

Myocardial strain and symptom severity in severe aortic stenosis: insights from cardiovascular magnetic resonance

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Background: Symptomatic severe aortic stenosis (AS) is a class I indication for replacement in patients when left ventricular ejection fraction (LVEF) is preserved. However, symptom reporting is often equivocal and decision making can be challenging. We aimed to quantify myocardial deformation using cardiovascular magnetic resonance (CMR) in patients classified by symptom severity.

Methods: Forty-two patients with severe AS referred to heart valve clinic were studied using tagged CMR imaging. All had preserved LVEF. Patients were grouped by symptoms as either “none/mild” (n=21, NYHA class I, II) or “significant” (n=21, NYHA class III, IV, angina, syncope) but were comparable for age (72.8±5.4 vs. 71.0±6.8 years old, P=0.345), surgical risk (EuroSCORE II: 1.90±1.7 vs. 1.31±0.4, P=0.302) and haemodynamics (peak aortic gradient: 55.1±20.8 vs. 50.4±15.6, P=0.450). Thirteen controls matched in age and LVEF were also studied. LV circumferential strain was calculated using inTag[®] software and longitudinal strain using feature tracking analysis.

Results: Compared to healthy controls, patients with severe AS had significantly worse longitudinal and circumferential strain, regardless of symptom status. Patients with “significant” symptoms had significantly worse peak longitudinal systolic strain rates (−83.352±24.802%/s vs. −106.301±43.276%/s, P=0.048) than those with “no/mild” symptoms, with comparable peak longitudinal strain (PLS), peak circumferential strain and systolic and diastolic strain rates.

Conclusions: Patients with severe AS who have no or only mild symptoms exhibit comparable reduction in circumferential and longitudinal fibre function to those with significant symptoms, in whom AVR is clearly indicated. Given these findings of equivalent subclinical dysfunction, reportedly borderline symptoms should be handled cautiously to avoid potentially adverse delays in intervention.

Keywords: Aortic stenosis (AS); myocardial tissue tagging; feature tracking; cardiovascular MRI

Submitted Nov 28, 2016. Accepted for publication Jan 10, 2017.

doi: 10.21037/qims.2017.02.05

View this article at: <http://dx.doi.org/10.21037/qims.2017.02.05>

Introduction

Aortic stenosis (AS) is the most frequent native valvular heart disease and typically presents as calcified degeneration in adults of advanced age (affecting 2–7% of those aged over

65 years) (1). Current guidelines recommend aortic valve replacement (AVR) with the onset of symptoms (angina, exertional dyspnoea, syncope) or cardiac dysfunction [left ventricular ejection fraction (LVEF) <50%] as class I

indications (2).

Calcific AS is associated with a long latent phase without symptoms, which varies widely in duration between individuals (3-6). In this asymptomatic group, 2-year event-free survival ranges from 20% to more than 50% (6). However, the onset of symptoms marks a bleak prognosis (7). Given the lack of a direct relation between hemodynamic severity and clinical outcome, guidelines indicate careful history taking at each visit as critical to proper patient management (7). However, symptom onset can be insidious and patients' reports are often ambiguous as they subconsciously reduce their activities or incorrectly ascribe a decline to other causes (8).

Left ventricular hypertrophy occurs in AS reflecting compensation for increased mid-wall stress from chronic pressure overload (9). Eventually an afterload mismatch impairs LV performance despite preservation of ejection fraction (10). Indeed, impaired LVEF represents an end stage of AS with worse outcomes even in those who receive corrective treatment (11).

Assessment of myocardial deformation parameters provides superior quantification of systolic function, with increased sensitivity to subtle myocardial dysfunction than global LVEF (12) and holds prognostic value in patients with AS (13) even when asymptomatic (14). Cardiovascular magnetic resonance (CMR) tagging is accepted by many as the gold standard for measurement of circumferential and longitudinal myocardial strain (15,16) and has good demonstrated reproducibility (17).

The aim of this study was to objectively define LV systolic and diastolic function, using CMR strain quantification, across a spectrum of symptom profiles in patients with severe AS and to determine whether strain assessment could potentially contribute to the decision-making process, particularly in patients with preserved LVEF and equivocal symptoms.

Methods

Study population

Forty two patients with severe degenerative AS were prospectively recruited between July 2008 and December 2013 from the University Hospitals of Leeds and Leicester, UK. Based upon transthoracic echocardiography (TTE), severe AS was defined as an aortic valve area (AVA) of $\leq 1.0 \text{ cm}^2$ or peak velocity $>4 \text{ m/s}$. Clinical evaluation comprised the elucidation of symptoms (NYHA functional

class, angina, syncope) and physical examination. Demographic data and risk factors for cardiovascular were also documented. Patients were then grouped into those reporting "no/mild" symptoms (NYHA class I, II) and those reporting "significant" symptoms (NYHA class III, IV, angina, syncope). We also enrolled 13 age-matched healthy volunteers who underwent an identical CMR protocol. Exclusion criteria included any patients with more than mild aortic regurgitation, any contraindication to CMR, and for the healthy volunteers, symptoms or history of heart disease, abnormal resting blood pressure or diabetes mellitus. The study was approved by a national ethics committee, complied with the Declaration of Helsinki and written informed consent was provided by participants.

CMR Protocol

For both patients and healthy volunteers, an identical scan protocol was performed at 1.5 T (Intera, Phillips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). Multi-slice, multi-phase cine imaging was performed using a standard steady-state free precession pulse sequence in the short axis (8 mm thickness, 0 mm gap, 30 phases, in-plane spatial resolution 1.1 mm \times 1.1 mm) ensuring full coverage of both left and right ventricles. Through-plane velocity encoded (VENC) phase contrast imaging was performed perpendicular to the aortic valve jet at the aortic sinotubular junction (typical VENC 250–500 cm/s, retrospective gating, slice thickness 6 mm, 40 phases, FOV 340 mm).

Complementary spatial modulation of magnetization (CSPAMM) imaging was carried out during a single breath hold at end expiration in the short axis orientation, at the apex, mid-, and basal LV [multishot echo planar imaging, flip angle sweep applied to the radiofrequency excitation pulses of subsequent cardiac phases, two orthogonal line tags acquired per slice, field of view: 300 mm, matrix 128 \times 128, slice thickness 10 mm, tag separation 8 mm, typically 18 phases, repetition time/echo time (TR/TE) 30/6 ms, flip angle 25 degrees]. The "3 of 5 technique" was utilised to optimise consistency of slice positioning between visits and has been demonstrated to be highly reproducible (17).

Image analysis

All analysis was performed blinded, using commercially available software (QMass 7.5 and Qflow 7.2, Medis Medical Imaging Systems, Leiden, the Netherlands).

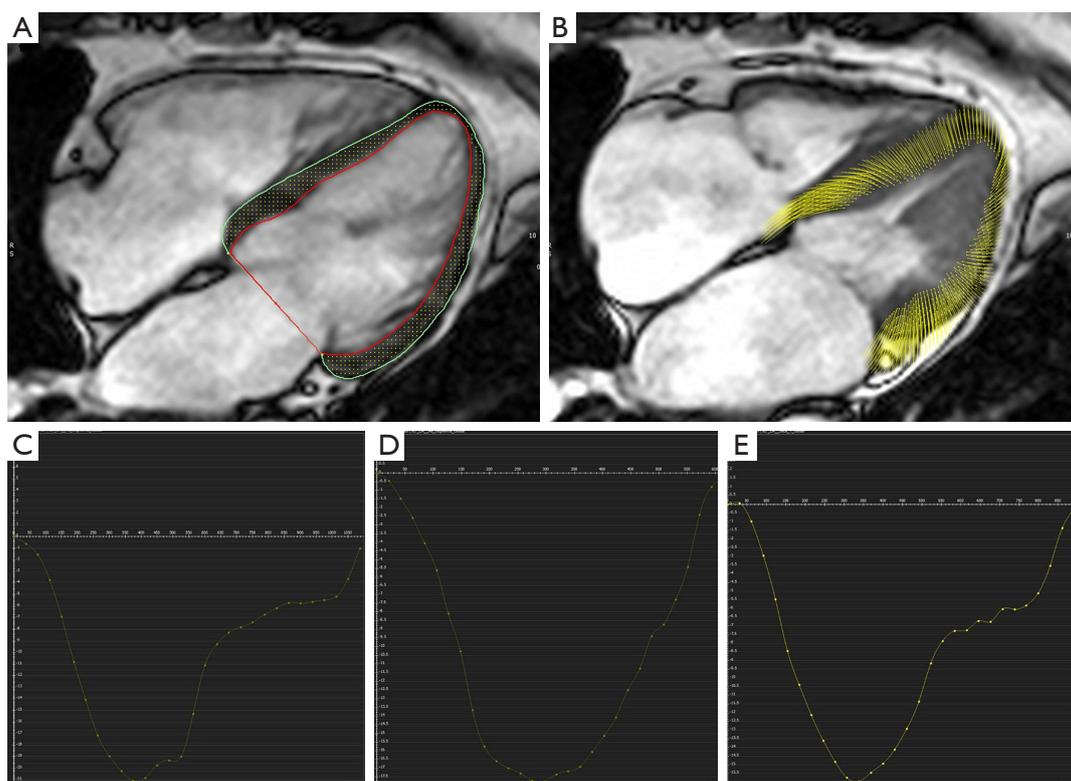


Figure 1 Feature tracking analysis demonstrating measurement of peak longitudinal strain (PLS) derived from LV contours in diastole (A) tracked through to systole (B); generating strain curves in a healthy control (C, PLS = -21), a patient with “no / mild” symptoms (D, PLS = -18) and a patient with “significant” symptoms (E, PLS = -16).

Standard ventricular and valvular assessment was performed as previously described (18).

CSPAMM analysis was performed using a dedicated tagging analysis package (inTag[®] software, Creatis, Lyon, France). Epicardial and endocardial contours were drawn for each slice. A mid-myocardial contour was automatically calculated and contours were propagated through all cardiac phases. Strain was measured in the mid-myocardial layer which has previously been reported to be the most reproducible (17). Peak circumferential LV strain was measured for the three slices at apex, mid-ventricle, and base. Peak systolic and diastolic LV strain rates were measured from the mid-ventricular slice.

Feature tracking analysis was performed using commercially available software (cvi42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Endocardial and epicardial contours were drawn on a long-axis 4-chamber cine using a semi-automated process (Figure 1). Peak LV longitudinal strain and systolic and diastolic strain rates were measured.

Statistical analysis

Continuous variables are presented as mean \pm SD. The Shapiro-Wilk test was used to determine normality. Frequencies are reported as number (%). The Student *t* test and Wilcoxon signed rank test were used to compare continuous variables as appropriate. All statistical analyses were performed using the PASW software package (V.21.0 SPSS, IBM, Chicago, Illinois, USA) with a two-sided significance level of $P < 0.05$ considered statistically significant.

Results

Study population

A total of 42 patients with severe AS were studied along with 13 healthy controls, matched for age, LVEF and body mass index (BMI) (Table 1). The patients with severe AS were further subdivided into two groups; those with “no/mild” symptoms (n=21), and those with “significant”

Table 1 Characteristics of AS patients and healthy controls

Characteristics	Severe AS (n=42)	Controls (n=13)	P Value*
Age (years)	71.8±6.1	68.8±4.0	0.100
Male gender, n (%)	31 (73.8)	2 (15.4)	0.001
BMI (kgm ⁻²)	27.4±4.1	28.8±4.2	0.283
Systolic BP (mmHg)	137±21	124±17	0.044
Diastolic BP (mmHg)	76±10	65±10	0.001
eGFR (mL/min/1.73 m ²)	74.2±14.0	82.7±17.3	0.082
LVEF (%)	57.8±11.0	61.2±4.3	0.282

Values are mean ± SD or n (%). *, P value for comparison between groups; AS, aortic stenosis; eGFR, estimated glomerular filtration rate; BMI, body mass index; LVEF, left ventricular ejection fraction.

Table 2 Comparison of AS patients with no/mild (NYHA I/II) and significant (NYHA III/IV) symptoms

Characteristics	“No/mild” symptoms (n=21)	“Significant” symptoms (n=21)	P value*
Age (years)	72.8±5.4	71.0±6.8	0.345
EuroSCORE II	1.90±1.7	1.31±0.4	0.302
Systolic BP (mmHg)	138.8±18.3	135.9±23.6	0.662
Diastolic BP (mmHg)	76.7±10.6	74.9±8.9	0.560
Peak aortic jet velocity (m/s)	4.0±1.3	4.5±0.5	0.177
Peak aortic PG (mmHg)	55.1±20.8	50.4±15.6	0.450
Mean aortic PG (mmHg)	45.8±16.4	46.0±8.8	0.977
AVA (cm ²)	0.95±0.6	0.71±0.2	0.194
PHT, n (%)	3 (14.3)	4 (19.0)	0.740
LVEF (%)	56.6±9.8	58.9±12.3	0.504
LVMI (g/m ²)	72.6±20.9	77.8±24.0	0.432
Mitral RF (%)	12.2±15.9	21.9±20.1	0.342
History of MI, n (%)	3 (14.3)	2 (9.5)	0.644
PCI, n (%)	0 (0)	1 (4.8)	0.329
CABG, n (%)	0 (0)	1 (4.8)	0.329

Values are mean ± SD or n (%). *, P value for comparison between groups; AS, aortic stenosis; PG, pressure gradient; AVA, aortic valve area; PHT, pulmonary hypertension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RF, regurgitant fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

symptoms (n=21). These two groups were comparable for age, surgical risk score, LV mass, measures of AS severity and history of ischaemic heart disease (*Table 2*). Across all three individual groups, average LVEF was above 50% (the defined cut-off for a class I indication for surgical valve replacement).

Comparison of healthy controls and severe AS

Compared to healthy controls matched for age and LVEF, patients with severe AS had significantly reduced (worse) peak longitudinal strain (PLS) (-17.1 ± 4.50 vs. -20.4 ± 2.04 , $P=0.001$). Similarly they exhibited significantly reduced (worse) peak circumferential strain at basal (-19.7 ± 5.8 vs. -23.9 ± 3.2 , $P=0.015$), mid (-21.3 ± 5.3 vs. -25.9 ± 3.8 , $P=0.005$) and apical (-20.3 ± 6.3 vs. -27.2 ± 3.0 , $P=0.001$) LV levels with significantly reduced peak circumferential systolic strain rate (-0.033 ± 0.009 vs. -0.039 ± 0.004 , $P=0.001$). Even patients with “no/mild” symptoms were found to have significantly worse strain parameters when compared with healthy controls (*Table 3*). Peak longitudinal systolic strain rates were an exception to this, being comparable between healthy volunteers and those with severe AS, regardless of symptom profile.

Comparison of severe AS patients reporting “no/mild” and “significant” symptoms

Compared to patients with “significant” symptoms, those reporting “no/mild” symptoms had statistically higher (better) peak longitudinal systolic strain rate (*Figure 2*), with comparable PLS and longitudinal diastolic strain rate. Peak circumferential strain at the basal, mid and apical LV levels and peak systolic and diastolic circumferential strain rates between the two symptom groups were also comparable (*Table 4*).

Discussion

This prospective two-centre study has comprehensively characterised LV mechanics using CMR in patients with severe AS and in healthy age-matched controls. Patients with severe AS exhibit diminished longitudinal and circumferential LV strain when compared to controls, despite preservation in LVEF. Importantly, we have demonstrated patients with severe AS and no or only minimal symptoms still exhibit LV systolic dysfunction that is comparable to those with significant symptoms who fulfil a class I indication for aortic valve surgery. CMR strain analysis may therefore have a future role in clarifying

Table 3 Comparison of markers of strain between healthy controls and *patients with “no/mild” symptoms, and †patients with “significant” symptoms

Strain parameter	Controls (n=13)	“No/mild” (n=21)	P Value*	“Significant” (n=21)	P value†
Peak circumferential strain (%)					
Base	-23.9±3.2	-19.9±4.6	0.010	-19.5±6.8	0.016
Mid	-25.9±3.8	-20.5±5.4	0.003	-22.1±5.2	0.028
Apex	-27.2±3.0	-19.8±5.9	0.001	-20.8±6.7	0.001
Peak circumferential strain rate (S ⁻¹)					
Systolic	-0.039±0.004	-0.033±0.011	0.021	-0.033±0.007	0.004
Diastolic	0.023±0.009	0.027±0.015	0.417	0.031±0.017	0.130
Peak longitudinal strain (PLS)					
Peak LS (%)	-20.406±2.041	-17.967±3.921	0.029	-16.337±4.937	0.002
PLS rate					
Systolic (%/s)	-98.1446±16.2573	-106.301±43.276	0.523	-83.352±24.802	0.067
Diastolic (%/s)	96.9319±20.6486	86.476±29.805	0.282	72.855±25.631	0.008

*, P value for comparison between controls and those with “no/mild” symptoms; †, P value for comparison between controls and those with “significant” symptoms.

patient selection for AVR, particularly when symptoms are equivocal, given the ability to detect LV functional decline in the AS disease process more sensitively than global LV ejection fraction.

Valvular AS is a slowly progressive disease and symptom onset can be insidious. However, in patients with preserved systolic function, it is the significance of symptoms that clinically determines referral for surgery. In the Euro Heart Survey, 24% of patients with severe AS presented with congestive heart failure and the use of medical therapy was frequent. These observations suggest a sizeable group of patients with severe AS were managed at an advanced stage of their disease process (16). Mild symptoms are often denied or erroneously dismissed to advancing age or an intercurrent illness (8) which may potentially reduce their survival. The Euro Heart Survey reflects real world practise in which equivocal symptom reporting in the context of high risk aortic valve surgery is frequently managed conservatively.

The origin of exercise intolerance or symptoms in patients with severe AS is poorly understood (19) and there is considerable variation in the degree of stenosis associated with symptom onset. In our study, patients with no/mild and significant symptoms were comparable in age, LVEF, LV mass, mitral regurgitation, presence of pulmonary

hypertension (PHT), history of coronary disease and aortic valve haemodynamics. It is notable LVEF is normal in most patients with severe AS, even when symptoms develop and that valve area and transvalvular gradients do not predict clinical outcomes following AVR (20). It can be challenging to clinicians to decipher a genuine change in symptoms attributable to AS. Similar to previous studies (19,21), our work highlights the need for novel objective measures of early LV decline that could guide a clinician to offering timely intervention.

This is the first study to use CMR strain analysis to attempt to differentiate patients with severe AS based on their symptomatic state. Our data suggests that those with significant symptoms (and thus clear surgical indication) have statistically worse peak longitudinal systolic strain rates than those with no/mild symptoms (in whom decision making can be challenging), despite other comparable measures of LV function by strain. Strain rate represents the rate of myocardial deformation and is an energy-requiring process (22). Compared with strain, it is less dependent upon pre-load, afterload and heart rate; and is representative of regional contractile function (23). Nonetheless, caution is required in interpreting this finding given the sample sizes, and larger study is required to clarify this reported depreciation of strain rate and its potential

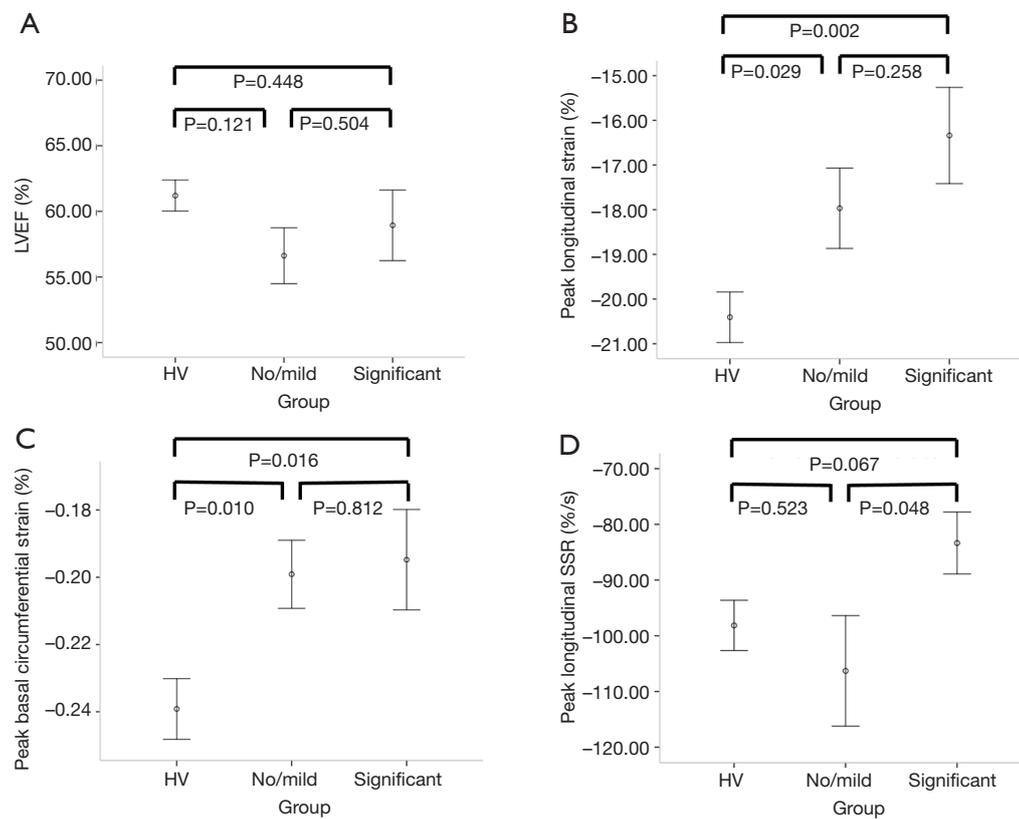


Figure 2 Error bars (mean and SE) of left ventricular ejection fraction (LVEF) (A), peak longitudinal strain (PLS) (B), peak basal circumferential strain (C) and peak longitudinal systolic strain rate (D) amongst healthy volunteers (HV), and those with no/mild and significant symptoms.

Table 4 Comparison of markers of strain between aortic stenosis (AS) patients with “no/mild” and “significant” symptoms

Strain parameter	“No / mild” (n=21)	“Significant” (n=21)	P value
Peak circumferential strain (%)			
Base	-19.9±4.6	-19.5±6.8	0.812
Mid	-20.5±5.4	-22.1±5.2	0.320
Apex	-19.8±5.9	-20.8±6.7	0.622
Peak circumferential strain rate (S ⁻¹)			
Systolic	-0.033±0.011	-0.033±0.007	0.791
Diastolic	0.027±0.015	0.031±0.017	0.400
Peak longitudinal strain (PLS)			
Peak LS (%)	-17.967±3.921	-16.337±4.937	0.258
PLS rate			
Systolic (%/s)	-106.301±43.276	-83.352±24.802	0.048
Diastolic (%/s)	86.476±29.805	72.855±25.631	0.134

impact on clinical surveillance.

Our study using CMR strain analysis compares with other studies using echocardiography to evaluate LV function in patients with severe AS. Longitudinal strain appears invariably depressed with a number of reports indicating reduced circumferential strain also (9,21,24). Our patients with severe AS all had reduced circumferential strain when compared to age matched healthy controls with comparable ejection fraction. Previous CMR work has indicated pronounced myocardial steatosis is present in severe AS, and is independently associated with the degree of circumferential strain impairment, regardless of symptom state (25). Our work suggests lower longitudinal and circumferential strain is inherent to patients with severe AS irrespective of symptom status. As such, an incidental depressed strain measurement may not reliably position a patient in the disease timeline. Clinically, surveillance imaging will help objectively assess decline, and in particular deterioration of longitudinal systolic strain rate, may suggest loss of compensation and trigger surgical referral despite a normal LVEF.

Our study using CMR confirms severe valvular AS confers a chronic pressure overload that is detrimental to myocardial fibre function. This subtle detection of both systolic and diastolic LV dysfunction even in those with no or mild symptoms may explain previous findings that early elective AVR in asymptomatic patients affords beneficial early and late outcomes (26,27). It is noteworthy that delayed surgical treatment is the principal determinant of reduced late survival (27). Our observation of comparable impairment between those with significant symptoms, in whom AVR is clearly indicated, and those with no/mild symptoms suggests referral for surgery based on assessment of LV mechanics (and thus earlier than current guidelines would recommend) could avert a delay of prognostic importance. Indeed, our observation is noteworthy in light of recent data. In a sizeable multicentre registry comprising 3,815 patients, conservative management of asymptomatic severe AS patients was associated with a dismally higher incidence of mortality and hospital admission at 5 years when compared with an initial AVR approach (28). It is entirely possible the poor outcomes in these reportedly “asymptomatic” patients related to advanced subclinical LV dysfunction comparable to those with symptoms who would ordinarily have been intervened upon earlier.

A number of studies indicate the clinical importance of longitudinal strain measurement in patients with severe AS. It has the potential to predict recovery of LV

dysfunction following surgery (9), the requirement for AVR in the future (29) and also independently predict all-cause mortality (30). Recently, deteriorating LV global longitudinal strain has also demonstrated incremental prognostic value in addition to symptom profile and surgical risk scoring; being superior to measures of aortic pressure gradient (PG) and stroke volume (13). Our study reflects this observation; demonstrating both longitudinal and circumferential strains are sensitive in detecting pathology before they are evident on conventional history taking. Given our observation of similar longitudinal strain between those with no/mild symptoms and those with significant symptoms, our study indicates the need to measure longitudinal strain in patients with ill-defined symptoms to determine whether they potentially fall into the same prognostic group as those with a manifest requirement for AVR.

Limitations

This was an observational study and associations do not prove causality. Our study population was relatively small and included patients with coronary artery disease and hypertension, rather than being restricted to isolated AS. This is however generalizable to real world clinical practice and reduces the effect of selection bias. Given the potential for type I statistical errors, our findings should be validated in a larger patient population to confirm any future clinical utility. We have used feature tracking, rather than CSPAMM, for the analysis of longitudinal strain. Tissue tagging is hampered by a lower temporal resolution and tag fading during diastole and feature tracking to determine longitudinal strain has demonstrated good reproducibility in patients with severe AS (31). Thresholds for normal versus pathological strain and strain rates may vary with different analysis software and pulse sequence acquisitions; thus our absolute values may not be translatable to other acquisition/analysis platforms.

Conclusions

In conclusion, LV deformation assessment using CMR offers a potentially valuable non-invasive assessment of patients with severe AS, more sensitive than the elucidation of symptoms at detecting a decline in LV performance. Patients with no or only mild symptoms exhibit comparable reduction in circumferential and longitudinal fibre function to those with significant symptoms in whom AVR

is clearly indicated. Thus, CMR characterisation of LV strain may guide optimal decision making when caring for asymptomatic patients or those with borderline symptoms. Future larger prospective studies are needed to validate this interesting observation.

Acknowledgements

The authors thank Mrs Fiona Richards and Ms Petra Bijsterveld for their immense help in patient recruitment.

Funding: This study was part-funded by the British Heart Foundation (PG/11/126/29321) and also the National Institute for Health Research (NIHR) Leeds Clinical Research Facility. GP McCann is supported by a NIHR career development fellowship.

Footnote

Conflicts of Interest: The authors declare no conflicts of interest.

Ethical Statement: The study was approved by a national ethics committee (REC 08/H1307/106), complied with the Declaration of Helsinki and written informed consent was provided by participants.

Disclaimer: The views expressed are those of the author(s) and not necessarily those of the NHS, NIHR or the Department of Health.

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Cite this article as: Musa TA, Uddin A, Swoboda PP, Garg P, Fairbairn TA, Dobson LE, Steadman CD, Singh A, Erhayiem B, Plein S, McCann GP, Greenwood JP. Myocardial strain and symptom severity in severe aortic stenosis: insights from cardiovascular magnetic resonance. *Quant Imaging Med Surg* 2017;7(1):38-47. doi: 10.21037/qims.2017.02.05