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EDITORIAL

The Left Ventricular Mass Regression Paradox following Surgical Valve Replacement: A Real Phenomenon or a Mathematical Glitch?

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LV mass regression: An important goal of AVR

The symptoms and adverse events in aortic stenosis (AS) are essentially determined by the imbalance between the increase in left ventricular (LV) hemodynamic load caused by valvular obstruction, on the one hand, and the capacity of the LV to overcome this increase in load on the other hand. Hence, AS results in increased LV systolic pressure and wall stress, which lead to hypertrophy of the cardiomyocytes and development of interstitial fibrosis.[1] The pattern of this LV adaptive response to pressure overload in AS is, however, highly heterogeneous and includes concentric remodelling, concentric hypertrophy and eccentric hypertrophy. The pattern and magnitude of LV hypertrophy are influenced not only by AS severity but also by several other factors including age, sex, genetic factors, metabolic factors and the coexistence of coronary artery disease, hypertension, mitral regurgitation, or aortic regurgitation.[1] For the same degree of AS, women tend to predominantly develop concentric remodelling/hypertrophy, whereas men are more prone to developing eccentric hypertrophy.[1,2] Severe LV concentric remodeling or hypertrophy has been linked to worse myocardial function and increased risk of cardiac events and mortality both before and after aortic valve replacement (AVR).[1] Recent studies suggest that the association between LV concentric hypertrophy and worse outcomes is stronger in women than in men.[2] Residual LV hypertrophy after surgical or transcatheter AVR is associated with increased risk of mortality and heart failure re-hospitalization.[1–3] The regression of LV hypertrophy thus represents an important goal of AVR. The presence of severe prosthesis-patient mismatch (PPM) and ensuing high residual transaortic gradients may hinder LV mass regression.[4] Recent studies report that PPM is more frequent and more often severe following surgical AVR (SAVR) than transcatheter AVR (TAVR), and this translated into less LV mass regression and worse survival than those without PPM.[4]

The paradox of LV mass regression following SAVR

In the PARTNER 1A trial and the Pivotal CoreValve trial,[5–8] LV mass regression was faster and greater after SAVR compared to TAVR despite higher transaortic pressure gradients and more frequent severe PPM after SAVR. The purpose of the article by Kadkhodayan and colleagues[7] published in this first issue of *Structural Heart* was to identify the reasons for this paradox by using the serial echocardiography data analyzed by an independent echocardiography core laboratory in patients with severe AS randomized to SAVR vs. TAVR with the CoreValve bioprosthesis.

The pattern of the time-related changes in LV mass after procedure differs markedly in SAVR versus TAVR (Figure 1). TAVR patients display a slow progressive decrease in LV mass from procedure to 1 year, whereas the SAVR patients exhibit a rapid and abrupt reduction in LV mass early after surgery followed by a plateau and even a small rebound at 6 months, and then some further decrease between 6 months and 1 year. These observations raise the following question: Is it physiologically plausible that the LV mass decreases markedly early after SAVR? The answer is: Probably not. It is indeed unlikely that an important reduction in the myocellular hypertrophy and/or interstitial fibrosis could occur within a few days after the relief of pressure overload by AVR. This therefore raises the possibility that the method that is used to estimate LV mass by 2D transthoracic echocardiography (TTE) may be inaccurate to measure the changes in LV mass after AVR. In fact, this 2D method estimates the myocardial mass of the whole left ventricle from three measures (LV end-diastolic diameter, posterior wall thickness and septal wall thickness) performed in a single plane. The LV mass is then calculated using the modified ASE formula, which has been validated by Devereux and coworkers with specimens obtained at autopsy.[9] One of the pitfalls of this formula is its over-dependency on the LV end-diastolic diameter. The LV mass assessed by the ASE formula is indeed influenced, to a larger extent, by the LV internal dimension than by the wall thickness of the LV cavity. Hence, this formula may not be adequate to accurately assess the reduction in LV mass in the case of an acute change in LV internal diameter such as occurs following SAVR (Figure 1). As mentioned by Kadkhodayan and colleagues,[7] accurate 2D determination of LV dimensions may also be challenging in postoperative patients because of septal dyssynchrony and asymmetrical hypertrophy. LV mass regression occurred sooner and to a larger extent in SAVR than in TAVR but the thickness of the septal and posterior walls decreased slightly and to a similar extent in both groups (Figure 1). The difference in LV mass regression between

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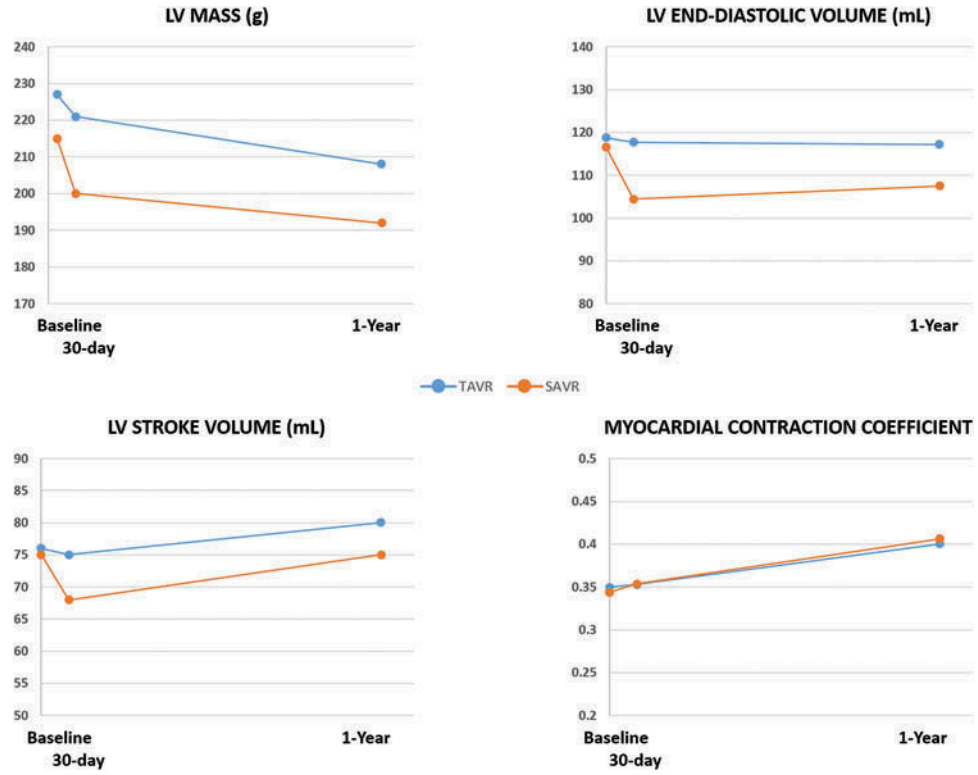

Figure 1. Post-procedural changes in left ventricular mass, end-diastolic volume, stroke volume, and myocardial contraction coefficient in the SAVR arm vs. TAVR arm of the pivotal CoreValve trial. The data of LV mass and stroke volume are the average values obtained from the article by Kadkhodayan and colleagues.[7] The LV end-diastolic volume was calculated with the Teichholz formula using the average values of LV end-diastolic diameter obtained from.[7] The myocardial contraction coefficient (MCF) was calculated using the formula: MCF = [stroke volume/(LV mass/1.04)].

SAVR vs. TAVR was solely explained by the decrease in LV end-diastolic diameter that occurred in SAVR but not in TAVR (Figure 1). Furthermore, the relative wall thickness ratio, a marker of LV concentric remodeling remained high at 30 days despite the apparent LV mass regression in SAVR, whereas it decreased in TAVR.

Hence, the reduction in the calculated LV mass regression that is observed early after SAVR may actually not be real but rather due to a mathematical epiphenomenon of the ASE formula (Figure 1). To overcome this limitation, most studies that examine the regression of LV mass after SAVR use the discharge rather than the preoperative echocardiogram as the baseline reference.[10,11] If such approach is applied to the study of Kadkhodayan and colleagues[7] the absolute LV mass regression between discharge and 1 year would be −23 g in SAVR vs. −19 g in TAVR. It is also likely that the marked regression in LV mass observed by 2D echocardiography early after SAVR would not had been observed with a 3D imaging method such as 3D TTE or cardiac magnetic resonance. These methods indeed directly measure the totality of the myocardial volume without applying the geometrical assumptions inherent to the ASE formula. Further studies with 3D imaging modalities are necessary to determine whether the regression of LV hypertrophy is superior, similar or inferior in SAVR vs. TAVR.

At 1 year, the LV mass was still significantly smaller in the SAVR arm than in the TAVR arm of the pivotal CoreValve trial (Figure 1) despite the smaller indexed effective orifice areas, the higher gradients and the lower survival in SAVR.[5–7,12] Again, the geometric assumptions of the ASE formula may have overestimated the LV mass regression in the SAVR arm because of the postoperative decrease in LV end-diastolic diameter (Figure 1). Furthermore, although TAVR patients harbor better indexed valve areas and gradients compared to SAVR patients, they also have more paravalvular regurgitation, which may contribute to hinder or slow the regression of LV hypertrophy in these patients.[5–7,12] In the study by Kadkhodayan and colleagues,[7] the results remained similar, i.e. the LV mass regression was more important in SAVR than in TAVR, even after excluding the patients with paravalvular regurgitation. One can, however, not completely exclude that paravalvular regurgitation may have, at least in small part, contributed to explain the differences in the time-related changes in LV mass between SAVR vs. TAVR. Another possible explanation for observed differences in LV mass regression may be the lower prevalence of postoperative mitral regurgitation observed in the surgery group, although the differences in mitral regurgitation were no longer present 6 months post-procedure. Finally, improved 1-year LV mass regression in the SAVR may have partially been due to survivor bias in the surgery group, since survival was higher in the TAVR group in the CoreValve pivotal trial.[5] Indeed, SAVR patients who had worse "real" LV mass regression may not have survived to undergo long-term echocardiographic examination, thereby making long-term LV regression appear better in the SAVR group.

In the pivotal CoreValve trial, survival was lower in SAVR than TAVR despite the greater LV mass regression.[5–7,12] In the present

study by Kadkhodayan and colleagues,[7] greater LV mass regression was associated with reduced survival in the SAVR arm but not in the TAVR arm. This paradoxical finding may be explained either by the fact that, following SAVR, the LV mass regression is not totally real but rather the result of the acute decrease in LV end-diastolic diameter after surgery and its disproportionate effect in the ASE formula. Hence, the reduction in the calculated LV mass may, in fact, reflect a decrease in LV end-diastolic volume and stroke volume (Figure 1). To this effect, the stroke volume index, which is a surrogate marker of the LV pump function, has been shown to be a powerful independent predictor of outcomes both prior and after AVR.[13–15] The stroke volume decreased significantly early after SAVR, whereas it remained stable after TAVR (Figure 1). It is plausible that the patients who had greater reduction of calculated LV mass after SAVR were also those who had a larger decrease in stroke volume and thus high risk of mortality within the first postoperative year.

Using the average values of the data reported in the paper by Kadkhodayan and colleagues,[7] it is possible to estimate the values of the myocardial contraction coefficient, which is the stroke volume divided by the LV myocardial volume: i.e. LV mass / 1.04 g/ml (density of myocardium).[16] A left ventricle is more efficient if it ejects a larger stroke volume in proportion to the myocardial volume (i.e. if the myocardial contraction coefficient is higher). The myocardial contraction coefficient has been shown to be superior to LV mass and LV ejection fraction to predict cardiovascular outcomes.[16] In the present study,[7] the coefficient was similar at baseline and increased in the exact same proportion in both groups at 30 days and 1 year (Figure 1). Hence, even if we assume that the smaller LV mass observed at 1 year in the SAVR group is real, it does not necessarily imply the LV is healthier and more efficient.

Conclusion

The elegant study presented by Kadkhodayan and colleagues[7] in this first issue of *Structural Heart* reveals that the reduction in the calculated LV mass following SAVR is, in large part, related to a postoperative decrease in the LV end-diastolic diameter and the ensuing overestimation of LV mass regression by the ASE formula. Nonetheless, the LV mass was still significantly smaller in SAVR vs. TAVR at 1 year, which might be explained, at least in part, by the higher prevalence of paravalvular regurgitation or mitral regurgitation in TAVR patients, or by survivor bias in SAVR patients. The decrease in the calculated LV mass observed in the SAVR arm was associated with a decrease in the stroke volume, which may contribute to explain the trend for the paradoxical association between greater LV mass regression and increased mortality observed in the SAVR arm. As demonstrated by Kadkhodayan and colleagues,[7] LV mass regression post-AVR is a complex issue and comparisons between TAVR and SAVR may be fraught by limitations of 2D imaging-derived calculations.

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