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CHANGES IN DYNAMIC LEFT VENTRICULAR FUNCTION, ASSESSED BY THE STRAIN-VOLUME LOOP, RELATE TO REVERSE REMODELLING AFTER AORTIC VALVE REPLACEMENT

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ABSTRACT

Objectives. Aortic valve replacement (AVR) leads to remodelling of the left ventricle (LV). Adopting a novel technique to examine dynamic LV function, our study explored whether post-AVR changes in dynamic LV function and/or changes in aortic valve characteristics are associated with LV mass regression during follow-up.

Methods and results. We retrospectively analysed 30 participants with severe aortic stenosis who underwent standard transthoracic echocardiographic assessment prior to AVR (88[22-143] days), post-AVR (13[6-22] days) and during follow-up (455[226-907] days). We assessed standard measures of LV structure, function and aortic valve characteristics. Novel insight into dynamic LV function was provided through a 4-chamber image by examination of the temporal relation between LV longitudinal strain (ε) and volume (ε-volume loops), representing the contribution of LV mechanics to volume change.

AVR resulted in immediate changes in structural valve characteristics, alongside a reduced LV longitudinal peak ε and improved coherence between the diastolic and systolic part of the ε-volume loop (all $P<0.05$). Follow-up revealed a decrease in LV mass ($P<0.05$) and improvements in LV ejection fraction and LV longitudinal peak ε ($P<0.05$). A significant relationship was present between decline in LV mass during follow-up and post-AVR improvement in coherence of the ε-volume loops ($r=0.439$, $P=0.03$), but not with post-AVR changes in aortic valve characteristics or LV function (all $P>0.05$).

Conclusions. We found that post-AVR improvements in dynamic LV function, are related to long-term remodelling of the left ventricle. This highlights the potential importance of assessing dynamic LV function for cardiac adaptations *in vivo*.

Keywords: cardiac adaptation, aortic valve replacement, LV mechanics, echocardiography, ultrasound

NEW & NOTEWORTHY

Combining temporal measures of left ventricular longitudinal strain and volume (strain-volume loop) provides novel insights in dynamic cardiac function. In patients with aortic stenosis who underwent aortic valve replacement, post-surgical changes in the strain-volume loop are associated to regression of left ventricular mass during follow-up. This provides novel insight into the relation between post-surgery changes in cardiac hemodynamics and long-term structural remodelling, but also supports the potential utility of the assessment of dynamic cardiac function.

INTRODUCTION

Severe aortic valve stenosis is associated with poor long-term survival, especially in symptomatic patients.(4) Severe aortic stenosis obstructs left ventricular (LV) outflow, causing an afterload mismatch that increases LV wall stress, which in turn leads to LV hypertrophy.(21) This leads to increased diastolic filling pressures, regardless of whether systolic function is normal.(9) Eventually the limit of preload reserve is reached and any further increase in afterload results in a decrease in stroke volume.(21) When systolic function is impaired, the functional ability of the LV to preserve sufficient systemic circulation is compromised. To overcome the physical obstruction, especially in the presence of symptoms and/or impaired LV ejection fraction (LVEF <50%), aortic valve replacement (AVR) is indicated.(3)

AVR immediately reduces blood flow velocity distal to the aortic valve and lowers the pressure gradient across the valve. A post-AVR decrease in LV wall stress and workload may serve as the trigger to initiate the characteristic long-term LV reverse remodelling seen in these patients.(1, 23) Although measures of LV function and structure (e.g. ejection fraction, strain (ε) and valvuloarterial impedance) may relate to long-term LV remodelling,(8, 11) relatively little is known whether other measurements of LV function that more closely relate to workload and/or dynamics relate to subsequent long-term adaptation in LV structure and function in humans *in vivo*.

The temporal relation between LV longitudinal ε and volume (ε-volume loop) may provide novel information on dynamic LV function.(10, 15, 18) This novel measurement allows for the assessment of the relative contribution of longitudinal ε to volume changes throughout the cardiac cycle. For example, changes in mechanical contribution to volume displacement may

induce a shift of the ε-volume relation during systole or diastole. Consequently, this leads to less coherence between the systolic and diastolic ε-volume relationship (i.e. uncoupling). In other words, less coherence means that the contribution of the longitudinal myocardial fibres to volume displacement is different between systole *versus* diastole. Recently, we found that aortic stenosis is associated with uncoupling between the systolic and diastolic ε-volume relationship, whilst traditional measures of LV function were preserved.(10) This suggests that the ε-volume loop may provide novel and potentially relevant insight into dynamic LV function as it reflects temporal data across the whole cardiac cycle.

For this purpose, the present study explored the short-term impact of AVR on dynamic LV function (ε-volume loop), LV function/structure and valve characteristics (aim 1). We hypothesised that AVR leads to short-term changes in dynamic LV function (i.e. ε-volume loop, specifically uncoupling), but also LV function/structure and valve characteristics. Subsequently, this study explored whether these short-term post-AVR changes in dynamic LV function (ε-volume loop), LV function/structure and/or valve characteristics are associated to LV reverse remodelling during follow-up (aim 2). We hypothesize that the short-term, post-AVR changes in these measures are associated to reduction in LV mass during follow-up.

METHODS

Ethics approval

Ethics approval was obtained from the Radboud University Medical Center ethics committee to perform the proposed work (reference number 2016-2357). This study was registered at the

Netherlands Trial Register (NTR5767). This study conforms to the standards set by the latest revision of the Declaration of Helsinki.

Study population

Thirty participants with severe aortic stenosis who underwent echocardiographic assessments and aortic valve replacement at the Radboud University Medical Center (Nijmegen) between 09-2004 and 05-2016 were retrospectively included in the study. All participants underwent echocardiographic assessment at three time points: 1) prior to (pre-AVR, 2) short-term after (<1 month; post-AVR), and 3) and during follow-up (>6 months; Follow-up) AVR. We first identified participants with chronic (calcified) severe aortic stenosis (using a cut-off value for aortic valve area of 1.0 cm^2), utilizing the echocardiographic diagnosis of severe aortic stenosis documented by a cardiologist and adopting the American Society of Echocardiography (ASE) guidelines for valve stenosis(2), who underwent AVR and echocardiographic assessment within the defined time frames. Starting with the participants with the most recent measurement, a single researcher (HH) selected participants (in chronological order) when echocardiographic measurements: *i.* included all required images/planes, and *ii.* achieved high quality imaging to ensure eligibility for our analysis. Participants were excluded if they presented with greater than mild co-existing aortic regurgitation, mitral, pulmonic or tricuspid valve disease, in case of the presence of atrial fibrillation, in case of signs of any kind of infiltrative cardiomyopathy or in case of any signs of complications influencing cardiac function post-surgery (i.e. inflammation, myocardial stunning or tamponade). Patients with a reduced LVEF, LV dilatation or low gradient aortic stenosis prior to AVR as well as patients with pericardial effusion without clinical or echocardiographic signs of tamponade, grade 1 paravalvular leakage or patient-prosthetic mismatch after AVR were not excluded. All included participants had either tricuspid (n=26)

or bicuspid (n=4) native aortic valves and received either a biological (n=23) or a mechanical (n=7) valve prosthesis during AVR. Additional information regarding the included study population can be found in Table 1.

Measurements

Echocardiographic data were obtained using a Vivid E series ultrasound machine (GE Medical System, Horton, Norway) with a 1.5-4 MHZ phased array transducer. The data was stored in raw DICOM format in a remote archive of the Department of Cardiology at the Radboud University Medical Center (Nijmegen). Data was analysed using commercially available software (EchoPac version 113.05, GE Medical, Horten, Norway).

2D Echocardiographic Assessment (aortic valve characteristics, LV structure, LV function)

Echocardiographic images were acquired in accordance with the recommendations of the ASE(13) by experienced and well-trained sonographers from the Radboudumc (Nijmegen, the Netherlands) with the patient in the left lateral position. To determine the severity of aortic stenosis, conventional Doppler flow measurements from the aortic valve and LV outflow tract (LVOT) were conducted. By tracing the flow curve of the aortic valve and LVOT, velocity time integrals (VTI) were established, from which maximum velocity and mean pressure gradient were derived and aortic valve area (AVA VTI) values were calculated using LVOT diameter. The dimensionless index was calculated by dividing the LVOT VTI by the aortic valve VTI. In addition to the measurements to determine valve disease severity, traditional structural and functional parameters of the LV and left atrium (LA) were calculated from appropriate images by a single operator with experience in echocardiographic imaging. LV linear dimensions were measured using 2-dimenisonal imaging from a parasternal long axis orientation and LV mass was calculated according to the ASE corrected Deveraux

formula.(14) LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), LVEF and LA end systolic volume (LAESV, i.e. the largest atrial volume) were calculated using Simpson's biplane method utilizing both apical four and two chamber orientations. The LV sphericity index was calculated applying the following formula, $\frac{EDV}{\frac{4}{3}\pi*\frac{LV\ length}{2}^3}$.(12) Finally, measurements to determine diastolic function were conducted, E and A wave velocity were calculated from a conventional Doppler flow measurement over the mitral valve and used to calculate the E/A ratio. Pulsed-wave tissue Doppler imaging from the annulus of the lateral and septal wall of the LV was conducted providing lateral and septal E' and the average E' was used to calculate E/E'. In addition, patient files were examined to check for signs of patient-prosthesis mismatch and prosthetic leaks after AVR. All parameters were re-measured from appropriate images by a single operator with experience in echocardiographic imaging.

2D Myocardial Speckle Tracking (longitudinal ε, ε-volume loops)

A LV focused apical four chamber view was used to assess simultaneous longitudinal ε and LV volume over a single cardiac cycle. Images were optimized to ensure adequate endocardial delineation using gain, compression and reject. Frame-rates were maintained between 40 and 90 fps and a focal zone was positioned at mid-cavity to reduce the impact of beam divergence. Myocardial ε and volume were assessed offline using dedicated software (EchoPac V113.05, GE Healthcare, Horton, Norway). A region of interest was placed from the basal septum to the basal lateral wall of the LV enclosing the myocardium. The region of interest was divided in six myocardial segments, providing segmental and global longitudinal ε. Global longitudinal ε was used for subsequent analysis of the ε-volume loops as previously described.(10)

Using the individual ε-volume loops a linear regression line and a polynomial of two orders were applied to both diastolic and systolic parts of the loop. This derived polynomial equation

allowed the derivation of ε-values per % increments of LVEDV, within the working range of the heart. The longitudinal ε-volume relationship was assessed by *1)* Early systolic ε (ε_ES), *2)* linear slope of ε-volume relation during systole (Sslope), *3)* End-systolic peak ε (peak ε), *4)* Diastolic uncoupling (difference between systolic vs diastolic ε), during early filling (UNCOUP_ED), *5)* during atrial contraction (UNCOUP_LD) and *6)* during the entire cardiac cycle (UNCOUP) (figure 1, adapted from (10)). The ε_ES was derived as the ε-value during systole at 90% of LVEDV. The Sslope was derived as the gradient of the linear regression line over the systolic ε-volume relation. Based on the individual LVEF values the working range of each patient was determined, based on this working range we divided the cardiac cycle in early diastole (i.e. 2/3 of the working range) and late diastole (i.e. 1/3 of the working range). Using the from the polynomial derived systolic and diastolic ε-values at a certain % of LVEDV we calculated the difference between systolic and diastolic ε contribution at each % of LVEDV. Using this differences per % of LVEDV a mean difference between the systolic and diastolic ε contribution to volume change was calculated for the entire cardiac cycle (i.e. UNCOUP), the early diastolic phase (i.e. UNCOUP_ED) and the late diastolic phase (i.e. UNCOUP_LD). The intra-user variability of all loop characteristics presented good to excellent (0.737-0.950) intraclass correlations, as reported previously.(10)

Statistical analysis

Data for each time point is expressed as mean ± standard deviation. Normality of data distribution was examined using the Shapiro-Wilk test. In case non-Gaussian distribution was observed, Ln-transformation was applied. To address aim 1, we compared the pre-AVR *versus* the post-AVR and the post-AVR *versus* follow-up echocardiographic measurements using linear mixed model analysis (IBM SPSS statistics version 23), with the time point as a fixed factor and time between the pre-AVR assessment and AVR as a covariate. A P-value of

<0.05 was considered significant. To address aim 2, a Pearson's correlation coefficient was used to assess whether LV mass regression (defined as the change in LV mass from Pre-AVR to follow-up) during follow-up relates to the post-AVR changes in ε-volume loop characteristics and aortic valve characteristics.

RESULTS

AVR-procedure

All patients underwent a successful AVR procedure. One patient developed two episodes of tachycardia during AVR which responded to cardioversion. All other procedures were uncomplicated. After AVR seven patients presented a paravalvular prosthetic leakage (grade 1), while eleven patients were diagnosed with a patient-prosthetic mismatch.

post-AVR changes

Valve characteristics. Pre-AVR measurements were performed 8 [22-143] days before surgery, whilst post-AVR measures were taken at 13 [6-22] days. Maximal blood flow velocities and mean pressure gradient across the aortic valve significantly decreased post-AVR, whilst the aortic valve area significantly increased (Table 2).

LV function and structure. We observed a significantly higher E and E' velocity post-AVR, whilst no changes in LV structure or systolic function was present (Table 2).

Dynamic LV function (i.e. LV longitudinal ε-volume loop). Changes in the LV longitudinal ε-volume loop were found post-AVR (Figure 2A). Specifically, we noted that AVR reduced LV longitudinal peak ε and decreased UNCOUP_LD and UNCOUP (Figure 3), whilst there were no changes in ε_ES, Sslope and UNCOUP_ED (Table 2). There was no significant correlation between the AVR-induced changes in valve flow characteristics and alterations in LV

longitudinal ε-volume loop characteristics or standard measures of LV function (all comparisons P>0.05).

Changes during follow-up

Valve characteristics. Follow-up assessment was performed 455 [226-907] days after AVR. When compared to post-AVR we noted no further changes in valve characteristics (Table 3).

LV function and structure. Structural adaptations in LV were apparent, including a decrease in LV mass and LV wall thicknesses (P<0.05). There was also a small but significant increase in LVEF and improvement in Peak ε (Table 3).

Dynamic LV function (i.e. LV longitudinal ε-volume loop). Except for an improved LV longitudinal peak ε, no further changes in LV longitudinal ε-volume loop characteristics were found during follow-up (Figure 2B).

Association of post-AVR changes to mass regression during follow-up

We observed a statistically significant moderate correlation between the post-AVR change in UNCOUP_LD and UNCOUP with the change in LV mass during follow-up (r=0.407 and r=0.439, P<0.05, Figure 4). No significant correlations were noted between the post-AVR changes in valve characteristics and changes in LV mass during follow-up (all P>0.05).

DISCUSSION

The aim of this study was to assess whether AVR mediates short-term changes in dynamic LV function (ε-volume loop), LV function and structure, and valve characteristics, and explore if these changes are associated to reverse remodelling of the LV during follow-up. We present the following novel findings; (1) Aortic prosthesis in post-AVR patients successfully

improved aortic valve characteristics, and immediately improved dynamic LV function as similarity between systolic and diastolic parts of the ε-volume loop improved (i.e. coupling), (2) post-AVR changes in dynamic LV function were not related to changes in aortic valve characteristics, (3) LV structural reverse remodelling during follow-up was accompanied by improved LV longitudinal peak ε, but not with changes in dynamic LV function (i.e. ε-volume loop) or aortic valve flow characteristics and (4) post-AVR improvements in dynamic LV function (i.e. coupling), but not changes in valve characteristics, were related to remodelling in LV mass during follow-up. Taken together, these data provide novel *in vivo* insight, suggesting that immediate post-AVR changes in dynamic LV function are associated with LV reverse remodelling.

Post-AVR changes

As expected, the increase in AVA post-AVR resulted in a decrease in valve flow velocity, which has been previously shown to resolve the afterload mismatch that was present due to stenosis.(11) This resulted in mechanical unloading of the LV.(21) In our study, in contrast to others who observed no change or a slight improvement in peak ε post-AVR(5-7), we found a reduction in LV longitudinal peak ε. This finding may relate to the relatively long time between baseline echocardiography and AVR. Indeed, when a sub-population (n=8) was examined who underwent echocardiography <1 month prior to AVR, we found no change in LV longitudinal peak ε post-AVR. Unlike LV longitudinal peak ε, there were clear improvements in LV longitudinal ε-volume loops post-AVR. A stronger coherence (or coupling) between the contribution of longitudinal ε to volume change between systole and diastole was found. The presence of a rightward shift of the diastolic ε-volume relation pre-AVR in patients with aortic stenosis (compared to healthy controls, Figure 1A and 1B) suggest a reduced contribution of longitudinal relaxation to ventricular filling (i.e. volume

displacement precedes relaxation) and thus the potential presence diastolic dynamic dysfunction. The leftward shift of the diastolic ε-volume relation short-term after AVR (Figure 1C) and further leftward shift long-term after AVR (Figure 1D) suggest restoration of the role of longitudinal relaxation in ventricular filling . The stronger coherence between the ε-volume relation of the systolic and diastolic part of the LV longitudinal ε-volume loop may therefore provide an initial indication for diastolic recovery post-AVR. Previous studies have demonstrated that prior to surgery, in an attempt to preserve LV function, patients with aortic stenosis show exaggerated LV global twist and apical rotation to compensate for the reduced longitudinal ε.(16, 19) These compensatory changes contribute to the increased filling pressure, which subsequently delays diastolic untwisting.(19)(24) Since diastolic untwisting is associated with the loss of LV suction, these changes likely contribute to diastolic dysfunction.(17) Indeed, the observed elevated E/E' ratio and decreased E' velocity (Table 2) suggest the presence of diastolic dysfunction(17) prior to AVR. Consequently, these changes contribute to the altered diastolic ε-volume relation and, subsequently, presence of uncoupling of the LV longitudinal ε-volume loop in patients before AVR. Post-AVR, however, the E/E' ratio decreases (although not statistically significant) and E' velocity increases, indicating an improvement in diastolic function. The immediate drop in LV filling pressure post-AVR may contribute to normalization of LV twist and untwist,(7, 22) restoring LV suction and allowing for a stronger coherence (i.e. coupling) between systolic and diastolic ε contribution to volume change.

In contrast to our hypothesis, immediate post-AVR improvements in dynamic LV function, i.e. coupling of the systolic and diastolic phase of the ε-volume loop, did not relate to changes in valve characteristics. The absence of a significant relationship may be explained by the different factors that influence changes in valve characteristics *versus* factors involved in LV

mechanics. AVR immediately alters valve hemodynamics, which are closely linked to valve structure. In contrast, changes in LV hemodynamics and mechanics are, in addition to valve characteristics, dependent on several other factors such as LV structure, preload, and/or contractility.(5, 25)

Post-surgical changes during follow-up

Nearly 2 years post-AVR, there were no further changes in valve characteristics or dynamic LV function, except for an improvement in LV longitudinal peak ε. This highlights the long-term success of surgery, but also the preservation of the short-term improvement in dynamic LV function. Confirming previous work,(5, 20, 23) we observed both LV reverse remodelling (i.e. decreased LV mass) and improved LV function (i.e. higher peak ε and LVEF) during follow-up. Despite these changes in LV morphology and systolic function, no further change was noted in coupling of the LV longitudinal ε-volume loop. This does not exclude the possibility for long-term adaptations in diastolic function. Villari *et al*. found that reversal of post-AVR LV diastolic function takes several years and is accompanied by (slow) regression of interstitial fibrosis, while reversal of LV systolic dysfunction occurs more rapidly.(25)

Association between changes post-AVR and during follow-up

Whilst the post-AVR changes in valve characteristics did not relate to subsequent LV remodelling during follow-up, a positive relationship was noted between the post-AVR change in uncoupling and the change in LV mass during follow-up. Moreover, most patients with improved coupling post-AVR showed a reduction in LV mass during follow-up, whilst patients with exaggerated uncoupling post-AVR presented no change LV mass. A possible explanation for this observation is that successful mechanical unloading of the LV after surgery will restore its contractile force and improving passive relaxation. Whilst this will

promote long-term restoration of systolic and diastolic function (and coupling), this change in dynamic LV function may also contribute to LV mass regression.(25)

Clinical Implications. We found that those with post-AVR improvement in dynamic LV function (i.e. coupling) likely present LV mass regression during follow-up, whilst such adaptation was not present in those with post-AVR worsening of dynamic LV function. This suggests that measuring dynamic LV function may provide valuable information to understand cardiac remodelling. Whilst valve flow characteristics have their relevance in immediate evaluation of the success of AVR, assessment of dynamic LV function may be relevant to understand the impact of AVR on LV hemodynamics; an important factor for cardiac workload and subsequent LV remodelling. This work warrants follow-up studies to facilitate automated analysis of the ε-volume loop analysis, but also the potency (for prediction and/or mechanistic insight) of dynamic LV function in other disease states affecting cardiac function.

Limitations. Due to its explorative and retrospective nature, timing of the pre- and post-AVR assessments differed between participants. To control for this limitation, time to AVR or time since AVR were included as covariates in our statistical analysis. A second limitation relates to the presence of missing data for some of the traditional echocardiographic measures. Adopting a mixed models analysis is a frequently used and validated strategy to correct for such missing data. A third limitation relates to the analyses of a single cardiac cycle for each participant in each measurement phase, causing possible variance in the outcomes due to inter-beat variability, to overcome this automated analyses and assessment of multiple cardiac cycles during each phase is needed. Finally, concomitant analysis of longitudinal ε and volume requires assessment during a single cardiac cycle. As a result monoplane longitudinal

ε and volume values (from a 4-chamber view) were used to construct the LV longitudinal ε-volume loops. To address this, future studies should consider using tri-plane imaging or 3D imaging.

Conclusion. Our findings indicate that AVR is associated with immediate (i.e. 2 weeks post-surgery) changes in valve characteristics, LV function as well as dynamic LV function. However, only changes in dynamic LV function, specifically the presence of stronger coupling between the systolic and diastolic strain-volume relation, were associated with structural LV reverse remodelling across a 2-year follow-up. This supports the potential utility of the assessment of dynamic LV function, which may represent an important factor in mediating cardiac adaptations *in vivo*.

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Disclosures

None

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Figure 1 – The derived ε-volume loop characteristics and the expected effect of AVR on the ε-volume loop.

Panel A) shows a schematic overview of the ε-volume loop in a healthy subject and the derived characteristics; Panel B) shows the ε-volume loop in a single patient prior to AVR; Panel C) shows the ε-volume loop in the same patient short-term after AVR; Panel D) shows the ε-volume loop long-term after AVR.

Figure 2 – Mean longitudinal ε-volume loops

Data represents mean longitudinal ε-volume loops (n=30) A) Pre-AVR (solid black lines) and post-AVR (solid grey lines) and B) Post-AVR (solid grey lines) and during follow-up (dashed lines). The thick lines represent the systolic ε-volume relationship while the thin lines represent the diastolic ε-volume relationship.

Figure 3 – Values for uncoupling of the systolic and diastolic ε-volume relation

Data represents the mean difference between systolic and diastolic ε values at different volumes over the entire cardiac cycle (i.e. UNCOUP). The left side represent the UNCOUP values prior to AVR and the right side the UNCOUP values short-term post AVR. The grey dots represent individual patients, the black dot represents the mean value for the entire group.

Figure 4 – Scatter plot of the short-term change in uncoupling of the ε-volume loop and long-term LV mass regression.

Data represent the relation between the change in uncoupling of the ε-volume loop between pre-AVR and short-term after AVR measurements and the change in LV mass between the pre-AVR and follow-up measurements. The black line represents the linear fit line, showing a

significant correlation between a short-term reduction in the amount of uncoupling and long-term LV mass regression.

TABLE 1: Population demographics

Age (y)	67±16
Sex (% female)	37%
Weight (kg)	74±16
Height (cm)	171±10
Risk factors	
- Hypertensive	15/30
Treated	15/15
- Diabetes	7/30
- Smoker	8/30

516 **TABLE 2:** Data represents the mean±SD values of the characteristics derived from
517 echocardiographic measurements prior to and post-AVR.

	Pre-AVR	*Post-AVR*	P-value
	88 [22-143] days	13 [6-22] days	
Valve characteristics			
AV Vmax ($m.s^{-1}$)	4.37±0.72	2.35±0.48	**<0.01**
AV mean PG (mmHg)	49±17	12±6	**<0.01**
LVOT Vmax ($m.s^{-1}$)	0.97±0.23	1.25±0.41	**<0.01**
AVA (cm^2)*	0.8±0.2	1.7±0.4	**<0.01**
Dimensionless index	0.24±0.07	0.58±0.17	**<0.01**
LV function and structure			
IVSd (cm)	1.1±0.2	1.1±0.2	0.60
LVIDd (cm)	4.5±0.7	4.4±0.6	0.38
LVPWDd (cm)	1.2±0.2	1.2±0.2	0.22
LV mass (g)	196±53	185±58	0.08
LVEDV (ml)	103±30	97±36	0.20
LVESV (ml)	48±20	50±28	0.58
LV length (cm)	8.8±1.0	8.7±1.0	0.37
Sphericity index	0.29±0.07	0.29±0.08	0.96
LAESV (ml)	69±29	74±29	0.46
LVEF (%)	54±10	51±11	0.44
E/A ratio	1.0±0.4	1.1±0.4	0.06
E/E'ratio	14.6±5.0	12.3±5.0	0.17
E (m/s)	0.86±0.21	1.01±0.21	**<0.01**
A (m/s)	0.92±0.27	0.95±0.31	0.27
E' (m/s)	0.06±0.02	0.09±0.03	**<0.01**

LV ε-volume loop			
Early systolic ε (%)	-1.8±1.4	-2.1±1.6	0.14
Sslope (%/ml)	0.35±0.15	0.33±0.12	0.45
Peak ε (%)	-16.7±4.3	-14.2±4.0	**0.01**
Uncoup_ED (AU)	1.2±2.1	0.6±2.1	0.12
Uncoup_LD (AU)	1.7±1.5	0.6±1.8	**<0.01**
Uncoup (AU)	1.4±1.8	0.6±2.0	**0.04**

Symbols denote *=calculated using the velocity time integral. AV=Aortic valve; LVOT=Left ventricular outflow tract; AVA=Aortic valve area; VTI=Velocity time integral; IVSd=Interventricular septal thickness at diastole; LVIDd=Left ventricle internal diameter at diastole; LVPWd=Left ventricle posterior wall at diastole; LVEDV=Left ventricle end diastolic volume; LVESV=Left ventricle end systolic volume; LAESV=Left ventricle end systolic volume; LVEF=Left ventricle ejection fraction; ε=Strain; Sslope=ε-volume relation across the systolic phase; UNCOUP=Uncoupling of the systolic and diastolic ε-volume relation; UNCOUP_ED=Uncoupling of the systolic and diastolic ε-volume relation during early filling; UNCOUP_LD= Uncoupling of the systolic and diastolic ε-volume relation during atrial contraction.

TABLE 3: Data represents the mean±SD values of the characteristics derived from echocardiographic measurements post-AVR and after follow-up.

	Post-AVR	*Follow-up*	P-value
	13 [6-22] days	455 [226-907] days	
Valve characteristics			
AV Vmax ($m.s^{-1}$)	2.35±0.48	2.39±0.62	0.77
AV mean PG (mmHg)	12±6	13±8	0.74
LVOT Vmax ($m.s^{-1}$)	1.25±0.41	1.16±0.28	0.41
AVA (cm^2)*	1.7±0.4	1.6±0.6	0.25
Dimensionless index	0.58±0.17	0.53±0.16	0.16
LV function and structure			
IVSd (cm)	1.1±0.2	1.0±0.2	**<0.01**
LVIDd (cm)	4.4±0.6	4.6±0.7	0.48
LVPWDd (cm)	1.2±0.2	1.1±0.2	**<0.01**
LV mass (g)	185±58	161±48	**0.04**
LVEDV (ml)	97±36	100±35	0.99
LVESV (ml)	50±28	46±24	**0.05**
LV length (cm)	8.7±1.0	8.7±1.0	0.81
Sphericity index	0.29±0.08	0.29±0.08	0.76
LAESV (ml)	74±29	67±28	0.23
LVEF (%)	51±11	55±9	**<0.01**
E/A ratio	1.1±0.4	1.0±0.4	0.18
E/E'ratio	12.3±5.0	12.1±6.0	0.71
E (m/s)	1.01±0.21	0.90±0.34	0.18
A (m/s)	0.95±0.31	0.96±0.32	0.35
E' (m/s)	0.09±0.03	0.08±0.02	0.39

LV ε-volume loop			
Early systolic ε (%)	-2.1±1.6	-2.4±1.4	0.34
Sslope (%/ml)	0.33±0.12	0.36±0.16	0.13
Peak ε (%)	-14.2±4.0	-16.9±3.2	**<0.01**
Uncoup_ED (AU)	0.6±2.1	0.6±2.4	0.90
Uncoup_LD (AU)	0.6±1.8	1.2±2.0	0.19
Uncoup (AU)	0.6±2.0	0.8±2.2	0.61

Symbols denote *=calculated using the velocity time integral. AV=Aortic valve; LVOT=Left ventricular outflow tract; AVA=Aortic valve area; VTI=Velocity time integral; IVSd=Interventricular septal thickness at diastole; LVIDd=Left ventricle internal diameter at diastole; LVPWd=Left ventricle posterior wall at diastole; LVEDV=Left ventricle end diastolic volume; LVESV=Left ventricle end systolic volume; LAESV=Left ventricle end systolic volume; LVEF=Left ventricle ejection fraction; ε=Strain; Sslope=ε-volume relation across the systolic phase; UNCOUP=Uncoupling of the systolic and diastolic ε-volume relation; UNCOUP_ED=Uncoupling of the systolic and diastolic ε-volume relation during early filling; UNCOUP_LD= Uncoupling of the systolic and diastolic ε-volume relation during atrial contraction.

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