The impact of MR on hemodynamics in AS can be appreciated within the context of pressure-volume analysis and cardiovascular simulation and provide insights into why the degree of MR is expected to be associated with the risk of HF events. On a more practical level, the explanations illustrate the limitations of LV EF as an index of LV contractility in the presence of MR and why LV EF itself does not correlate well with the risk of HF events. Availability of better means of risk stratifying patients with AS and MR would help to identify patients most suitable for TAVR and/or a combined mitral procedure. eEF is simple to quantify with standard clinical measures and may serve such a purpose. Other, more rigorous approaches coupled with patient specific simulations may offer additional specificity.

The combination of AS and MR is but one variation of multivalvular disease encountered in patients with AS.<sup>1,24</sup> Indeed, the recent statistical analysis revealed a multitude of other risk factors for future HF events.<sup>4</sup> Among those, aortic regurgitation (AR), paravalvular leak (a iatrogenic form of AR), mitral stenosis and tricuspid regurgitation are common, each presenting its own unique clinical therapeutic challenges. Pressure-volume analysis serves as the foundation for explaining the pathophysiology and hemodynamics of these entities as well. Future, prospective studies aimed at deeper understanding of the hemodynamics of multivalvular disease and the impact of intervention that take into account true measures of LV contractility and remodeling may improve diagnostic or prognostic capabilities and ultimately lead to improved patient selection criteria and therapeutic intervention planning to achieve better overall clinical outcomes.

## Disclosure statements

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