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

91 induce a shift of the ε-volume relation during systole or diastole. Consequently, this leads to

92 less coherence between the systolic and diastolic ε-volume relationship (i.e. uncoupling). In

93 other words, less coherence means that the contribution of the longitudinal myocardial fibres

94 to volume displacement is different between systole *versus* diastole. Recently, we found that

95 aortic stenosis is associated with uncoupling between the systolic and diastolic ε-volume

96 relationship, whilst traditional measures of LV function were preserved.(10) This suggests

97 that the ε-volume loop may provide novel and potentially relevant insight into dynamic LV

98 function as it reflects temporal data across the whole cardiac cycle.

99

100 For this purpose, the present study explored the short-term impact of AVR on dynamic LV

101 function (ε-volume loop), LV function/structure and valve characteristics (aim 1). We

102 hypothesised that AVR leads to short-term changes in dynamic LV function (i.e. ε-volume

103 loop, specifically uncoupling), but also LV function/structure and valve characteristics.

104 Subsequently, this study explored whether these short-term post-AVR changes in dynamic

105 LV function (ε-volume loop), LV function/structure and/or valve characteristics are associated

106 to LV reverse remodelling during follow-up (aim 2). We hypothesize that the short-term,

107 post-AVR changes in these measures are associated to reduction in LV mass during follow-

108 up.

109

110

111 **METHODS**

112 *Ethics approval*

113 Ethics approval was obtained from the Radboud University Medical Center ethics committee

114 to perform the proposed work (reference number 2016-2357). This study was registered at the

115   Netherlands Trial Register (NTR5767). This study conforms to the standards set by the latest

116   revision of the Declaration of Helsinki.

117

118   *Study population*

119   Thirty participants with severe aortic stenosis who underwent echocardiographic assessments

120   and aortic valve replacement at the Radboud University Medical Center (Nijmegen) between

121   09-2004 and 05-2016 were retrospectively included in the study. All participants underwent

122   echocardiographic assessment at three time points: 1) prior to (pre-AVR, 2) short-term after

123   (<1 month; post-AVR), and 3) and during follow-up (>6 months; Follow-up) AVR. We first

124   identified participants with chronic (calcified) severe aortic stenosis (using a cut-off value for

125   aortic valve area of 1.0 cm^2), utilizing the echocardiographic diagnosis of severe aortic

126   stenosis documented by a cardiologist and adopting the American Society of

127   Echocardiography (ASE) guidelines for valve stenosis(2), who underwent AVR and

128   echocardiographic assessment within the defined time frames. Starting with the participants

129   with the most recent measurement, a single researcher (HH) selected participants (in

130   chronological order) when echocardiographic measurements: *i.* included all required

131   images/planes, and *ii.* achieved high quality imaging to ensure eligibility for our analysis.

132   Participants were excluded if they presented with greater than mild co-existing aortic

133   regurgitation, mitral, pulmonic or tricuspid valve disease, in case of the presence of atrial

134   fibrillation, in case of signs of any kind of infiltrative cardiomyopathy or in case of any signs

135   of complications influencing cardiac function post-surgery (i.e. inflammation, myocardial

136   stunning or tamponade). Patients with a reduced LVEF, LV dilatation or low gradient aortic

137   stenosis prior to AVR as well as patients with pericardial effusion without clinical or

138   echocardiographic signs of tamponade, grade 1 paravalvular leakage or patient-prosthetic

139   mismatch after AVR were not excluded. All included participants had either tricuspid (n=26)

140 or bicuspid (n=4) native aortic valves and received either a biological (n=23) or a mechanical

141 (n=7) valve prosthesis during AVR. Additional information regarding the included study

142 population can be found in Table 1.

143

144 *Measurements*

145 Echocardiographic data were obtained using a Vivid E series ultrasound machine (GE

146 Medical System, Horton, Norway) with a 1.5-4 MHZ phased array transducer. The data was

147 stored in raw DICOM format in a remote archive of the Department of Cardiology at the

148 Radboud University Medical Center (Nijmegen). Data was analysed using commercially

149 available software (EchoPac version 113.05, GE Medical, Horten, Norway).

150

151 *2D Echocardiographic Assessment (aortic valve characteristics, LV structure, LV function)*

152 Echocardiographic images were acquired in accordance with the recommendations of the

153 ASE(13) by experienced and well-trained sonographers from the Radboudumc (Nijmegen, the

154 Netherlands) with the patient in the left lateral position. To determine the severity of aortic

155 stenosis, conventional Doppler flow measurements from the aortic valve and LV outflow tract

156 (LVOT) were conducted. By tracing the flow curve of the aortic valve and LVOT, velocity

157 time integrals (VTI) were established, from which maximum velocity and mean pressure

158 gradient were derived and aortic valve area (AVA VTI) values were calculated using LVOT

159 diameter. The dimensionless index was calculated by dividing the LVOT VTI by the aortic

160 valve VTI. In addition to the measurements to determine valve disease severity, traditional

161 structural and functional parameters of the LV and left atrium (LA) were calculated from

162 appropriate images by a single operator with experience in echocardiographic imaging. LV

163 linear dimensions were measured using 2-dimensonal imaging from a parasternal long axis

164 orientation and LV mass was calculated according to the ASE corrected Deveraux

165 formula.(14) LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), LVEF

166 and LA end systolic volume (LAESV, i.e. the largest atrial volume) were calculated using

167 Simpson's biplane method utilizing both apical four and two chamber orientations. The LV

168 sphericity index was calculated applying the following formula, $\frac{EDV}{\frac{4}{3}\pi * \frac{LV\ length^3}{2}}$.(12) Finally,

169 measurements to determine diastolic function were conducted, E and A wave velocity were

170 calculated from a conventional Doppler flow measurement over the mitral valve and used to

171 calculate the E/A ratio. Pulsed-wave tissue Doppler imaging from the annulus of the lateral

172 and septal wall of the LV was conducted providing lateral and septal E' and the average E'

173 was used to calculate E/E'. In addition, patient files were examined to check for signs of

174 patient-prosthesis mismatch and prosthetic leaks after AVR. All parameters were re-measured

175 from appropriate images by a single operator with experience in echocardiographic imaging.

176

177 *2D Myocardial Speckle Tracking (longitudinal ε, ε-volume loops)*

178 A LV focused apical four chamber view was used to assess simultaneous longitudinal ε and

179 LV volume over a single cardiac cycle. Images were optimized to ensure adequate

180 endocardial delineation using gain, compression and reject. Frame-rates were maintained

181 between 40 and 90 fps and a focal zone was positioned at mid-cavity to reduce the impact of

182 beam divergence. Myocardial ε and volume were assessed offline using dedicated software

183 (EchoPac V113.05, GE Healthcare, Horton, Norway). A region of interest was placed from

184 the basal septum to the basal lateral wall of the LV enclosing the myocardium. The region of

185 interest was divided in six myocardial segments, providing segmental and global longitudinal

186 ε. Global longitudinal ε was used for subsequent analysis of the ε-volume loops as previously

187 described.(10)

188 Using the individual ε-volume loops a linear regression line and a polynomial of two orders

189 were applied to both diastolic and systolic parts of the loop. This derived polynomial equation

190   allowed the derivation of ε-values per % increments of LVEDV, within the working range of

191   the heart. The longitudinal ε-volume relationship was assessed by *1)* Early systolic ε (ε_ES),

192   *2)* linear slope of ε-volume relation during systole (Sslope), *3)* End-systolic peak ε (peak ε), *4)*

193   Diastolic uncoupling (difference between systolic vs diastolic ε), during early filling

194   (UNCOUP_ED), *5)* during atrial contraction (UNCOUP_LD) and *6)* during the entire cardiac

195   cycle (UNCOUP) (figure 1, adapted from (10)). The ε_ES was derived as the ε-value during

196   systole at 90% of LVEDV. The Sslope was derived as the gradient of the linear regression

197   line over the systolic ε-volume relation. Based on the individual LVEF values the working

198   range of each patient was determined, based on this working range we divided the cardiac

199   cycle in early diastole (i.e. 2/3 of the working range) and late diastole (i.e. 1/3 of the working

200   range). Using the from the polynomial derived systolic and diastolic ε-values at a certain % of

201   LVEDV we calculated the difference between systolic and diastolic ε contribution at each %

202   of LVEDV. Using this differences per % of LVEDV a mean difference between the systolic

203   and diastolic ε contribution to volume change was calculated for the entire cardiac cycle (i.e.

204   UNCOUP), the early diastolic phase (i.e. UNCOUP_ED) and the late diastolic phase (i.e.

205   UNCOUP_LD). The intra-user variability of all loop characteristics presented good to

206   excellent (0.737-0.950) intraclass correlations, as reported previously.(10)

207

208   *Statistical analysis*

209   Data for each time point is expressed as mean ± standard deviation. Normality of data

210   distribution was examined using the Shapiro-Wilk test. In case non-Gaussian distribution was

211   observed, Ln-transformation was applied. To address aim 1, we compared the pre-AVR

212   *versus* the post-AVR and the post-AVR *versus* follow-up echocardiographic measurements

213   using linear mixed model analysis (IBM SPSS statistics version 23), with the time point as a

214   fixed factor and time between the pre-AVR assessment and AVR as a covariate. A P-value of

215   <0.05 was considered significant. To address aim 2, a Pearson's correlation coefficient was

216   used to assess whether LV mass regression (defined as the change in LV mass from Pre-AVR

217   to follow-up) during follow-up relates to the post-AVR changes in ε-volume loop

218   characteristics and aortic valve characteristics.

219

220

221   **RESULTS**

222   **AVR-procedure**

223   All patients underwent a successful AVR procedure. One patient developed two episodes of

224   tachycardia during AVR which responded to cardioversion. All other procedures were

225   uncomplicated. After AVR seven patients presented a paravalvular prosthetic leakage (grade

226   1), while eleven patients were diagnosed with a patient-prosthetic mismatch.

227   **post-AVR changes**

228   *Valve characteristics*. Pre-AVR measurements were performed 8 [22-143] days before

229   surgery, whilst post-AVR measures were taken at 13 [6-22] days. Maximal blood flow

230   velocities and mean pressure gradient across the aortic valve significantly decreased post-

231   AVR, whilst the aortic valve area significantly increased (Table 2).

232   *LV function and structure*. We observed a significantly higher E and E' velocity post-AVR,

233   whilst no changes in LV structure or systolic function was present (Table 2).

234   *Dynamic LV function (i.e. LV longitudinal ε-volume loop).* Changes in the LV longitudinal ε-

235   volume loop were found post-AVR (Figure 2A). Specifically, we noted that AVR reduced LV

236   longitudinal peak ε and decreased UNCOUP_LD and UNCOUP (Figure 3), whilst there were

237   no changes in ε_ES, Sslope and UNCOUP_ED (Table 2). There was no significant correlation

238   between the AVR-induced changes in valve flow characteristics and alterations in LV

239 longitudinal ε-volume loop characteristics or standard measures of LV function (all

240 comparisons P>0.05).

241

242 **Changes during follow-up**

243 *Valve characteristics*. Follow-up assessment was performed 455 [226-907] days after AVR.

244 When compared to post-AVR we noted no further changes in valve characteristics (Table 3).

245 *LV function and structure*. Structural adaptations in LV were apparent, including a decrease in

246 LV mass and LV wall thicknesses (P<0.05). There was also a small but significant increase in

247 LVEF and improvement in Peak ε (Table 3).

248 *Dynamic LV function (i.e. LV longitudinal ε-volume loop).* Except for an improved LV

249 longitudinal peak ε, no further changes in LV longitudinal ε-volume loop characteristics were

250 found during follow-up (Figure 2B).

251

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

253 We observed a statistically significant moderate correlation between the post-AVR change in

254 UNCOUP_LD and UNCOUP with the change in LV mass during follow-up (r=0.407 and

255 r=0.439, P<0.05, Figure 4). No significant correlations were noted between the post-AVR

256 changes in valve characteristics and changes in LV mass during follow-up (all P>0.05).

257

258

259 **DISCUSSION**

260 The aim of this study was to assess whether AVR mediates short-term changes in dynamic

261 LV function (ε-volume loop), LV function and structure, and valve characteristics, and

262 explore if these changes are associated to reverse remodelling of the LV during follow-up. We

263 present the following novel findings; (1) Aortic prosthesis in post-AVR patients successfully

264 improved aortic valve characteristics, and immediately improved dynamic LV function as

265 similarity between systolic and diastolic parts of the ε-volume loop improved (i.e. coupling),

266 (2) post-AVR changes in dynamic LV function were not related to changes in aortic valve

267 characteristics, (3) LV structural reverse remodelling during follow-up was accompanied by

268 improved LV longitudinal peak ε, but not with changes in dynamic LV function (i.e. ε-volume

269 loop) or aortic valve flow characteristics and (4) post-AVR improvements in dynamic LV

270 function (i.e. coupling), but not changes in valve characteristics, were related to remodelling

271 in LV mass during follow-up. Taken together, these data provide novel *in vivo* insight,

272 suggesting that immediate post-AVR changes in dynamic LV function are associated with LV

273 reverse remodelling.

274

275 *Post-AVR changes*

276 As expected, the increase in AVA post-AVR resulted in a decrease in valve flow velocity,

277 which has been previously shown to resolve the afterload mismatch that was present due to

278 stenosis.(11) This resulted in mechanical unloading of the LV.(21) In our study, in contrast to

279 others who observed no change or a slight improvement in peak ε post-AVR(5-7), we found a

280 reduction in LV longitudinal peak ε. This finding may relate to the relatively long time

281 between baseline echocardiography and AVR. Indeed, when a sub-population (n=8) was

282 examined who underwent echocardiography <1 month prior to AVR, we found no change in

283 LV longitudinal peak ε post-AVR. Unlike LV longitudinal peak ε, there were clear

284 improvements in LV longitudinal ε-volume loops post-AVR. A stronger coherence (or

285 coupling) between the contribution of longitudinal ε to volume change between systole and

286 diastole was found. The presence of a rightward shift of the diastolic ε-volume relation pre-

287 AVR in patients with aortic stenosis (compared to healthy controls, Figure 1A and 1B)

288 suggest a reduced contribution of longitudinal relaxation to ventricular filling (i.e. volume

289 displacement precedes relaxation) and thus the potential presence diastolic dynamic

290 dysfunction. The leftward shift of the diastolic ε-volume relation short-term after AVR

291 (Figure 1C) and further leftward shift long-term after AVR (Figure 1D) suggest restoration of

292 the role of longitudinal relaxation in ventricular filling . The stronger coherence between the

293 ε-volume relation of the systolic and diastolic part of the LV longitudinal ε-volume loop may

294 therefore provide an initial indication for diastolic recovery post-AVR. Previous studies have

295 demonstrated that prior to surgery, in an attempt to preserve LV function, patients with aortic

296 stenosis show exaggerated LV global twist and apical rotation to compensate for the reduced

297 longitudinal ε.(16, 19) These compensatory changes contribute to the increased filling

298 pressure, which subsequently delays diastolic untwisting.(19)(24) Since diastolic untwisting is

299 associated with the loss of LV suction, these changes likely contribute to diastolic

300 dysfunction.(17) Indeed, the observed elevated E/E' ratio and decreased E' velocity (Table 2)

301 suggest the presence of diastolic dysfunction(17) prior to AVR. Consequently, these changes

302 contribute to the altered diastolic ε-volume relation and, subsequently, presence of uncoupling

303 of the LV longitudinal ε-volume loop in patients before AVR. Post-AVR, however, the E/E'

304 ratio decreases (although not statistically significant) and E' velocity increases, indicating an

305 improvement in diastolic function. The immediate drop in LV filling pressure post-AVR may

306 contribute to normalization of LV twist and untwist,(7, 22) restoring LV suction and allowing

307 for a stronger coherence (i.e. coupling) between systolic and diastolic ε contribution to

308 volume change.

309

310 In contrast to our hypothesis, immediate post-AVR improvements in dynamic LV function,

311 i.e. coupling of the systolic and diastolic phase of the ε-volume loop, did not relate to changes

312 in valve characteristics. The absence of a significant relationship may be explained by the

313 different factors that influence changes in valve characteristics *versus* factors involved in LV

314 mechanics. AVR immediately alters valve hemodynamics, which are closely linked to valve

315 structure. In contrast, changes in LV hemodynamics and mechanics are, in addition to valve

316 characteristics, dependent on several other factors such as LV structure, preload, and/or

317 contractility.(5, 25)

318

319 *Post-surgical changes during follow-up*

320 Nearly 2 years post-AVR, there were no further changes in valve characteristics or dynamic

321 LV function, except for an improvement in LV longitudinal peak ε. This highlights the long-

322 term success of surgery, but also the preservation of the short-term improvement in dynamic

323 LV function. Confirming previous work,(5, 20, 23) we observed both LV reverse remodelling

324 (i.e. decreased LV mass) and improved LV function (i.e. higher peak ε and LVEF) during

325 follow-up. Despite these changes in LV morphology and systolic function, no further change

326 was noted in coupling of the LV longitudinal ε-volume loop. This does not exclude the

327 possibility for long-term adaptations in diastolic function. Villari *et al.* found that reversal of

328 post-AVR LV diastolic function takes several years and is accompanied by (slow) regression

329 of interstitial fibrosis, while reversal of LV systolic dysfunction occurs more rapidly.(25)

330

331 *Association between changes post-AVR and during follow-up*

332 Whilst the post-AVR changes in valve characteristics did not relate to subsequent LV

333 remodelling during follow-up, a positive relationship was noted between the post-AVR

334 change in uncoupling and the change in LV mass during follow-up. Moreover, most patients

335 with improved coupling post-AVR showed a reduction in LV mass during follow-up, whilst

336 patients with exaggerated uncoupling post-AVR presented no change LV mass. A possible

337 explanation for this observation is that successful mechanical unloading of the LV after

338 surgery will restore its contractile force and improving passive relaxation. Whilst this will

339 promote long-term restoration of systolic and diastolic function (and coupling), this change in

340 dynamic LV function may also contribute to LV mass regression.(25)

341

342 *Clinical Implications.* We found that those with post-AVR improvement in dynamic LV

343 function (i.e. coupling) likely present LV mass regression during follow-up, whilst such

344 adaptation was not present in those with post-AVR worsening of dynamic LV function. This

345 suggests that measuring dynamic LV function may provide valuable information to

346 understand cardiac remodelling. Whilst valve flow characteristics have their relevance in

347 immediate evaluation of the success of AVR, assessment of dynamic LV function may be

348 relevant to understand the impact of AVR on LV hemodynamics; an important factor for

349 cardiac workload and subsequent LV remodelling. This work warrants follow-up studies to

350 facilitate automated analysis of the ε-volume loop analysis, but also the potency (for

351 prediction and/or mechanistic insight) of dynamic LV function in other disease states

352 affecting cardiac function.

353

354 *Limitations.* Due to its explorative and retrospective nature, timing of the pre- and post-AVR

355 assessments differed between participants. To control for this limitation, time to AVR or time

356 since AVR were included as covariates in our statistical analysis. A second limitation relates

357 to the presence of missing data for some of the traditional echocardiographic measures.

358 Adopting a mixed models analysis is a frequently used and validated strategy to correct for

359 such missing data. A third limitation relates to the analyses of a single cardiac cycle for each

360 participant in each measurement phase, causing possible variance in the outcomes due to

361 inter-beat variability, to overcome this automated analyses and assessment of multiple cardiac

362 cycles during each phase is needed. Finally, concomitant analysis of longitudinal ε and

363 volume requires assessment during a single cardiac cycle. As a result monoplane longitudinal

364 ε and volume values (from a 4-chamber view) were used to construct the LV longitudinal ε-

365 volume loops. To address this, future studies should consider using tri-plane imaging or 3D

366 imaging.

367

368 *Conclusion.* Our findings indicate that AVR is associated with immediate (i.e. 2 weeks post-

369 surgery) changes in valve characteristics, LV function as well as dynamic LV function.

370 However, only changes in dynamic LV function, specifically the presence of stronger

371 coupling between the systolic and diastolic strain-volume relation, were associated with

372 structural LV reverse remodelling across a 2-year follow-up. This supports the potential utility

373 of the assessment of dynamic LV function, which may represent an important factor in

374 mediating cardiac adaptations *in vivo*.

375

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377 None

378

382

383 **Disclosures**

384 None

385

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

486 **the ε-volume loop.**

487 Panel A) shows a schematic overview of the ε-volume loop in a healthy subject and the

488 derived characteristics; Panel B) shows the ε-volume loop in a single patient prior to AVR;

489 Panel C) shows the ε-volume loop in the same patient short-term after AVR; Panel D) shows

490 the ε-volume loop long-term after AVR.

491

492

493 **Figure 2 – Mean longitudinal ε-volume loops**

494 Data represents mean longitudinal ε-volume loops (n=30) A) Pre-AVR (solid black lines) and

495 post-AVR (solid grey lines) and B) Post-AVR (solid grey lines) and during follow-up (dashed

496 lines). The thick lines represent the systolic ε-volume relationship while the thin lines

497 represent the diastolic ε-volume relationship.

498

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

500 Data represents the mean difference between systolic and diastolic ε values at different

501 volumes over the entire cardiac cycle (i.e. UNCOUP). The left side represent the UNCOUP

502 values prior to AVR and the right side the UNCOUP values short-term post AVR. The grey

503 dots represent individual patients, the black dot represents the mean value for the entire group.

504

505 **Figure 4 – Scatter plot of the short-term change in uncoupling of the ε-volume loop and**

506 **long-term LV mass regression.**

507 Data represent the relation between the change in uncoupling of the ε-volume loop between

508 pre-AVR and short-term after AVR measurements and the change in LV mass between the

509 pre-AVR and follow-up measurements. The black line represents the linear fit line, showing a

510   significant correlation between a short-term reduction in the amount of uncoupling and long-

511   term LV mass regression.

512

513

514 **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

515

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**

518 Symbols denote *=calculated using the velocity time integral. AV=Aortic valve; LVOT=Left

519 ventricular outflow tract; AVA=Aortic valve area; VTI=Velocity time integral;

520 IVSd=Interventricular septal thickness at diastole; LVIDd=Left ventricle internal diameter at

521 diastole; LVPWd=Left ventricle posterior wall at diastole; LVEDV=Left ventricle end

522 diastolic volume; LVESV=Left ventricle end systolic volume; LAESV=Left ventricle end

523 systolic volume; LVEF=Left ventricle ejection fraction; ε=Strain; Sslope=ε-volume relation

524 across the systolic phase; UNCOUP=Uncoupling of the systolic and diastolic ε-volume

525 relation; UNCOUP_ED=Uncoupling of the systolic and diastolic ε-volume relation during

526 early filling; UNCOUP_LD= Uncoupling of the systolic and diastolic ε-volume relation

527 during atrial contraction.

528

529 **TABLE 3:** Data represents the mean±SD values of the characteristics derived from
530 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

531 Symbols denote *=calculated using the velocity time integral. AV=Aortic valve; LVOT=Left

532 ventricular outflow tract; AVA=Aortic valve area; VTI=Velocity time integral;

533 IVSd=Interventricular septal thickness at diastole; LVIDd=Left ventricle internal diameter at

534 diastole; LVPWd=Left ventricle posterior wall at diastole; LVEDV=Left ventricle end

535 diastolic volume; LVESV=Left ventricle end systolic volume; LAESV=Left ventricle end

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540 during atrial contraction.

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