Effects of Aortic Valve Replacement on Left Ventricular Diastolic Function in Patients With Aortic Valve Stenosis

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The afterload increase imposed by severe aortic valve stenosis (AS) creates concentric left ventricular (LV) remodeling and diastolic dysfunction (DD), which are both markers of poor clinical outcome. Ideally, a correctly timed surgery for isolated AS can reverse the LV remodeling. However, data on LV DD after aortic valve replacement (AVR) are sparse and contrasting. Aims of the study are to define the markers of a favorable evolution of the DD at follow-up. Patients with severe isolated AS, scheduled for AVR were prospectively enrolled. Transthoracic echocardiography with DD assessment was performed before surgery, and at 12 months after surgery. Global LV longitudinal and circumferential strain, peak atrial longitudinal and contraction strain (PALS, PACS) were obtained at baseline. LV septal biopsy to assess fibrosis was performed at the time of AVR. Sixty-seven patients were enrolled, age 72 ± 8 years, 66% female, ejection fraction 61 ± 8%, E/e' 13 ± 6, PALS 23 ± 7%. Normal estimated left atrial pressure was detected in 19/67 (28%) versus 43/67 (64%) at follow-up ($p < 0.0001$). In the 37 patients with biopsy available, fibrosis was 24 ± 12%. PALS and AS severity were correlated with LV fibrosis ($R^2 = 0.19$; $p = 0.006$, and $R^2 = 0.15$; $p = 0.02$, respectively). PALS (odds ratio: 1.19 [1.05 to 1.41], $p = 0.02$) and PACS (odds ratio: 1.24 [1.06 to 1.50], $p = 0.006$) were the only baseline noninvasive parameters independently associated with normal left atrial pressure at follow-up. Mean follow-up time was 791 ± 245 days, and 8 (12%) patients had cardiovascular events (death, hospital admission due to heart failure or ischemic disease, and onset of atrial fibrillation). Myocardial fibrosis ($p = 0.05$), baseline PALS ($p = 0.004$), and PACS ($p = 0.03$) were associated with cardiovascular events. In conclusion, LV diastolic function generally improves after AVR for severe AS. Baseline PALS, PACS, and LV fibrosis were related to the DD and clinical outcome at follow-up; these parameters might cue a better diastolic response to the afterload correction. **(Am J Cardiol 2019;124:409−415)**

Abbreviations: AS, Aortic valve Stenosis; AVR, Aortic Valve Replacement; DD, Diastolic Dysfunction; LV, Left Ventricle; LA, Left Atrium; GLS, Global Longitudinal Strain; PALS, Peak Atrial Longitudinal Strain; PACS, Peak Atrial Contraction Strain

The increased afterload imposed by degenerative aortic valve stenosis (AS) can affect the left ventricular (LV) function inducing LV remodeling and diastolic dysfunction (DD) over time.[1,2] In AS patients, an overt decrease in ejection fraction often emerges only as a late stage of the natural history of LV impairment, whereas DD appear earlier.[1,3] Multiple echocardiographic indices (diastolic function, LV mass, valvular function, and pulmonary pressure level) are adopted to assess the consequences of the pressure overload when ejection fraction is preserved.[4−6] Ideally, a correctly timed surgery for isolated AS can reverse the LV remodeling, but this is not always achievable in routine practice.[7,8] Therefore, predicting the evolution of LV remodeling after aortic valve replacement (AVR) remains extremely challenging for the clinicians. At present, only limited data support the usefulness of speckle tracking echocardiography in this setting. Left chambers strain parameters are promising tools for the estimation of left atrial (LA) pressure and have been linked to postsurgical outcomes in patients with AS, as atrial fibrillation onset and longer intensive care unit stay.[9] The presence and extent of myocardial fibrosis at the time of surgery is considered a cue for less favorable LV remodeling after AVR.[1,10−12] However, myocardial fibrosis is not routinely assessed before AVR in clinical practice, and pathophysiology of LV remodeling after AVR in literature has been mostly inferred using noninvasive parameters.[1,10,13−16] Aims of the study are to define the changes in diastolic function after AVR for severe AS and to

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test noninvasive parameters and tissue fibrosis as markers of the evolution of the diastolic pattern after surgery.

Methods

Between January 2015 and March 2016, we prospectively enrolled patients with severe isolated AS, scheduled for AVR, according to guidelines.[2] Exclusion criteria were: significant coronary artery disease; history or presence of atrial fibrillation; more than moderate associated valvular disease or valvular prosthesis; congenital cardiac abnormalities; emergency surgery; severe chronic obstructive pulmonary disease; mechanical prosthesis implantation; inadequate acoustic window. All subjects provided written informed consent in accordance with the research protocol approved by the local institutional review board (University Hospital of Verona Ethic Committee). All patients underwent complete transthoracic echocardiography the day before surgery and after 12 months using HD15 or ie33 ultrasound system (Philips, The Netherlands). LV diameters and wall thickness were measured by 2D echocardiography from the parasternal long-axis view and LV mass was calculated by linear method.[17] LV ejection fraction was calculated with Simpson's biplane method. LV diastolic function was graded as recommended in the latest recommendations, taking into account mitral inflow Doppler measurements, tricuspid regurgitation velocity, tissue Doppler indexes, and indexed LA volume.[18] AS severity was evaluated and aortic valve area calculated by continuity equation.[19] Since a quantitative method was not possible in all patients for technical reasons, we performed a multiparametric semiquantitative evaluation of mitral regurgitation and aortic regurgitation as recommended.[2]

For the 2-dimensional speckle-tracking echocardiography analysis of LV and LA function, 2D greyscale images were acquired in the standard apical 4-, 3-, and 2-chamber views at a frame rate of at least 40 frames/s. The off-line analysis was performed by an experienced cardiologist, using dedicated software (QLab 9, Philips, The Netherlands). LV global longitudinal strain (GLS) was automatically calculated from the mean strain in the 3 LV apical views, and LA longitudinal strain was semiautomatically traced in a 4-chamber view with optimal visualization of the atrium during the cardiac cycle. The peak left atrial strain (PALS) and the peak atrial contraction strain (PACS) were obtained. To assess the reproducibility of LA strain, 15 randomly selected cases were reanalyzed more than 30 days later by the same cardiologist and by a second physician of our echo lab team. A myocardial

Table 1
Population characteristics at baseline and 12-month follow-up in the overall cohort and in patients with normal/grade I versus grade II/III diastolic function at 12 months

Variables	Overall (n = 67)	Normal/grade I diastolic function at 12-month follow-up (n = 43)	Grade II or III diastolic dysfunction at 12 months follow-up (n = 24)	p Value
Age (years)	72 ± 8	71 ± 9	74 ± 7	0.3
Women	44 (66%)	29 (67%)	15 (63%)	0.6
Body surface area (m^2)	1.87 ± 0.21	1.88 ± 0.21	1.86 ± 0.18	0.6
Hypertension	50 (78%)	31 (72%)	19 (79%)	0.5
Diabetes mellitus	12 (19%)	7 (16%)	5 (21%)	0.2
Baseline				
Left atrial volume index (ml/m^2)	38 ± 11	38 ± 11	38 ± 9	0.9
End-diastolic volume (ml)	124 ± 29	123 ± 33	126 ± 22	0.6
Ejection fraction (%)	61 ± 8	61 ± 8	59 ± 8	0.6
E (m/s)	82.8 ± 26.5	79.7 ± 21.0	88.9 ± 34.6	0.1
e' (m/s)	6.17 ± 1.80	6.07 ± 1.77	6.06 ± 1.87	0.5
E/e' ratio	13.0 ± 6.1	12.0 ± 5.0	13.1 ± 8.0	0.8
Mass index (g/m^2)	145 ± 41	150 ± 41	135 ± 37	0.1
Systolic pulmonary artery pressure (mm Hg)	35 ± 9	33 ± 7	37 ± 11	0.1
Aortic valve area (cm^2)	0.77 ± 0.19	0.77 ± 0.19	0.76 ± 0.20	0.9
Mean gradient (mm Hg)	49 ± 13	48 ± 13	51 ± 14	0.3
Peak gradient (mm Hg)	80 ± 19	77 ± 11	82 ± 20	0.2
Global longitudinal strain (%)	15 ± 3	16 ± 3	14 ± 3	0.03
Global contraction strain (%)	22 ± 5	22 ± 5	21 ± 6	0.5
Peak atrial longitudinal strain (%)	23 ± 7	25 ± 7	21 ± 4	0.004
Peak atrial contraction strain (%)	11 ± 4	12 ± 4	10 ± 3	0.009
Left ventricular fibrosis* (%)	24 ± 12	21 ± 11	29 ± 13	0.06
Left atrial volume index (ml/m^2)	33 ± 10	27 ± 8	43 ± 6	<0.0001
12 Months after surgery				
End-diastolic volume (ml)	101 ± 19	98 ± 17	105 ± 22	0.1
Ejection fraction (%)	60 ± 5	61 ± 4	60 ± 6	0.7
E/e' ratio	8.3 ± 2.6	7.4 ± 2.7	10.1 ± 3.0	<0.0001
Mass index (g/m^2)	94 ± 28	87 ± 27	108 ± 26	0.003
Systolic pulmonary artery pressure (mm Hg)	26 ± 5	24 ± 5	27 ± 5	0.06

* Available for 37 patients.

biopsy was obtained at the LV septal level during AVR. On the available samples, 5 μm paraffin-embedded LV sections were stained with Masson's trichrome to visualize fibrotic tissue, according to the manufacturer's protocol (Bio-Optica, 20134 Milano, Italy). Slides were analyzed and stored using EVOS FL Auto Cell Imaging System with EVOS Onstage Incubator (Thermo Fisher Scientific) photomicroscope. ImageJ software 1.49o version was used to measure collagen deposition by calculating the percentage of blue staining, indicative of fibrosis, by automated color deconvolution. Masson Trichrome vector and manual threshold correction where necessary.

Statistical analyses were performed using SPSS software release 20.0 (Statistical Package for the Social Sciences, Chicago, Illinois). Kolmogorov-Smirnov's test was used to assess the normal distribution of data. Then variables are shown as mean ± SD. A p value <0.05 was considered statistically significant. Patients were divided in 2 groups based on the grade of diastolic function at 1 year of follow-up and differences were analyzed using Student *t*tests (continuous variables) or chi-square analyses (categorical variables). The possible predictors of normal/grade I diastolic function have been tested using the logistic regression analysis.

Clinical follow-up was performed up to 18 months to record cardiovascular events (cardiovascular death, hospital admission due to heart failure or ischemic disease, and newly onset of atrial fibrillation).

Intraclass correlation coefficients were calculated to assess inter- and intraobserver agreement regarding measurements of LA strain. Coefficients of variations were calculated with the Logarithmic method.

Results

Sixty-seven patients met the eligibility criteria within the study period, and underwent a complete echocardiography examination 12 months after AVR. The patients' characteristics are reported in Table 1. Mean age was 72 ± 8 years, women were 66%. The majority of patients presented with the typical echocardiographic feature of isolated severe AS. Preoperatively normal-filling/grade I DD (normal LA pressure) was found in 19 (28%) patients, grade II DD in 47 (70%) patients, and grade III DD in 1 (2%) patient (Figure 1). Overall, at 2-dimensional speckle-tracking echocardiography analysis, GLS was 15 ± 3%, PALS was 23 ± 7 %, and PACS 11 ± 4%. Although not significant, PALS and PACS showed a gradual reduction across the nonsevere mitral regurgitation grades (PALS: 26 ± 6% for absent, 23 ± 7% for mild, and 19 ± 1% for moderate mitral regurgitation; PACS: 12 ± 3% for absent, 11 ± 5% for mild, and 10 ± 3% for moderate mitral regurgitation), whereas trend was found for GLS. The reproducibility in our echo lab showed interobserver agreement of 0.97 for PALS and 0.94 for PACS; the coefficients of variations were 5.3% (3.2% to 7.4%) for PALS and 16.4% (9.7% to 23.6%) for PACS. The intraobserver agreement was 0.98 for PALS and 0.96 PACS; the variations were 4.6% (2.8% to 6.5%) for PALS and 17.4% (10.3% to 25.0%) for PACS.

Follow-up echocardiographic examination was performed between 9 and 14 months after surgery for all

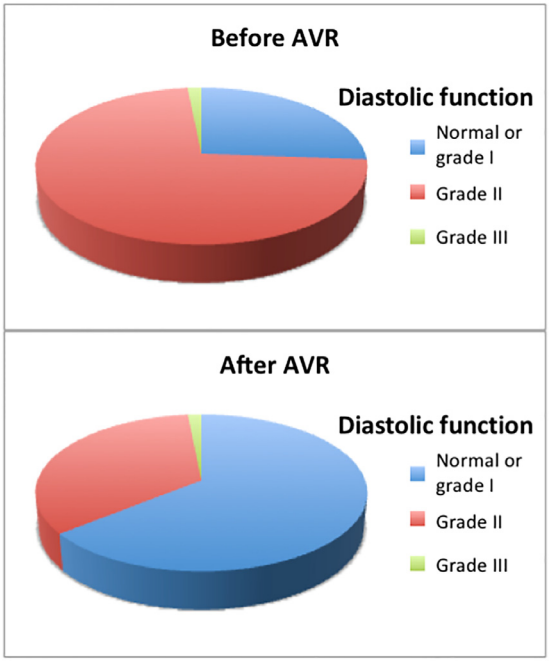

Figure 1. Proportion of patients with the different diastolic function degrees at baseline before surgery and at 12 months after aortic valve replacement.

patients. At matched-pair analysis (baseline vs follow-up), ejection fraction did not change significantly (mean difference 1 ± 3%, p = 0.9), whereas there was a significant decrease in end-diastolic volume (−23 ± 7 ml, p <0.0001), LV mass index (−50 ± 10 g/m^2; p <0.0001), E/e' (−4.6 ± 1.41; p <0.0001), systolic pulmonary arterial pressure (−8.3 ± 1.9 mm Hg, p <0.0001), and LA volume index (−5 ± 3 ml/m^2; p = 0.02). Of note, the changes in E/e' ratio came from a nonproportional increase in both E (+10.9 ± 7.1 m/s, p <0.0001) and e' (+1.72 ± 0.41 m/s, p <0.0001) peak velocities. Overall, diastolic function after AVR was categorized as normal-filling/grade I (normal LA pressure) in 43 (64%) patients, grade II DD in 23 (34%) patients, and grade III DD in 1 (2%) patient (Figure 1); Interestingly, downgrading from grade II/III DD into normal/grade I diastolic function was frequent during follow-up, but no opposite shifting was recorded.

In the right section of Table 1, patients are divided in normal-filling/grade I versus grade II/III DD as detected at follow-up. Atrial strain parameters at baseline were significantly lower in grade II/III DD (25 ± 7 vs 21 ± 4%; p = 0.004 for PALS, and 12 ± 4 vs 10 ± 3 %; p = 0.009 for PACS), and GLS revealed a significant trend (16 ± 3 vs 14 ± 2%, p = 0.03). Tested in a logistic regression model (Table 2), baseline PALS and PACS displayed a significant predictive value for normal LA pressure at follow-up (odds ratio [OR] 1.19 [95% confidence interval [CI] 1.05 to 1.41], p = 0.02 for PALS, and OR 1.24 [1.06 to 1.50], p = 0.006 for PACS). This role was maintained after adjusting for GLS (Table 2). Indeed, LA function (PALS and PACS) and GLS were associated with the some of the classic components of DD algorithm: baseline GLS correlated with follow-up e' values (R = 0.25, p = 0.04), and baseline PALS with both follow-up LA volume index (R = 0.29, p = 0.02) and e' values (R = 0.24, p = 0.01).

Table 2
Logistic regression analysis to predict normal/grade I diastolic function at 12 months of follow-up

Baseline parameter	Unadjusted OR (95% CI)	p	AUC	Adjusted OR (95% CI)	p	AUC	Adjusted OR (95% CI)	p	AUC	Adjusted OR (95% CI)	p	AUC
Peak atrial longitudinal strain	1.19 (1.05-1.41)	0.02	0.69	1.13 (1.01-1.28)	0.04	0.73	–		0.75	1.17 (1.02-1.42)	0.02	0.82
Peak atrial contraction strain	1.24 (1.06-1.50)	0.006	0.70	–			1.26 (1.06-1.53)	0.006		–		
Global longitudinal strain	1.25 (1.01-1.59)	0.04	0.67	1.20 (0.97-1.52)	0.09		1.26 (1.01-1.61)	0.04		1.23 (0.95-1.69)	0.1	
Left ventricular mass reduction	1.05(1.02-1.08)	0.0001	0.77				–			1.04 (1.00-1.09)	0.02	

The relative mass reduction (baseline vs follow-up) was of 30 ± 25%; this reduction was prominent in patients with normal/grade I versus grade II/III DD at follow-up (30 ± 19% vs 15 ± 26%, p = 0.0001). We tested this variable in the regression model in Table 2. LV mass reduction was associated to normal LA pressure after AVR (OR 1.05 [95% CI: 1.02 to 1.08], p = 0.0001). Interestingly, adjusting for LA and LV strain parameters, both LV mass reduction and PALS were independent predictors of DD grade at follow-up. PALS and GLS, were able to provide and area under the curve of 0.73 to predict the improvement of DD after valve surgery (Table 2). Furthermore, PALS provided incremental value to the GLS-based model (chi-square grew from 19.6 to 24.6, p for change = 0.02); similar result was obtained for PACS (chi-square grew from 19.6 to 24.0, p for change = 0.03).Baseline LV mass or mass index did not predict the change in diastolic function during follow-up (p >0.1). However, LV fibrosis/LV mass ratio in the subgroup of patients with LV biopsy was able to predict normal/grade I diastolic function at follow-up (OR: 1.16 [95% CI 1.02 to 1.38; p = 0.04]).

The total number of available myocardial biopsies was 37/67 (55%). The reasons for the missing data were: patient consented only to undergo the echocardiographic part of the study or inadequate biosample. Overall, the average extent of LV fibrosis in the samples was 23 ± 12%; 11/37 (30%) patients in this group presented grade II or III DD at follow-up and showed a trend toward higher LV fibrosis versus patients with normal/grade I DD (29 ± 11% vs 21 ± 11, p = 0.06). Of note, the amount of LV fibrosis correlated with the severity of AS (R = 0.44, p = 0.007 for Vmax, and R = 0.39 p = 0.02 for mean transaortic gradient). In our cohort, LV mass index, septum thickness, or age were not associated with the amount of LV fibrosis. None of the traditional echocardiographic diastolic parameters at baseline were significantly correlated with LV fibrosis, whereas GLS (R = −0.32, p = 0.005), PALS (R = −0.45, p = 0.006), and PACS (R = −0.33, p = 0.04) showed a significant negative association with the amount of fibrosis (Figure 2). In a bivariate model including mean transaortic gradient and the LA or LV strain parameters, PALS (p = 0.008) and PACS (p = 0.03), but not GLS (p = 0.3), were associated to the LV fibrosis. As for PALS and PACS, there was a nonsignificant trend in the association between the mitral regurgitation grades and LV fibrosis (21 ± 8% for no regurgitation, 24 ± 6% for mild, and 32 ± 16% for moderate regurgitation). A paradigmatic example of the relationship between PALS and LV fibrosis is displayed in Figure 3.

Mean follow-up time was 791 ± 245 days and was completed, beyond the first year, for 62 patients (92%). Overall, 8 (12%) patients had cardiovascular events (2 cardiovascular deaths, 2 hospitalization for heart failure, 2 hospitalization for ischemic heart disease, and 2 hospitalization for newly onset atrial fibrillation). The extent of myocardial fibrosis (hazard ratio [HR]: 1.06 [1.00 to 1.12], p = 0.05), PALS (HR: 0.75 [0.61 to 0.90], p = 0.004), as well as baseline PACS (HR: 0.79 [0.62 to 0.67], p = 0.03) were associated with these clinical events. PALS and PACS, remained significantly associated with the outcome in an age-adjusted model (p = 0.004 and p = 0.04, respectively) whereas GLS did not show significance (p = 0.3).

Discussion

The main findings of this prospective study are:

1) Normal estimated LA pressure is expected for half of the patients with isolated AS after AVR.
2) The improvement of DD is difficult to predict based on the classic clinical and echocardiographic parameters, but might be revealed by 2-dimensional speckle-tracking echocardiography evaluation, particularly of the LA function.
3) The extent of LV fibrosis at the time of surgery could be estimated by LA strain parameters. This might explain the different evolution of the LV filling pattern and remodeling post-AVR.

Normal LA pressure, estimated by echocardiography, was found in more than half of patients after surgical AVR for isolated AS. LV filling pressure seems to decreases early after AVR, and subsequently might be accompanied by a reduction in LV mass. These changes can persist for years and have been linked to both muscular and nonmuscular tissue reduction.[20] According to other authors, the percentage of patients with moderate to severe LV DD was almost unchanged between the preoperative (7%) and 2-year follow-up (13%) examinations.[21] Different intrinsic myocardial properties of AS patients, despite the similar ejection fraction and severity of the valvular disease, might explain these apparently contradictory results. In the present study, we included isolated severe AS, excluding all patients with cardiac and extra cardiac features which could interact with the LV hemodynamic and the degree of LV remodeling; this might be a reason for the high rate of LA

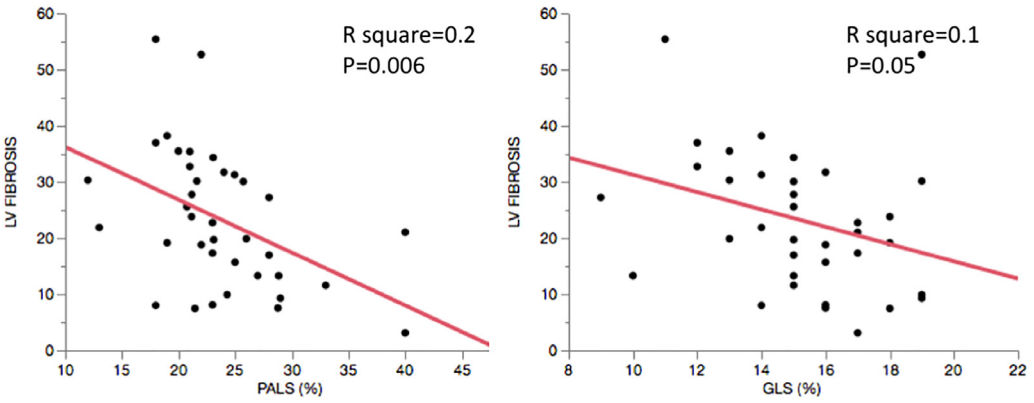

Figure 2. Association between atrial and ventricular strain parameters and left ventricular fibrosis in the 37 patients with available left ventricular biopsy.

pressure normalization (+38%) after AVR in our cohort. Beyond the different rate of improvement in diastolic filling, the real clinical challenge is to predict the evolution of the filling pattern based on preoperative clinical and echocardiographic features.[11,22] Our data support the role of atrial strain parameters (PALS and PACS), as well as GLS at baseline, in predicting a normal LA pressure at follow-up.

The usefulness of GLS has already been proposed by a pilot study, where GLS could predict LV mass regression in patients with AS who underwent AVR.[23] The ventricular strain might detect changes in LV mechanics or subtle modifications in LV contractility even in the presence of preserved ejection fraction.[2,24]

The possible explanation for the LA strain role is the more interesting, as it may reflect both hemodynamic and nonhemodynamic factors. As for GLS, the LA strain parameters can detect hemodynamic changes at the LV level, occurring in both systole and diastole. Moreover, the LA chamber is placed in a key position, interacting with LV function but also modulating LV repercussion on the pulmonary pressure level.[25,26] In fact, in the present study, LA strain is also significantly associated with clinical outcome in an age-adjusted model.

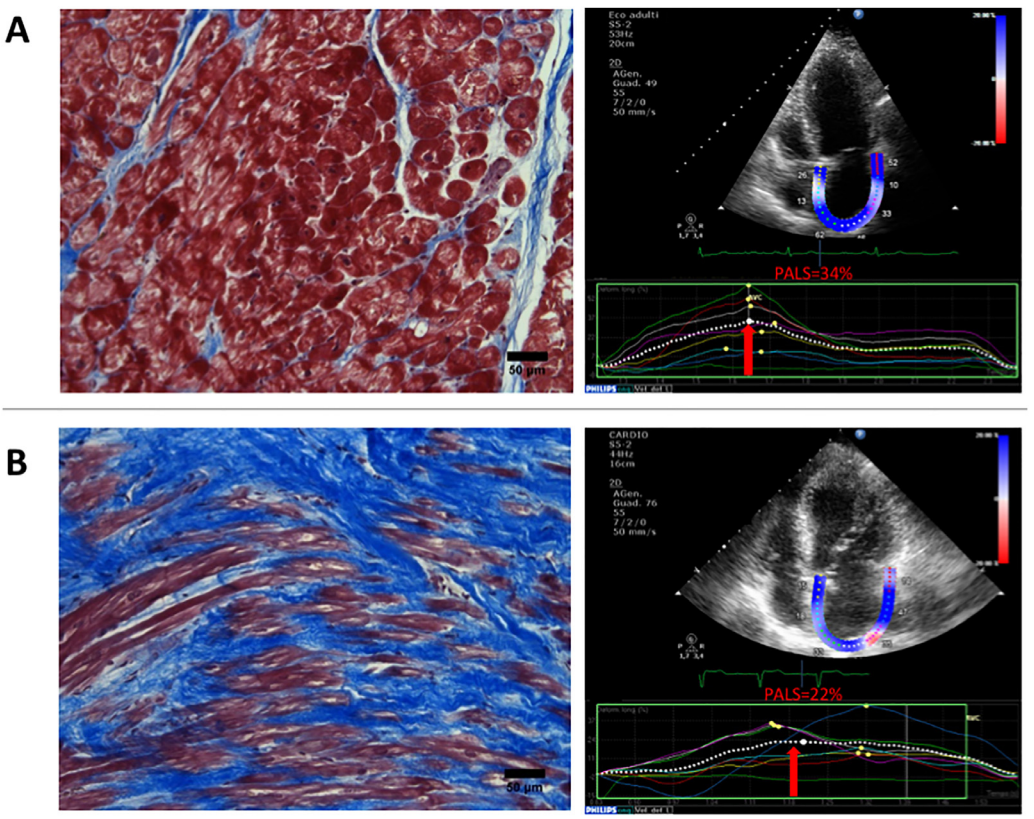

Figure 3. Patient with low % of left ventricular fibrosis and preserved left atrial strain values (A), and patient with high % of left ventricular fibrosis and reduced left atrial strain values (B)

Hence, the integration of systo-diastolic, hemodynamic and structural influences, the strategic modulator role, and the prognostic value might explain PALS and PACS better relationship to LV fibrosis and to the evolution of diastolic function after AVR as compared with GLS. The incremental value showed by PALS and PACS versus LV mass reduction is in agreement with this idea.

A previous study from our institution suggested the existence of different quality of LV remodeling in patients with AS; myocardial fibrosis has been recognized as the critical abnormality to differentiate adaptive and maladaptive response to the increased afterload.[1]

In the present study, PALS showed the strongest association with LV fibrosis, independently from AS severity, reinforcing the concept that changes in LA function are an integrative and sensible marker of LV response to the AS. This is just one of the similarities that AS shares with heart failure with preserved ejection fraction. But even more intriguing is demonstrated correlation between LA strain and LA fibrosis.[27] Thus, it is not possible to exclude that LA strain impairment reflects a systemic neurohormonal activation which could influence the development of both LV and LA fibrosis.[27]

The ventricular-atrial interaction in AS is complex and might be affected by slightly dilated LA or modest mitral incompetence, which are frequently encountered in this setting. The mitral regurgitation presence is of particular concern, and a recent quantitative study showed that an even modest amount of regurgitation can have a detectable hemodynamic impact in the context of concentric LV remodeling and relatively small LV cavity size as in AS patients.[28] Finally, all the above-mentioned results are coherent with the recently proposed staging classification of AS based on the extent of extra-aortic cardiac damage, which showed important prognostic implications after AVR.[29] Patients with adverse LV remodeling in response to the high afterload are at risk of evolving into overt LV dysfunction and may benefit from AVR irrespectively of ejection fraction value. This hypothesis needs to be further tested in clinical trials.[13]

This is a single center study, patients are prospectively enrolled, although they are not consecutive. The major limitation is the relatively low number of patients with available data on LV fibrosis. However, this study is the proof of concept for the relation between LA function and LV structural changes. Also, we could not test the fibrosis in the so called "paradoxical low-flow low-gradient" subgroup of patients: only 1 patient with available LV biopsy had this hemodynamic pattern at baseline; he had 17% of fibrosis. It is important to underline that the fibrosis assessment is based on 1 biosample at LV septum level and it might not reflect the global fibrotic burden of the LV. Another consequence of the limited sample size is that only the most sensitive parameters (speckle-tracking echocardiography) could show their relationship with diastolic function at 12 months. A larger sample size could unmask other less sensitive echocardiographic predictors of diastolic function after AVR. Regarding the follow-up, the major limitation is the limited number of recorded events; the incomplete data on paroxysmal atrial fibrillation at 18 months, and the lack of quantitative mitral regurgitation evaluation, which could have provided more insights into the evolution of diastolic function.[25] In addition, the planned echocardiographic follow-up was at only 12 months, whereas changes in LV interstitial structure can occur for years after AVR.[20]

In conclusion, after AVR for isolated severe AS there is significant although nonhomogeneous LV diastolic filling improvement and myocardial mass reduction. Preoperative LA strain parameters seem to provide insight into the LV remodeling in AS patients, thus helping to predict the evolution of diastolic function after aortic valve surgery.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.04.046.

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