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1 **EXPLORATORY ASSESSMENT OF LEFT VENTRICULAR**
2 **STRAIN-VOLUME LOOPS IN SEVERE AORTIC VALVE**
3 **DISEASES**

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20
21 **Short title:** Cardiac strain-volume loops to identify pathology

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29 **Key points summary**

- 30 • Severe aortic valve diseases represent common cardiac abnormalities that are associated
31 with poor long-term survival.
- 32 • Prior to any reduction in left ventricular function, the left ventricle undergoes structural
33 remodeling under the influence of a changing haemodynamic conditions.
- 34 • In this study, we combined temporal changes in LV structure (volume) to alterations in LV
35 functional characteristics (strain, ϵ) into a ϵ -volume loop, to provide novel insight into the
36 haemodynamic cardiac consequences of aortic valve diseases in those with preserved LV
37 ejection fraction.
- 38 • We showed that our novel ϵ -volume loop and the specific loop characteristics provides
39 additional insight in the functional and mechanical haemodynamic consequences of severe
40 aortic valve diseases (with preserved LV ejection fraction).
- 41 • Finally we showed that the ϵ -volume loop characteristics provide discriminative capacity
42 compared to conventional measures of left ventricular function.

43

44 **ABSTRACT**

45 **Objectives.** The purpose of this study was to examine left ventricular (LV) strain (ϵ)-volume
46 loops to provide novel insight into the haemodynamic cardiac consequences of aortic valve
47 stenosis (AS) and aortic valve regurgitation (AR).

48 **Methods.** 27 participants were retrospectively recruited: AR (n=7), AS (n=10) and controls
49 (n=10). Standard transthoracic echocardiography was utilised to obtain apical 4 chamber
50 images to construct ϵ -volume relationships were assessed by: Early systolic ϵ (ϵ_{ES}), slope of
51 ϵ -volume relation during systole (Sslope), End-systolic peak ϵ (peak ϵ), Diastolic uncoupling
52 (systolic ϵ -diastolic ϵ at same volume) during early diastole (UNCOUP_ED) and late diastole
53 (UNCOUP_LD). ROC-curves were used to determine the ability to detect impaired LV
54 function.

55 **Results.** Whilst LV ejection fraction was comparable between groups, longitudinal peak ϵ was
56 similarly reduced compared to controls. In contrast, ϵ_{ES} and Sslope were lower in both
57 pathologies compared to controls ($P<0.01$), but also different between AS and AR ($P<0.05$).
58 UNCOUP_ED as UNCOUP_LD were significantly higher in both patient groups compared to
59 controls ($P<0.05$). ROC-curves revealed that loop characteristics (AUC=0.99, 1.00, 1.00; all
60 $P<0.01$) were better able than peak ϵ (AUC=0.75, 0.89, 0.76; $P=0.06$, <0.01 and 0.08,
61 respectively) and LV ejection fraction (AUC=0.56, 0.69, 0.69; all $P>0.05$) to distinguish AS vs
62 Controls, AR vs Controls and AS vs AR, respectively.

63 **Conclusions.** Temporal changes in ϵ -volume characteristics provide novel insight into the
64 haemodynamic cardiac impact of AS and AR. Contrary to traditional measures (i.e. ejection
65 fraction, peak ϵ), these novel measures successfully distinguish between the haemodynamic
66 cardiac impact of AS and AR.

67

68 **KEYWORDS:** Cardiovascular disease; cardiac strain; echocardiography; aortic valve
69 disease; haemodynamic

70

71 **ABBREVIATIONS**

72 American Society of Echocardiography (ASE)

73 Aortic Valve Area (AVA)

74 Aortic valve stenosis (AS)

75 Aortic valve regurgitation (AR)

76 Cardiac output (CO)

77 Diastolic uncoupling during early diastole (UNCOUP_ED)

78 Diastolic uncoupling during late diastole (UNCOUP_LD)

79 Early systolic ϵ (ϵ_{ES})

80 Heart rate (HR)

81 Left atrial (LA)

82 Left atrial diameter (LAdiam)

83 Left atrial end systolic volume (LAESV)

84 Left ventricular (LV)

85 Left ventricular end diastolic volume (LVEDV)

86 Left ventricular ejection fraction (LVEF)

87 Left ventricular end systolic volume (LVESV)

88 Linear slope during systole (Sslope)

89 Peak strain (peak ϵ)

90 Region of interest (ROI)

91 Strain (ϵ)

92 Stroke volume (SV)

93 Vena contracta (VC)

94 **INTRODUCTION**

95 Severe aortic valve stenosis (AS) and severe aortic valve regurgitation (AR) represent common
96 cardiac abnormalities that are associated with poor long-term survival (Dujardin *et al.*, 1999;
97 Carabello, 2008; Samad *et al.*, 2016). Current management of these conditions is based on serial
98 echocardiographic assessment with current guidelines recommending valve replacement in case
99 of symptoms or reduced left ventricle ejection fraction (LVEF) below 50% (Bonow *et al.*, 2008;
100 Galli *et al.*, 2014). The inherent limitations and load dependency (Mangano *et al.*, 1980; Dong
101 *et al.*, 1999) make LVEF a suboptimal marker to assess progression and status of AS and AR
102 (Hachicha *et al.*, 2007; Galli *et al.*, 2014). Prior to any reduction in LVEF, the LV undergoes
103 structural remodeling under the influence of an increased afterload in AS and a significant
104 volume overload in AR (Bonow *et al.*, 2008; Maganti *et al.*, 2010; Kamperidis *et al.*, 2016).
105 Temporally linking the changes in LV structure to alterations in functional characteristics of
106 the LV may provide more detailed insight into the haemodynamic cardiac consequences of both
107 aortic valve disease states.

108
109 The introduction of speckle tracking techniques in echocardiography has allowed for the
110 measurement of strain (ϵ) (Artis *et al.*, 2008; Dandel *et al.*, 2009; Mondillo *et al.*, 2011), which
111 is a valid technique for assessment of LV deformation. Previous work has demonstrated a lower
112 longitudinal (global or segmental) peak ϵ in AS or AR patients with preserved LVEF (Delgado
113 *et al.*, 2009; Smedsrud *et al.*, 2011; Adda *et al.*, 2012; Lavine & Al Balbissi, 2015). Nonetheless,
114 marked overlap remained in longitudinal peak ϵ between these disease states and healthy
115 controls which is further limited by a single measurement of longitudinal peak ϵ not reflecting
116 the temporal changes throughout the cardiac cycle.

117

118 In this exploratory study, we adopted a novel approach to assess LV ϵ across the cardiac cycle
119 and subsequently relate these to simultaneous assessment of LV volume (Lord *et al.*, 2016;
120 Oxborough *et al.*, 2016). This simultaneous assessment establishes the relative contribution of
121 longitudinal ϵ to volume changes throughout the cardiac cycle providing a ϵ -volume loop.
122 The ϵ -volume loop can establish relative longitudinal strain's contribution to volume change in
123 systole and diastole. Our previous work has demonstrated a similar ϵ value for any given volume
124 during diastole and systole in healthy individuals and athletes (Oxborough *et al.*, 2016),
125 suggesting the presence of strong systolic-diastolic coupling. This observation suggests that
126 longitudinal ϵ is closely related during contraction (i.e. systole) or relaxation (i.e. diastole).
127 Previously, it was found that upon alterations in cardiac load (Lord *et al.*, 2016), dissociation
128 occurs between systolic and diastolic ϵ at the same volume (i.e. uncoupling). Also in severe
129 chronic valve disease, where differences are present in structural integrity and load alterations,
130 uncoupling may be present. This measure, through combining functional and structural
131 information, may therefore provide additional, novel insight into the haemodynamic cardiac
132 consequences of AS and AR. Consequently, we aimed to determine whether traditional
133 echocardiographic measures (e.g. LVEF and peak ϵ) and characteristics of the LV ϵ -volume
134 loop are different between healthy controls, patients with severe AS, and patients with severe
135 AR. We hypothesise that, in contrast to traditional echocardiographic measures, temporal
136 changes in the ϵ -volume loop would provide data that could distinguish between the
137 haemodynamic cardiac impact of AS (i.e. driven by increased afterload) and AR (i.e. driven by
138 increased volume overload).

139

140 **METHODS**

141 *Ethical approval*

142 We received approval from the Radboud University Medical Center ethics committee to
143 perform the proposed work (reference number 2015-1727) and in this process, informed
144 consent from participants was received to perform data analysis as executed in the present
145 study. This study conforms to the standards set by the latest revision of the Declaration of
146 Helsinki.

147

148 *Study population*

149 We retrospectively included 27 participants, consisting of severe AR (n=7; 45±10 years; 14%
150 Female), severe AS (n=10; 47±11 years; 40% Female) and controls (n=10; 50±10 years; 50%
151 Female), who underwent an echocardiographic assessment at the Radboud University Medical
152 Center (Nijmegen). Participants were randomly selected from a database that includes
153 echocardiographic data from patients that underwent echocardiography at the Department of
154 Cardiology of the Radboud University Medical Center since 2009. We first identified subjects
155 with chronic severe disease, utilizing the echocardiographic diagnosis of severe AS or severe
156 AR documented by a cardiologist using the American Society of Echocardiography (ASE)
157 guidelines for valve stenosis (Baumgartner *et al.*, 2009) and valve regurgitation (Lancellotti *et*
158 *al.*, 2010). For severe AS, a cut off value for Aortic Valve Area of 1.0 cm² was used. For AR,
159 a classification of severe was determined using a combination of qualitative and quantitative
160 adjunctive parameters (Table 1) in accordance with international guidelines (Lancellotti *et al.*,
161 2010). Participants were excluded if they had a history of coronary artery disease, the presence
162 of LV regional wall motion abnormalities, an abnormal LVEF, co-existing mitral, pulmonic or
163 tricuspid valve disease (greater than mild in severity) or any other documented cardiac
164 pathology. After identifying eligible patients, a single researcher went through the list in
165 chronological order (starting with the most recent measurements) and selected the participants
166 from the list when the echocardiographic measurements: *i.* included all required images/planes,

167 and *ii.* achieved high quality imaging to ensure eligibility for our analysis. In this procedure,
168 the researcher was blinded for health status and other subject characteristics. Before final
169 inclusion, all participants that were selected by the researcher were verified (regarding in- and
170 exclusion criteria and quality of the echocardiography data) by a single experienced cardiologist
171 (AvD). Controls were selected in the absence of documented cardiovascular diseases,
172 hypertension, history of cardiovascular medication and in the presence of normal cardiac
173 function using the ASE guidelines for cardiac chamber quantification (Lang *et al.*, 2015).

174

175 *Measurements*

176 Echocardiographic data was obtained using a Vivid E9 ultrasound machine (GE Medical
177 System, Horton, Norway) with a 1.5-4 MHZ phased array transducer. The data was stored in
178 raw DICOM format in a remote archive of the Department of Cardiology at the Radboud
179 University Medical Center (Nijmegen). Data was analysed using commercially available
180 software (EchoPac version 113.05, GE Medical, Horten, Norway).

181

182 *2D Echocardiographic Assessment*

183 Echocardiographic images were acquired in accordance with the recommendations of the ASE
184 (Lang *et al.*, 2015) by an experienced sonographer from the Radboudumc (Nijmegen) with the
185 patient in the left lateral decubitus position. In addition to the measurements to determine valve
186 disease severity, traditional structural and functional LV and left atrial (LA) parameters were
187 calculated from appropriate images by a single operator with experience in echocardiographic
188 imaging. LV linear dimensions and LA diameter (LAdiam) were measured using 2-dimensional
189 imaging from a parasternal long axis orientation and LV mass was calculated according to the
190 ASE corrected Devereaux formula (Lang *et al.*, 2006). LV end diastolic volume (LVEDV), LV
191 end systolic volume (LVESV), LVEF and LA end systolic volume (LAESV) were calculated

192 using Simpson's biplane method utilizing both apical four and two chamber orientations. Stroke
193 volume (SV) was calculated by subtracting LVESV from LVEDV and cardiac output (CO) was
194 calculated by multiplying SV and heart rate (HR).

195

196 *2D Myocardial Speckle Tracking*

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

206

207 *ϵ -volume Loops*

208 Temporal longitudinal ϵ values were exported to a spreadsheet (Excel, Microsoft Corp,
209 Washington, US). Using cubic spline interpolation the global temporal longitudinal ϵ values
210 were divided in 300 points for systole and 300 points for diastole. For both systole and diastole
211 the 300 ϵ values were then split into 5% increments of the cardiac cycle providing longitudinal
212 ϵ values at 10 time points in systole and 10 time points in diastole. Concomitant time points for
213 the ϵ values were used in the same image and cardiac cycle to trace LV monoplane volumes to
214 provide simultaneous ϵ and volume values. For each patient a longitudinal ϵ -volume loop was
215 created after which a mean longitudinal ϵ -volume loops for each group was calculated.

216

217 Using the individual ϵ -volume loops a linear regression line and a polynomial of two orders
218 were applied to both diastolic and systolic parts of the loop. This derived polynomial equation
219 allowed the derivation of ϵ at % increments of LVEDV. The longitudinal ϵ -volume relationship
220 was assessed by 1) Early systolic ϵ (ϵ_{ES}), 2) linear slope of ϵ -volume relation during systole
221 (Sslope), 3) End-systolic peak ϵ (peak ϵ), 4) Diastolic uncoupling (i.e difference systolic vs
222 diastolic ϵ) during early filling (UNCOUP_ED) and 5) Diastolic uncoupling during late diastole
223 (UNCOUP_LD) (fig. 1).

224

225 ϵ_{ES} was determined by calculating the volume at 90% of EDV, the resulting volume was then
226 implemented in the formula of the polynomial regression line to calculate the matching systolic
227 ϵ value at 90% of EDV. The Sslope was derived as the gradient of the linear regression line
228 over the systolic phase of the ϵ -volume loop. Longitudinal peak ϵ was derived as the raw peak
229 ϵ value from the longitudinal ϵ data. UNCOUP_ED and UNCOUP_LD were calculated across
230 the area between the systolic and diastolic polynomial curves. Using the same method as for
231 ϵ_{ES} systolic and diastolic ϵ values were calculated at 10% increments between 40 and 90% of
232 EDV. By subtracting diastolic from systolic ϵ the difference at each point was calculated. Based
233 on individual LVEF the working range of the heart was determined, after which UNCOUP_ED
234 was calculated as the sum of the differences at the lowest 2/3 of increments of EDV in the
235 working range of the heart, UNCOUP_LD was calculated as the sum of the differences at the
236 highest 1/3 increments of EDV in the working range of the heart. All data from individual loops
237 were averaged across the cohort to provide peak values and ϵ -volume loops for all three groups.
238 Intra-user variability analysis revealed the following intra-class correlations for the loop
239 characteristics: ϵ_{ES} (ICC: 0.945, $P < 0.001$), Sslope (ICC: 0.950, $P < 0.001$), Peak_ ϵ (ICC:
240 0.831, $P < 0.01$), UNCOUP_ED (ICC: 0.779, $P < 0.01$) and UNCOUP_LD (ICC: 0.737, $P < 0.05$).

241

242 *Statistical analysis*

243 The resulting data for each group is expressed as mean \pm standard deviation. Normality of data
244 distribution was examined using a Kolmogorov-Smirnov test. In case non-Gaussian distribution
245 was observed, log-transformation was applied after which the data was re-examined. A one-
246 way sample ANOVA (IBM SPSS statistics version 22) was used to assess differences between
247 groups for all parametric variables. Sex was compared using a Chi-square test. A P-value of
248 <0.05 was considered significant. In case of significant differences between groups, a LSD Post
249 Hoc analysis was applied to establish differences between pairwise group comparisons.
250 Additionally we compared the loop characteristics within each group for sex related differences.
251 To better understand the potential added value of the novel loop characteristics, a correlation
252 between measures of the ϵ -volume relationship was calculated with traditional measures of LV
253 function (LVEF and peak ϵ) using the Pearson's bivariate correlation coefficient. Additionally
254 we used ROC-curves to determine whether traditional (i.e. LVEF) and more novel (i.e. peak ϵ
255 and our combined ϵ -volume loop characteristics) markers of LV function can distinguish
256 between healthy controls, AS and AR. Furthermore, we explored overlap in longitudinal peak
257 ϵ between the 3 groups and compared overlap in 95% confidence intervals between groups for
258 the newly derived characteristics in a figure. Finally, we performed a sub-analysis of controls
259 (n=3), AS (n=3) and AR patients (n=3) to examine potential differences in the ϵ -volume loop
260 characteristics in the presence of comparable longitudinal peak ϵ values.

261

262

263 **RESULTS**

264 There were no significant differences in age, weight, height, BSA or HR between all groups
265 (Table 1). Structural parameters of the LV and LA, were significantly larger in AR compared

266 to AS and controls with no difference between controls and AS. We observed no differences in
267 LVEF between groups.

268

269 *ε-volume loop (longitudinal)*. Longitudinal peak ϵ was significantly lower in both pathologies
270 compared to controls, but no difference was observed between AS and AR (Table 2). In
271 contrast, ϵ_{ES} and S_{slope} were lower in AR and AS compared to controls and AR
272 demonstrating lower values compared to AS. UNCOUP_ED and UNCOUP_LD are
273 significantly higher in both pathologies compared to controls, while no difference between AS
274 and AR was present. No significant differences in the loop characteristics were observed
275 between male and female participants within groups (all comparisons $P>0.05$).

276

277 We observed a moderate and significant correlation between longitudinal peak ϵ and ϵ_{ES} ($r=-$
278 0.464 $P<0.05$) and S_{slope} ($r=-0.675$ $P<0.01$). Peak ϵ was not significantly correlated with
279 UNCOUP_ED or UNCOUP_LD ($P=0.380$ and 0.201 , respectively). There were no significant
280 correlations between LVEF and any of the characteristics of the ϵ -volume loop (all $P>0.05$).

281

282 We found no discriminative capacity of LVEF for controls-AS (AUC=0.56; $P=0.68$), controls-
283 AR (AUC=0.69; $P=0.13$) or AS-AR (AUC=0.69; $P=0.21$). Whilst peak ϵ did not distinguish
284 between controls-AS (AUC=0.75; $P=0.06$) or AS-AR (AUC=0.76; $P=0.08$), differences were
285 found between controls-AR (AUC=0.89 [1.000-0.718]; $P<0.01$). Finally, loop characteristics
286 significantly distinguished groups for each comparison; controls-AS (AUC=0.99 [1.000-
287 0.985]; $P<0.01$), controls-AR (AUC=1.00 [1.000-1.000]; $P<0.01$), and AS-AR (AUC=1.00
288 [1.000-1.000]; $P<0.01$).

289

290 To better understand the ability of the ϵ -volume loop values to characterise AS or AR, we have
291 plotted the loop characteristics against peak ϵ (Figure 3). The marked overlap of peak ϵ values
292 across the 3 groups (i.e. horizontal grey area) contrasts with the smaller overlap of Sslope, ϵ_{ES} ,
293 UNCOUP_ED and UNCOUP_LD (vertical grey area). Finally, distinct ϵ -volume loop
294 characteristics were present in subgroups of healthy controls, AS and AR who show comparable
295 longitudinal peak ϵ (Figure 4).

296

297

298 **DISCUSSION**

299 The purpose of this study was to examine whether characteristics of the LV ϵ -volume loop, a
300 novel method used here for the first time to link changes in cardiac ϵ to alterations in LV cavity
301 volume across the cardiac cycle, provides additional insight into the haemodynamic cardiac
302 consequences of AS and AR. The key findings of the current study were that both valve
303 pathologies lead to characteristic remodeling, with concentric remodeling of the LV in AS (i.e.
304 pressure-overload) and eccentric remodeling in AR (i.e. volume-overload) (Bonow *et al.*,
305 2008). Importantly, and despite significant remodeling, traditional measures of LV function
306 provide no (LVEF) or little (peak ϵ) discriminative capacity between valve pathology *versus*
307 controls or AS *versus* AR. In marked contrast, all characteristics of the ϵ -volume loop were
308 different between controls and valve pathology, whilst it successfully can distinguish between
309 AS, AR and controls. More specifically, the initial change in ϵ during systole (i.e. ϵ_{ES}) and
310 the relation between ϵ and volume (i.e. Sslope) were different between AS and AR.
311 Furthermore, in the presence of comparable longitudinal peak ϵ , characteristics of the ϵ -volume
312 loop differed among the 3 groups. These data suggest that the ϵ -volume loop of the LV provides
313 novel insight and additional discriminative capacity to understand functional consequences of
314 (distinct) haemodynamic loading on the left ventricle in AS and AR.

315

316 Both AS and AR demonstrated significant left ventricular remodeling, either due to an increased
317 afterload (i.e. AS) or increased volume (i.e. AR). In addition to structural remodeling, previous
318 work revealed significant fibrosis in the endocardial layer in both AS and AR (Taniguchi *et al.*,
319 2000; Rassi *et al.*, 2014). Given the longitudinal orientation of myocardial fibres, fibrosis of
320 these fibres likely represents a key modulator of the reduction in longitudinal peak ϵ
321 (Weidemann *et al.*, 2009; Rassi *et al.*, 2014). Despite the reduction in longitudinal peak ϵ ,
322 preserved LVEF was present in AS and AR. One potential explanation may relate to
323 compensatory changes in circumferential ϵ . An increase in circumferential ϵ may contribute to
324 preservation of ventricular function and LVEF (Carasso *et al.*, 2011; Iida *et al.*, 2012).
325 Preserved LVEF and altered peak ϵ may reflect compensatory remodeling, which are largely
326 independent on the type of cardiac overload (pressure *versus* volume) and presence of
327 remodeling (concentric *versus* eccentric).

328

329 To further understand the impact of valve pathology on the heart, we explored longitudinal ϵ -
330 volume loops and described differences in the temporal ϵ -volume relationship across groups.
331 First, during early systole, we observed smaller initial changes in longitudinal ϵ . Whilst these
332 changes were present in both disease states compared to controls, the attenuated ϵ -responses
333 were significantly larger in AR compared to AS. Presence of cardiac fibrosis may contribute to
334 this observation, as fibrosis reflects myocyte degeneration, impairing ventricular contractility
335 (Hein *et al.*, 2003). The altered relation between an increase in ϵ alongside increases in volume
336 (i.e. S_{slope}) persists in both valve pathologies throughout the remainder of systole. Similar to
337 early systolic changes, AR shows a further attenuation of this relation compared to AS. The
338 larger attenuation of ϵ_{ES} and S_{slope} in AR may be due to volume overload in AR, causing a
339 further reduction in contractility due to loss of connection between myofibrils.

340

341 Controls show a close relation between changes in longitudinal ϵ for a change in LV volume
342 during diastole and systole. In marked contrast, AS and AR demonstrated dissociation between
343 the diastolic *versus* systolic longitudinal ϵ at any given volume change, indicating the presence
344 of significant uncoupling between ϵ and volume relation. During early diastole, which is linked
345 to active relaxation of the LV, both AS and AR demonstrate ‘delayed’ relaxation. LV relaxation
346 is affected by the LV diastolic untwisting rate, which in turn is affected by filling pressures,
347 restoring forces (energy stored during systole) and thus systolic function (Nagueh *et al.*, 2016).
348 Delayed or prolonged diastolic relaxation therefore is assumed to be the result of delayed and
349 prolonged diastolic untwisting of the LV, which has been described before in chronic overload
350 situations (Stuber *et al.*, 1999; Nagel *et al.*, 2000). A reduction of diastolic untwist is associated
351 with attenuated or loss of the suction created by the LV and assumed to contribute to diastolic
352 dysfunction (Nagueh *et al.*, 2009). Additional insights in the dissociation between the systolic
353 and diastolic ϵ -volume relation could therefore provide valuable insight in the shift in
354 mechanics and haemodynamic changes that occur during chronic overload situations. Also
355 during late diastole, associated with atrial contraction and chamber compliance, AS and AR
356 show dissociation between the systolic and diastolic ϵ for any given LV volume. Remodeling
357 of the ventricles in AS and AR possibly contributes to an increase in passive stiffness and
358 reduced chamber compliance (Aurigemma *et al.*, 2006; Dostal & Watson, 2006). Less
359 compliant ventricles may show an impaired ability to alter ϵ levels upon the return of ventricular
360 volume. Due to these changes in early and late diastole, possibly as a result of structural
361 remodeling, a rightward shift is present in the ϵ -volume relationship during diastole. Although
362 the underlying mechanisms are unclear, the presence of uncoupling between the systolic and
363 diastolic ϵ -volume relationship in AS and AR provide further evidence for a significant impact
364 of both valve pathologies on LV function, which are not simply detected by current methods.

365

366 To explore the (clinical) value of the ϵ -volume loop, we compared the ROC-curves for LVEF,
367 longitudinal peak ϵ and the combined loop characteristics between all groups. Whilst no (for
368 LVEF) or limited (for peak ϵ) discriminative capacity was found for current techniques between
369 the 3 groups, the novel loop characteristics provided strong, significant discriminative capacity
370 between all groups. Additionally, we have compared overlap in these measures of the ϵ -volume
371 loop across the 3 groups. Remarkably, significant overlap is present for longitudinal peak ϵ
372 across groups, highlighting the limited ability for longitudinal peak ϵ to distinguish between
373 groups. In contrast, marginal overlap is present between groups when comparing ϵ _ES and
374 Sslope (Figure 3A-B), whilst also ϵ _ES and Sslope show limited overlap between groups. To
375 further support the potential discriminative capacity of the ϵ -volume loop, we have compared
376 ϵ -volume loops between subgroups of controls (n=3), AS (n=3) and AR (n=3) who demonstrate
377 comparable longitudinal peak ϵ (and LVEF). The different loop characteristics between groups
378 highlight the potential clinical value of presenting ϵ -volume loops when comparing cardiac
379 function between groups.

380

381 *Clinical implication.* LVEF and longitudinal peak ϵ provide limited insight and thus impact
382 upon clinical decision making in AS and AR. The marked differences in ϵ -volume loop
383 characteristics across the 3 groups, even in the presence of preserved peak ϵ , highlight the
384 potential value of the ϵ -volume loop. These observations, including the strong ROC-curves that
385 support the discriminative capacity of ϵ -volume loop characteristics, reinforce early suggestions
386 from Gibson *et al.* who showed the usefulness of combining echocardiographic estimates of
387 LV wall displacement and volume to assess temporal information of LV function (Gibson &
388 Brown, 1973, 1974). Given the non-invasive character, use of traditional echocardiography
389 protocols, and improved ability to discriminate between the variable load challenges in valve

390 pathology, this technique may be useful for relevant physiological insights in specific disease
391 states and/or prognosis. Follow-up studies should therefore examine the clinical and prognostic
392 value of the ϵ -volume loop more extensively and consider the diagnostic and prognostic value
393 of the loop characteristics over longitudinal peak ϵ .

394

395 *Limitations.* Due to contemporary technological difficulties, we could only calculate and
396 present longitudinal ϵ -volume loops. Whilst the application to circumferential, radial and twist
397 is feasible, concomitant volumes cannot be derived using contemporary 2D-techniques. Whilst
398 3D-imaging potentially provides simultaneous ϵ and volume in all planes, temporal resolution
399 of current 3D-techniques provide too low frame rates (± 10 fps) for valid assessment of ϵ -volume
400 loops. Currently applied methods are time-consuming taking up to 30 min per subject to acquire
401 the ϵ -volume loops. Automated temporal LV volume tracking would improve efficiency and
402 feasibility to apply this method in daily clinical practice.

403

404 In conclusion, this exploratory study reinforces the marked structural remodeling observed in
405 AS and AR and the presence of preserved LVEF as well as the attenuation of longitudinal ϵ in
406 both valve pathologies. Our novel measure of the temporal changes in the ϵ -volume
407 characteristics of the LV provides further insight into the haemodynamic cardiac impact of AS
408 and AR, and is even able to distinguish between the impact of AS (i.e. increased afterload) and
409 AR (i.e. increased volume overload). Therefore, this paper, using the ϵ -volume relationship,
410 provides novel insight in the functional and mechanical haemodynamic consequences of AS
411 and AR, but also demonstrates improved ability (compared to traditional echocardiographic
412 measures) to distinguish between the functional consequences of AS *versus* AR on LV function.

413 **Additional information**

414

415 **Disclosures**

416 None

417

418 **Author Contributions**

419 Experiments were performed at the departments of Physiology and Cardiology of the Radboud
420 University Medical Center in Nijmegen. The conception and design of the work were carried
421 out by all authors, acquisition, analysis and interpretation of the Data were performed by DT,
422 DO, AvD and HH. All authors contributed in drafting or critically revising the manuscript. All
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426

427

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608

609 **FIGURE AND TABLE LEGENDS**

610 **Figure 1** – A schematic view of the methods used to assess the ϵ -volume loops. The black line
611 represents the ϵ -volume loop, the thick part represents the systolic phase and the thin line the
612 diastolic phase. We assessed the ϵ -volume loop by a) systolic ϵ at 90% of EDV (i.e. ϵ_{ES} ; red
613 dotted line), b) ϵ -volume relation across the systolic phase (i.e. S_{slope} , orange dashed line), c)
614 peak ϵ at end-systole (i.e. peak ϵ), d) difference in systolic vs diastolic ϵ during early filling (i.e.
615 UNCOUP_ED) and e) difference in systolic vs diastolic ϵ during atrial contraction (i.e.
616 UNCOUP_LD).

617

618 **Figure 2** – Data represents average longitudinal ϵ -volume loops in controls (n=10, solid lines),
619 aortic stenosis (AS, n=10, short dashed line) and aortic regurgitation (AR, n=7, long dashed
620 lines). All data represents the mean value at the various time points.

621

622 **Figure 3** – Comparison between longitudinal peak ϵ (Y-axis, in %) and ϵ -volume loop
623 characteristics S_{slope} (A), ϵ_{ES} (B), UNCOUP_ED (C) and UNCOUP_LD (D) for controls
624 (solid circle), AS (solid square) and AR (solid triangle). The grey areas represent the reference
625 areas, based on data from the control group. Error bars represent SD. Note the large variation
626 in longitudinal peak ϵ that overlaps across groups, whilst smaller variation with less overlap is
627 present for the ϵ -volume loop characteristics.

628

629 **Figure 4** – Data represents average longitudinal ϵ -volume loops in a subgroup of healthy
630 controls (n=3, solid lines), aortic stenosis (AS, n=3, short dashed line) and aortic regurgitation
631 (AR, n=3, long dashed lines) with comparable longitudinal peak ϵ . Note the marked differences
632 in ϵ -volume loops characteristics between groups, despite comparable longitudinal peak ϵ .

633 **Table 1** – Baseline demographics.

Baseline characteristics	Controls	Cardiac valve pathology		
		AS	AR	P-Value
Age (yrs)	50±10	47±11	45±10	0.539
Height (cm)	176±9	178±9	178±6	0.752
Weight (cm)	77±13	80±12	79±8	0.830
BSA (m ²)	1.93±0.19	1.98±0.19	1.96±0.12	0.766
HR (bpm)	71±12	68±10	62±8	0.283
Female:male	5:5	4:6	1:6	0.315
Echocardiographic				
IVSd (cm)	0.8±0.2	1.1±0.2*	1.1±0.1*	<0.01
LVIDd (cm)	4.5±0.4	4.7±0.3 [†]	6.2±0.7* [†]	<0.01
LVPWd (cm)	0.9±0.2	1.1±0.2	1.2±0.1*	0.04
LVD Mass Index (g/m ²)	65.7±12.7	92.0±15.3 [†]	177.2±57.1* [†]	<0.01
LVEDV (ml)	98±25	121±22 [†]	244±37* [†]	<0.01
LVESV (ml)	36±14	48±11 [†]	104±25* [†]	<0.01
LVEF (%)	62±7	60±4	58±4	0.32
SV (ml)	61±17	73±13 [†]	140±17* [†]	<0.01
CO (L/min)	4.2±0.7	5.0±1.5 [†]	8.7±1.5* [†]	<0.01
LAESV(ml)	37.1±9.9	46.1±11.1 [†]	68.1±35.0* [†]	0.01
LADiam (cm)	3.5±0.5	3.5±0.6	3.7±0.6	0.73
AS specific				
AVA (cm ²)	-	0.8±0.1	-	-
Mean pressure gradient (mmHg)	-	50±13	-	-

Dimensionless Index	-	0.19±0.03	-	-
AR specific				
VC (mm)	-	-	8.3±1.2	-
ED Vmax (m/s)	-	-	0.26±0.07	-

634

635 Symbols denote P<0.05 to Controls=*, between AS and AR=† (AS=Aortic stenosis; AR=Aortic
636 regurgitation; BSA=Body surface area; HR=Heart rate; IVSd=Interventricular septal thickness
637 at diastole; LVIDd=Left ventricle internal diameter at diastole; LVPWd=Left ventricle
638 posterior wall at diastole; LVEDV=Left ventricle end diastolic volume; LVESV=Left ventricle
639 end systolic volume; LVEF=Left ventricle ejection fraction; SV=Stroke volume; CO=Cardiac
640 output; LAESV=Left ventricle end systolic volume; LADiam=Left atrial diameter;
641 AVA=Aortic Valve Area; VC = Vena contracta; ED Vmax = End diastolic velocity)

642

643 **Table 2** – Characteristics derived from ϵ -volume loop.

Longitudinal ϵ -volume loop	Controls	Cardiac pathology		P-Value
		AS	AR	
$\epsilon_{ES}(\%)$	-2.5±1.1 (-4.3;-1.4)	-1.4±0.9* [†] (-3.0;-0.4)	-0.1±1.1* [†] (-2.2;1.0)	<0.01
Sslope (%/ml)	-0.35±0.05 (-0.44;-0.28)	-0.26±0.07* [†] (-0.37;-0.16)	-0.11±0.02* [†] (-0.14;-0.07)	<0.01
Peak ϵ (%)	-19.6±3.7 (-28.4;-15.8)	-16.7±1.3* (-18.2;-14.0)	-15.0±1.9* (-18.4;-12.7)	<0.01
UNCOUP_ED	-3.6±5.0 (-11.5;6.2)	3.1±6.2* (-8.4;13.9)	5.5±5.1* (-2.7;12.1)	<0.01
UNCOUP_LD	-0.3±3.3 (-4.4;6.0)	3.9±3.8* (-0.4;12.6)	4.7±4.4* (-2.4;9.9)	0.02

644 Symbols denote P<0.05 to Controls=* , between AS and AR=[†] (AS=Aortic stenosis; AR=Aortic
645 regurgitation)