EXPLORATORY ASSESSMENT OF LEFT VENTRICULAR STRAIN-VOLUME LOOPS IN SEVERE AORTIC VALVE DISEASES

HUGO G. HULSHOF, MSC[1]
ARIE P. VAN DIJK, MD PHD[1]
KEITH P. GEORGE, PHD[2]
MARIA T.E. HOPMAN, MD PHD[1]
DICK H.J. THIJSSEN, PHD[1,2]
DAVID L. OXBOROUGH, PHD[2]

[1]Radboud Institute for Health Sciences, Departments of Physiology and Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands
[2]Research institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

Short title: Cardiac strain-volume loops to identify pathology

Author for correspondence:
Dr. David Oxborough, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Tom Reilly Building, Byrom Street, L3 3AF, Liverpool, United Kingdom, Email: D.L.Oxborough@ljmu.ac.uk, Tel: 0151 904 6231, Fax: 0151 904 6230

Key points summary

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

ABSTRACT

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

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

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

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

KEYWORDS: Cardiovascular disease; cardiac strain; echocardiography; aortic valve disease; haemodynamic

ABBREVIATIONS

American Society of Echocardiography (ASE)

Aortic Valve Area (AVA)

Aortic valve stenosis (AS)

Aortic valve regurgitation (AR)

Cardiac output (CO)

Diastolic uncoupling during early diastole (UNCOUP_ED)

Diastolic uncoupling during late diastole (UNCOUP_LD)

Early systolic ε (ε_ES)

Heart rate (HR)

Left atrial (LA)

Left atrial diameter (LAdiam)

Left atrial end systolic volume (LAESV)

Left ventricular (LV)

Left ventricular end diastolic volume (LVEDV)

Left ventricular ejection fraction (LVEF)

Left ventricular end systolic volume (LVESV)

Linear slope during systole (Sslope)

Peak strain (peak ε)

Region of interest (ROI)

Strain (ε)

Stroke volume (SV)

Vena contracta (VC)

INTRODUCTION

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

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

In this exploratory study, we adopted a novel approach to assess LV ε across the cardiac cycle and subsequently relate these to simultaneous assessment of LV volume (Lord *et al.*, 2016; Oxborough *et al.*, 2016). This simultaneous assessment establishes the relative contribution of longitudinal ε to volume changes throughout the cardiac cycle providing a ε-volume loop.

The ε-volume loop can establish relative longitudinal strain's contribution to volume change in systole and diastole. Our previous work has demonstrated a similar ε value for any given volume during diastole and systole in healthy individuals and athletes (Oxborough *et al.*, 2016), suggesting the presence of strong systolic-diastolic coupling. This observation suggests that longitudinal ε is closely related during contraction (i.e. systole) or relaxation (i.e. diastole). Previously, it was found that upon alterations in cardiac load (Lord *et al.*, 2016), dissociation occurs between systolic and diastolic ε at the same volume (i.e. uncoupling). Also in severe chronic valve disease, where differences are present in structural integrity and load alterations, uncoupling may be present. This measure, through combining functional and structural information, may therefore provide additional, novel insight into the haemodynamic cardiac consequences of AS and AR. Consequently, we aimed to determine whether traditional echocardiographic measures (e.g. LVEF and peak ε) and characteristics of the LV ε-volume loop are different between healthy controls, patients with severe AS, and patients with severe AR. We hypothesise that, in contrast to traditional echocardiographic measures, temporal changes in the ε-volume loop would provide data that could distinguish between the haemodynamic cardiac impact of AS (i.e. driven by increased afterload) and AR (i.e. driven by increased volume overload).

METHODS

Ethical approval

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

Study population

We retrospectively included 27 participants, consisting of severe AR (n=7; 45±10 years; 14% Female), severe AS (n=10; 47±11 years; 40% Female) and controls (n=10; 50±10 years; 50% Female), who underwent an echocardiographic assessment at the Radboud University Medical Center (Nijmegen). Participants were randomly selected from a database that includes echocardiographic data from patients that underwent echocardiography at the Department of Cardiology of the Radboud University Medical Center since 2009. We first identified subjects with chronic severe disease, utilizing the echocardiographic diagnosis of severe AS or severe AR documented by a cardiologist using the American Society of Echocardiography (ASE) guidelines for valve stenosis (Baumgartner *et al.*, 2009) and valve regurgitation (Lancellotti *et al.*, 2010). For severe AS, a cut off value for Aortic Valve Area of 1.0 cm^2 was used. For AR, a classification of severe was determined using a combination of qualitative and quantitative adjunctive parameters (Table 1) in accordance with international guidelines (Lancellotti *et al.*, 2010). Participants were excluded if they had a history of coronary artery disease, the presence of LV regional wall motion abnormalities, an abnormal LVEF, co-existing mitral, pulmonic or tricuspid valve disease (greater than mild in severity) or any other documented cardiac pathology. After identifying eligible patients, a single researcher went through the list in chronological order (starting with the most recent measurements) and selected the participants from the list when the echocardiographic measurements: *i.* included all required images/planes,

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

Measurements

Echocardiographic data was obtained using a Vivid E9 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

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

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

2D Myocardial Speckle Tracking

A LV focused apical four chamber view was used to assess simultaneous longitudinal ε and LV volume. 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 (ROI) was placed from the basal septum to the basal lateral wall of the LV enclosing the myocardium. The ROI was divided in six myocardial segments, providing segmental and global longitudinal ε. Global longitudinal ε was used for subsequent analysis.

ε-volume Loops

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

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 at % increments of LVEDV. 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 (i.e difference systolic vs diastolic ε) during early filling (UNCOUP_ED) and *5)* Diastolic uncoupling during late diastole (UNCOUP_LD) (fig. 1).

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

Statistical analysis

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

RESULTS

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

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

ε-volume loop (longitudinal). Longitudinal peak ε was significantly lower in both pathologies compared to controls, but no difference was observed between AS and AR (Table 2). In contrast, ε_ES and Sslope were lower in AR and AS compared to controls and AR demonstrating lower values compared to AS. UNCOUP_ED and UNCOUP_LD are significantly higher in both pathologies compared to controls, while no difference between AS and AR was present. No significant differences in the loop characteristics were observed between male and female participants within groups (all comparisons $P>0.05$).

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

Additional information

Disclosures

None

Author Contributions

Experiments were performed at the departments of Physiology and Cardiology of the Radboud University Medical Center in Nijmegen. The conception and design of the work were carried out by all authors, acquisition, analysis and interpretation of the Data were performed by DT, DO, AvD and HH. All authors contributed in drafting or critically revising the manuscript. All authors approved the final version of this manuscript and agreed to be accountable for all aspects of the work. All persons designated as authors qualify for authorship and all those who qualify for authorship are listed.

Sources of Funding

This study was supported by a junior researcher grant from the Radboud Institute for Health Sciences

Acknowledgements

None

REFERENCES

Adda J, Mielot C, Giorgi R, Cransac F, Zirphile X, Donal E, Sportouch-Dukhan C, Reant P, Laffitte S, Cade S, Le Dolley Y, Thuny F, Touboul N, Lavoute C, Avierinos JF, Lancellotti P & Habib G. (2012). Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. *Circ Cardiovasc Imaging* **5,** 27-35.

Artis NJ, Oxborough DL, Williams G, Pepper CB & Tan LB. (2008). Two-dimensional strain imaging: a new echocardiographic advance with research and clinical applications. *Int J Cardiol* **123,** 240-248.

Aurigemma GP, Zile MR & Gaasch WH. (2006). Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation* **113,** 296-304.

Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quinones M, American Society of E & European Association of E. (2009). Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* **22,** 1-23; quiz 101-102.

Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Writing Committee M & American College of Cardiology/American Heart Association Task F. (2008). 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* **118,** e523-661.

Carabello BA. (2008). Aortic stenosis: a fatal disease with but a single cure. *JACC Cardiovasc Interv* **1,** 127-128.

Carasso S, Cohen O, Mutlak D, Adler Z, Lessick J, Aronson D, Reisner SA, Rakowski H, Bolotin G & Agmon Y. (2011). Relation of myocardial mechanics in severe aortic stenosis to left ventricular ejection fraction and response to aortic valve replacement. *Am J Cardiol* **107,** 1052-1057.

Dandel M, Lehmkuhl H, Knosalla C, Suramelashvili N & Hetzer R. (2009). Strain and strain rate imaging by echocardiography - basic concepts and clinical applicability. *Curr Cardiol Rev* **5,** 133-148.

Delgado V, Tops LF, van Bommel RJ, van der Kley F, Marsan NA, Klautz RJ, Versteegh MI, Holman ER, Schalij MJ & Bax JJ. (2009). Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. *Eur Heart J* **30,** 3037-3047.

Dong SJ, Hees PS, Huang WM, Buffer SA, Jr., Weiss JL & Shapiro EP. (1999). Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol* **277,** H1053-1060.

Dostal DE & Watson LE. (2006). Understanding diastolic heart failure with preserved ejection fraction: choosing the right model. *Hypertension* **47,** 830-832.

Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB & Tajik AJ. (1999). Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. *Circulation* **99,** 1851-1857.

Galli E, Lancellotti P, Sengupta PP & Donal E. (2014). LV mechanics in mitral and aortic valve diseases: value of functional assessment beyond ejection fraction. *JACC Cardiovasc Imaging* **7,** 1151-1166.

Gibson DG & Brown D. (1973). Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *Br Heart J* **35,** 1141-1149.

Gibson DG & Brown D. (1974). Use of echocardiography in the evaluation of left ventricular function. *Proc R Soc Med* **67,** 140-142.

Hachicha Z, Dumesnil JG, Bogaty P & Pibarot P. (2007). Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation* **115,** 2856-2864.

Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V, Bauer EP, Klovekorn WP & Schaper J. (2003). Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation* **107,** 984-991.

Iida N, Seo Y, Ishizu T, Nakajima H, Atsumi A, Yamamoto M, Machino-Ohtsuka T, Kawamura R, Enomoto M, Kawakami Y & Aonuma K. (2012). Transmural compensation of myocardial deformation to preserve left ventricular ejection performance in chronic aortic regurgitation. *J Am Soc Echocardiogr* **25,** 620-628.

Kamperidis V, Delgado V, van Mieghem NM, Kappetein AP, Leon MB & Bax JJ. (2016). Diagnosis and management of aortic valve stenosis in patients with heart failure. *Eur J Heart Fail*.

Lancellotti P, Tribouilloy C, Hagendorff A, Moura L, Popescu BA, Agricola E, Monin JL, Pierard LA, Badano L, Zamorano JL & European Association of E. (2010). European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr* **11,** 223-244.

Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W & Voigt JU. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American

Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* **16,** 233-270.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W, American Society of Echocardiography's N, Standards C, Task Force on Chamber Q, American College of Cardiology Echocardiography C, American Heart A & European Association of Echocardiography ESoC. (2006). Recommendations for chamber quantification. *Eur J Echocardiogr* **7,** 79-108.

Lavine SJ & Al Balbissi KA. (2015). Reduced Longitudinal Function in Chronic Aortic Regurgitation. *J Cardiovasc Ultrasound* **23,** 219-227.

Lord R, George K, Somauroo J, Stembridge M, Jain N, Hoffman MD, Shave R, Haddad F, Ashley E, Jones H & Oxborough D. (2016). Alterations in Cardiac Mechanics Following Ultra-Endurance Exercise: Insights from Left and Right Ventricular Area-Deformation Loops. *J Am Soc Echocardiogr* **29,** 879-887 e871.

Maganti K, Rigolin VH, Sarano ME & Bonow RO. (2010). Valvular heart disease: diagnosis and management. *Mayo Clin Proc* **85,** 483-500.

Mangano DT, Van Dyke DC & Ellis RJ. (1980). The effect of increasing preload on ventricular output and ejection in man. Limitations of the Frank-Starling Mechanism. *Circulation* **62,** 535-541.

Mondillo S, Galderisi M, Mele D, Cameli M, Lomoriello VS, Zaca V, Ballo P, D'Andrea A, Muraru D, Losi M, Agricola E, D'Errico A, Buralli S, Sciomer S, Nistri S, Badano L & Echocardiography Study Group Of The Italian Society Of C. (2011). Speckle-tracking echocardiography: a new technique for assessing myocardial function. *J Ultrasound Med* **30,** 71-83.

Nagel E, Stuber M, Burkhard B, Fischer SE, Scheidegger MB, Boesiger P & Hess OM. (2000). Cardiac rotation and relaxation in patients with aortic valve stenosis. *Eur Heart J* **21,** 582-589.

Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA & Evangelisa A. (2009). Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* **10,** 165-193.

Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA & Waggoner AD. (2016). Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* **29,** 277-314.

Oxborough D, Heemels A, Somauroo J, McClean G, Mistry P, Lord R, Utomi V, Jones N, Thijssen D, Sharma S, Osborne R, Sculthorpe N & George K. (2016). Left and right

ventricular longitudinal strain-volume/area relationships in elite athletes. *Int J Cardiovasc Imaging* **32,** 1199-1211.

Rassi AN, Pibarot P & Elmariah S. (2014). Left ventricular remodelling in aortic stenosis. *Can J Cardiol* **30,** 1004-1011.

Samad Z, Vora AN, Dunning A, Schulte PJ, Shaw LK, Al-Enezi F, Ersboll M, McGarrah RW, 3rd, Vavalle JP, Shah SH, Kisslo J, Glower D, Harrison JK & Velazquez EJ. (2016). Aortic valve surgery and survival in patients with moderate or severe aortic stenosis and left ventricular dysfunction. *Eur Heart J*.

Smedsrud MK, Pettersen E, Gjesdal O, Svennevig JL, Andersen K, Ihlen H & Edvardsen T. (2011). Detection of left ventricular dysfunction by global longitudinal systolic strain in patients with chronic aortic regurgitation. *J Am Soc Echocardiogr* **24,** 1253-1259.

Stuber M, Scheidegger MB, Fischer SE, Nagel E, Steinemann F, Hess OM & Boesiger P. (1999). Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation* **100,** 361-368.

Taniguchi K, Kawamaoto T, Kuki S, Masai T, Mitsuno M, Nakano S, Kawashima Y & Matsuda H. (2000). Left ventricular myocardial remodeling and contractile state in chronic aortic regurgitation. *Clin Cardiol* **23,** 608-614.

Weidemann F, Herrmann S, Stork S, Niemann M, Frantz S, Lange V, Beer M, Gattenlohner S, Voelker W, Ertl G & Strotmann JM. (2009). Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation* **120,** 577-584.

FIGURE AND TABLE LEGENDS

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

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

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

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

Table 1 – Baseline demographics.

Baseline characteristics	*Controls*	Cardiac valve pathology		P-Value
		AS	*AR*	
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	-

Symbols denote P<0.05 to Controls=*, between AS and AR=† (AS=Aortic stenosis; AR=Aortic regurgitation; BSA=Body surface area; HR=Heart rate; 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; LVEF=Left ventricle ejection fraction; SV=Stroke volume; CO=Cardiac output; LAESV=Left ventricle end systolic volume; LADiam=Left atrial diameter; AVA=Aortic Valve Area; VC = Vena contracta; ED Vmax = End diastolic velocity)

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

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

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