


# Impact of arterio–ventricular interaction on first-phase ejection fraction in aortic stenosis

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## Aims

First-phase ejection fraction (EF1), the EF at the time to peak aortic jet velocity, has been proposed as a novel marker of peak systolic function in aortic stenosis (AS). This study aimed to explore the association of myocardial contractility and arterial load with EF1 in AS patients.

## Methods and results

Data from a prospective, cross-sectional study of 114 patients with mild, moderate, and severe AS with preserved left ventricular EF (>50%) were analysed. EF1 was measured as the volume change from end-diastole to the time that corresponded to peak aortic jet velocity. Myocardial contractility was assessed by strain rate measured by speckle tracking echocardiography. Arterial stiffness was assessed by central pulse pressure/stroke volume index ratio (PP/SVi). The total study population included 48% women, median age was 73 years, and mean peak aortic jet velocity was 3.47 m/s. In univariable linear regression analyses, lower EF1 was associated with higher age, higher peak aortic jet velocity, lower global EF, lower global longitudinal strain, lower strain rate, and higher PP/SVi. There was no significant association between EF1 and heart rate or sex. In multivariable linear regression analysis, EF1 was associated with lower strain rate and higher PP/SVi, independent of AS severity. Replacing PP/SVi by valvular impedance did not change the results.

## Conclusion

In patients with AS, reduced myocardial contractility and increased arterial load were associated with lower EF1 independent of the severity of valve stenosis.

## Keywords

aortic stenosis • ejection fraction • myocardial function • arterial stiffness

## Introduction

Aortic stenosis (AS) is the most common cause of aortic valve replacement in developed countries.<sup>1,2</sup> Once symptoms occur or there is a reduction in left ventricular ejection fraction (LVEF) <50%, the current guidelines recommend aortic valve intervention.<sup>3,4</sup> The transition to symptoms partly reflects maladaptive compensatory mechanisms,<sup>5</sup> particularly characterized by myocardial fibrosis which may not reverse following aortic valve replacement.<sup>6</sup>

Experimental research has suggested that when systolic function is impaired in early systole an intrinsic mechanism may exist to preserve LVEF, but at the expense of a slower and sustained contraction.<sup>7,8</sup>

However, in AS it is well known that LVEF may be preserved by compensatory remodelling and hypertrophy,<sup>9</sup> despite reduced myocardial contractility.<sup>10</sup> Recently, the first-phase EF (EF1), a measurement of the LVEF at the time of peak aortic jet velocity, has emerged as a novel marker of early LV systolic impairment both in hypertension and AS patients.<sup>11,12</sup> Early and accurate recognition of subclinical LV systolic dysfunction offers the potential to optimize the timing of intervention in AS. In patients with moderate or severe AS, lower EF1 showed incremental prognostic value compared with LVEF and global longitudinal strain.<sup>12</sup> However, more information on the underlying factors influencing EF1 is needed. In particular, the interaction between EF1 with myocardial contractility and increased

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arterial load needs further exploration. Increased arterial load is highly prevalent in AS patients due to higher age, hypertension, and large arterial stiffening. Previous studies have documented the association of arterial stiffness with impaired myocardial function.<sup>13</sup> This study aimed at exploring the associations between myocardial contractility and arterial load with EF1 in AS.

## Methods

### Study population

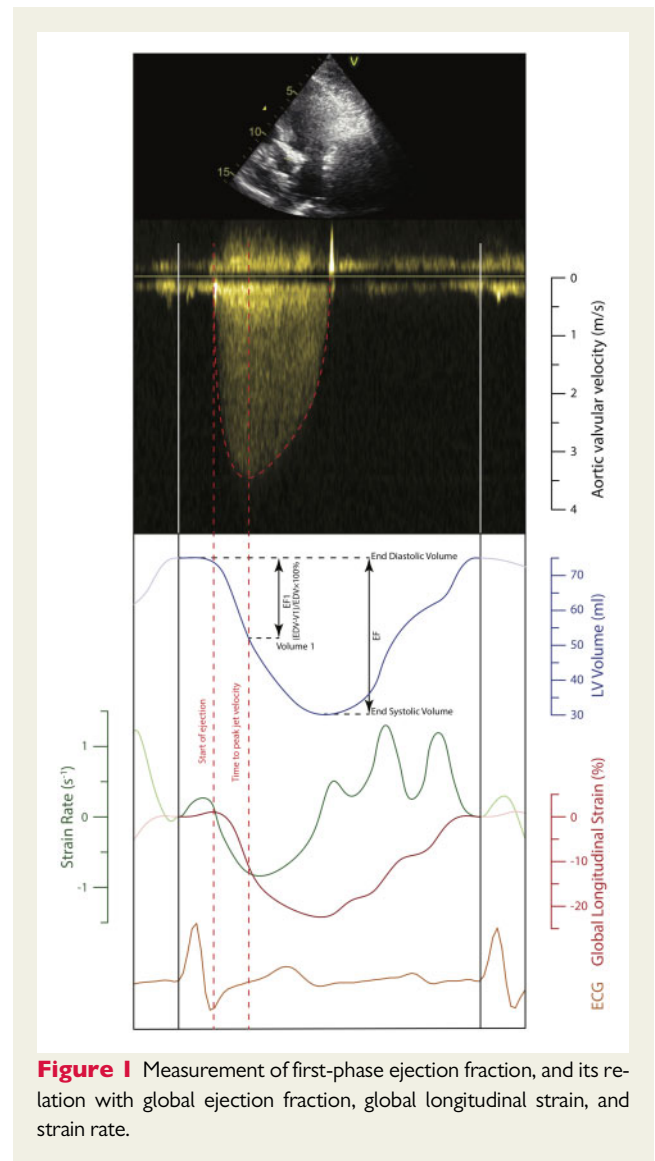
We prospectively recruited 120 patients with AS from the outpatient clinic, Department of Heart Disease, Haukeland University Hospital, Bergen, Norway, between October 2015 and December 2017. Patients were considered eligible if they had at least mild AS defined as aortic valve thickening and peak aortic jet velocity >2 m/s. Exclusion criteria were cardiac arrhythmias, prior pacemaker implantation, other concomitant valvular disease of more than moderate grade, known coronary artery disease (myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention), or previous cardiac surgery. Patients with reduced LVEF (<50%) ( $n = 3$ ) were excluded from the present analysis. The study was approved by the local Regional Committee for Medical and Health Research Ethics, and was conducted in accordance with the Declaration of Helsinki. All patients signed a written informed consent prior to study examinations.

### Cardiovascular risk factors

Following inclusion, all participants underwent a clinical examination at the outpatient clinic. Before the echocardiographic examination, brachial blood pressure (BP) was measured in triplicate with 1-minute intervals after an initial 5 minute rest in the seated position using a regularly calibrated aneroid sphygmomanometer and appropriate cuff size.<sup>14</sup> The average of the last two measurements was taken as the clinic BP. Hypertension was defined as use of antihypertensive medication, history of hypertension, or clinical BP  $\geq 140/90$  mmHg. Self-reported health was recorded on a standardized questionnaire including information on cardiovascular risk factors, medication, and known diseases and was quality assured by study personnel.

### Echocardiography

A standardized transthoracic echocardiogram was performed in all patients using a Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway). Digital images were stored and analysed at the Bergen Echocardiographic Core Laboratory using TomTec workstations equipped with Image Arena 4.6 soft-ware (TomTec, Unterschleissheim, Germany). Conventional measurements in all studies were first analysed by the same reader (E.E.) and later proof-read by an experienced reader (E.G.). Quantitative assessment of the LV and AS severity were performed according to the joint European Association of Echocardiography and American Society of Echocardiography recommendations.<sup>3,15</sup> LV mass was calculated using the Devereux formula, and indexed to body height in the allometric power of 2.7 to obtain LV mass index.<sup>16</sup> LV hypertrophy was defined by the prognostically validated cut-off values of LV mass index  $>49.2$  g/m<sup>2.7</sup> in men and LV mass index  $>46.7$  g/m<sup>2.7</sup> in women.<sup>16</sup> LVEF was calculated using the Simpson biplane method. Peak aortic jet velocity was measured from different acoustic windows including the use of a stand-alone probe, and the highest velocity was used for tracing of the time-velocity integral. The effective aortic orifice area was calculated by the continuity equation. Mild AS was defined as peak aortic jet velocity of 2.0–2.9 m/s, moderate AS as peak aortic jet velocity of 3.0–3.9 m/s, and severe AS as peak aortic jet velocity  $\geq 4.0$  m/s.



**Figure 1** Measurement of first-phase ejection fraction, and its relation with global ejection fraction, global longitudinal strain, and strain rate.

Stroke volume (SV) was assessed by Doppler and indexed for body surface area, as recommended by the guidelines.<sup>4</sup> Central pulse pressure (PP) was estimated using a validated formula: brachial PP  $\times 0.49 + \text{age} \times 0.30 + 7.11$ .<sup>17,18</sup> Arterial stiffness was estimated by the ratio from central PP/SV index (PP/SVi).<sup>17</sup> Global LV load was assessed from valvuloarterial impedance ( $Z_{va}$ ), calculated as systolic BP + mean aortic pressure gradient/SVi.<sup>19</sup> Peak systolic annular velocities were measured by tissue Doppler imaging at the medial and lateral annulus, and averaged to obtain peak  $S'$ .

EF1 was measured by the biplane method of discs by measuring the volume change from end-diastole to the time that corresponded to peak aortic jet velocity by spectral Doppler. EF1 was thus derived by:

$$EF1 = \frac{(EDV - V1)}{EDV}$$

where EDV is the LV volume at end-diastole and V1 is the LV volume at the time corresponding to peak aortic jet velocity in the cardiac cycle (Figure 1).<sup>12</sup> EF1 was measured manually at the exact frame of peak aortic

**Table 1** Clinical characteristics across patients with mild, moderate, and severe AS

	Mild (n = 38)	Moderate (n = 44)	Severe (n = 32)	P (ANOVA)
Age (years)	72 ± 10	71 ± 12	76 ± 9	0.133
Sex (male)	45%	57%	47%	0.513
Systolic blood pressure (mmHg)	153 ± 25	146 ± 18	143 ± 15	0.063
Diastolic blood pressure (mmHg)	84 ± 11	83 ± 7	79 ± 9*	0.036
Heart rate (bpm)	66 ± 10	68 ± 9	71 ± 12	0.119
Body surface area (m <sup>2</sup> )	1.89 ± 0.19	1.91 ± 0.24	1.84 ± 0.23	0.278
Weight (kg)	78 ± 14	78 ± 18	72 ± 16	0.159
Height (cm)	170 ± 10	171 ± 9	170 ± 9	0.803
Body mass index (kg/m <sup>2</sup> )	26.9 ± 4.1	26.6 ± 4.6	25.0 ± 3.8	0.066
Hypertension, n (%)	33 (90)	40 (91)	29 (88)	0.912
Diabetes, n (%)	5 (13)	6 (14)	2 (6)	0.563
Current smokers, n (%)	1 (3)	4 (9)	3 (9)	0.109
Symptoms, n (%)	0 (0)	7 (16)	9 (28)*	0.011
NYHA functional class, n (%)				
2	0 (0)	6 (14)	8 (25)	
3	0 (0)	1 (2)	1 (3)	
Hypercholesterolaemia, n (%)	7 (18)	9 (20)	7 (22)	0.938

NYHA, New York Heart Association; bpm, beats per minute.

\*P < 0.05 vs. mild AS.

jet velocity by taking into account the frame rate and time in milliseconds from aortic valve opening to peak aortic jet velocity.

Two-dimensional speckle tracking echocardiography and EF1 analyses were performed offline on a dedicated workstation equipped with EchoPac BT 202 (GE Vingmed Ultrasound, Horten, Norway), using apical two-, three-, and four-chamber views with frame rate optimized to 60–90 frames/s (median 74 frames/s, mean 73 frames/s). The endocardial border of the LV was traced, and the region of interest was adjusted at the epicardial border per segment, as appropriate. After software processing, tracking quality was checked visually, and all segments were adjusted manually if needed. The time of aortic valve closure was measured from a pulsed wave Doppler recording in the LV outflow tract, and was defined as the end of systole. Drift compensation was used during analysis, and smoothing parameters were kept at default. Global longitudinal strain was calculated as the average peak negative longitudinal shortening from the 18 LV segments. Longitudinal strain rate values from the 18 LV segments were averaged to obtain peak systolic strain rate.

Diastolic function was defined in accordance with current guidelines,<sup>20</sup> if at least three of the following parameters were present: reduced annular  $e'$  velocity by tissue Doppler (septal  $e' < 7$  cm/s or lateral  $e' < 10$  cm/s); early transmitral E-wave/average mitral annular velocity ratio ( $E/e'$ ) > 14; biplane left atrial volume index > 34 mL/m<sup>2</sup>; tricuspid regurgitant jet velocity > 2.8 m/s.

### Statistical analyses

Statistical analyses were performed using IBM SPSS version 25.0 (IBM, Armonk, NY, USA). The study population was divided into three groups: mild, moderate, and severe AS. Findings are reported as mean ± standard deviation for continuous variables and as percentages for categorical variables. Normal distribution was checked prior to analyses by Q–Q plots and normality tests (Kolmogorov–Smirnov). Groups were compared by analysis of variance (ANOVA) with Scheffe's post-hoc test for continuous

variables and by general linear model with Sidak's post-hoc test for categorical variables, respectively. Covariates of EF1 were identified in univariable and multivariable linear regression analyses using an enter or stepwise procedure. The core assumptions of normality of the error distribution, homoscedasticity, and linearity were tested and not violated. Multicollinearity was assessed by the variance of inflation factor. Results are presented as standardized  $\beta$ -coefficients and  $P$  values. Goodness of fit is expressed as the adjusted  $R^2$ . Independent covariates of EF1 < 25% were tested in univariable and multivariable binary logistics regression analyses. Results are presented as odds ratio (OR) and 95% confidence interval (CI). Goodness of fit was tested with Hosmer–Lemeshow's test. For intra- and interobserver variability, intraclass correlation coefficients were calculated to assess agreement between EF1 measurements. Intra- and interobserver variability of EF1 measurements were assessed in 18 randomly selected subjects by repeated analyses 3 months after initial reading. A two-tailed  $P$  value < 0.05 was considered statistically significant in all analyses.

### Results

A total of 120 patients (48% women) were recruited and median age was 73 years (age range 31–94 years). Six patients were excluded, three because of suboptimal echocardiographic images, and three due to reduced LVEF (< 50%), leaving 114 patients eligible for the inclusion in the present analysis. 16 patients (nine with severe AS and seven with moderate AS) had mild symptoms. Among those with symptomatic severe AS, six patients received aortic valve intervention, one patient was offered aortic valve replacement but declined, while two patients were considered not eligible for valve replacement due to severe comorbidities including cancer. The prevalence

**Table 2** Echocardiographic characteristics across patients with mild, moderate, and severe AS

	Mild (n = 38)	Moderate (n = 44)	Severe (n = 32)	P (ANOVA)
Peak aortic jet velocity (m/s)	2.5 ± 0.3	3.5 ± 0.3*	4.6 ± 0.5**	<0.001
Mean aortic gradient (mmHg)	13 ± 3.5	26 ± 4.1*	50 ± 13**	<0.001
Aortic valve area (cm <sup>2</sup> )	1.83 ± 0.34	1.26 ± 0.32*	0.91 ± 0.21**	<0.001
Zva (mmHg/mL/m <sup>2</sup> )	2.9 ± 0.8	3.3 ± 0.9	3.6 ± 0.8*	0.001
LV end-diastolic diameter (mm)	47 ± 6	47 ± 6	45 ± 6	0.246
LV end-systolic diameter (mm)	31 ± 5	31 ± 5	29 ± 5	0.116
Septal wall thickness (mm)	13 ± 2	13 ± 3	16 ± 3**	<0.001
Posterior wall thickness (mm)	9 ± 1	10 ± 2	11 ± 2*	0.014
Relative wall thickness	0.41 ± 0.08	0.42 ± 0.09	0.48 ± 0.10**	0.003
LV hypertrophy (%)	34	39	56	0.151
LV mass (g)	195 ± 59	198 ± 65	235 ± 90	0.040
LV mass index (g/m <sup>2.7</sup> )	46.2 ± 11.9	45.6 ± 11.6	54.8 ± 16.0**	0.006
PP/SVi (mmHg/mL/m <sup>2</sup> )	1.19 ± 0.29	1.17 ± 0.34	1.20 ± 0.28	0.922
Meridional end-systolic stress (dyne/cm <sup>2</sup> )	179 ± 37	184 ± 42	192 ± 41	0.376
Systolic function				
Global ejection fraction (%)	63 ± 4	62 ± 5	64 ± 5	0.216
Global longitudinal strain (%)	-20.5 ± 2.0	-20.0 ± 2.3	-19.1 ± 3.2	0.061
Peak S' (cm/s)	8.1 ± 1.6	7.8 ± 1.2	7.0 ± 1.2**	0.002
Stroke volume index (mL/m <sup>2</sup> )	55 ± 10	52 ± 10	55 ± 11	0.319
Global longitudinal strain rate (s <sup>-1</sup> )	-1.05 ± 0.16	-1.03 ± 0.15	-0.94 ± 1.17*	0.017
Mechanical dispersion (ms)	44 ± 12	43 ± 17	57 ± 21**	0.001
First-phase ejection fraction (%)	31 ± 4	30 ± 4	27 ± 4**	<0.001
Diastolic function				
Filling pressure (E/e')	11.1 ± 5.5	12.4 ± 5.2	13.9 ± 4.6*	0.010
Peak e' (cm/s)	6.9 ± 1.6	6.9 ± 1.5	5.7 ± 1.2**	<0.001
Tricuspid jet (m/s)	2.47 ± 0.47	2.59 ± 0.33	2.54 ± 0.38	0.460
Left atrial volume index (mL/m <sup>2</sup> )	33.5 ± 8.5	36.0 ± 12.3	38.9 ± 11.6	0.139
Diastolic dysfunction, n (%)	5 (11)	13 (30)	11 (36)*	0.036
Ejection dynamics				
Acceleration time (ms)	78 ± 17	93 ± 18*	111 ± 15**	<0.001
Ejection time (ms)	314 ± 31	313 ± 27	323 ± 36	0.353
Acceleration/ejection time ratio	0.25 ± 0.05	0.30 ± 0.05*	0.35 ± 0.05**	<0.001

LV, left ventricular; ms, milliseconds; PP/SVi, pulse pressure/stroke volume index; Zva, valvuloarterial impedance.

\*P < 0.05 vs. mild AS

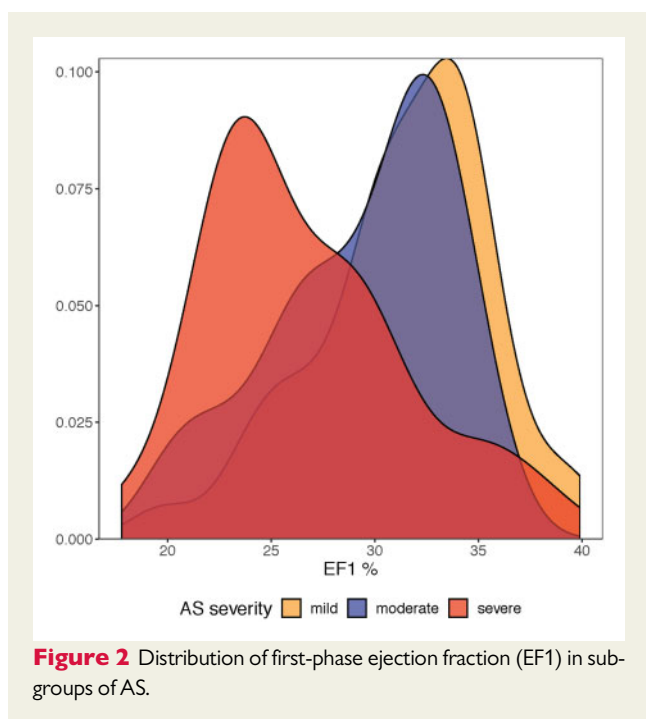
\*\*P < 0.05 vs. mild and moderate AS.

of hypertension was 89.5%, diabetes 11.4%, hypercholesterolemia 46.5%, and diastolic dysfunction 25.4%. Clinical characteristics between groups of mild, moderate, and severe AS did not differ, except for diastolic BP which was lower in patients with severe AS (Table 1).

Patients with severe AS had significantly higher LV mass index and relative wall thickness (both  $P < 0.05$ ). Global longitudinal strain, LVEF, and SVi did not differ between groups (Table 2). Indices of peak LV systolic function, including acceleration time, strain rate, and EF1 all progressively declined from mild to severe AS (all  $P < 0.05$ ) (Table 2 and Figure 2). Filling pressure ( $E/e'$ ) increased in parallel with the increasing AS severity grade ( $P < 0.05$ ).

The intraclass correlation coefficient for EF1 was 0.94 (95% CI 0.85–0.98) for intra-observer variability and 0.88 (95% CI 0.67–0.95) for interobserver variability, reflecting excellent reproducibility. In univariable linear regression analyses in the total study population,

lower EF1 was associated with higher LV mass index, older age, and end-systolic wall stress (Table 3). Lower EF1 was also associated with lower global longitudinal strain, lower strain rate, and with higher peak aortic jet velocity. Higher EF1 was associated with a higher peak S'. In bivariate analyses, EF1 was negatively correlated with higher Zva ( $r = -0.33$ ,  $P < 0.001$ ), PP/SVi ( $r = -0.29$ ,  $P = 0.002$ ), higher central PP ( $r = -0.29$ ,  $P = 0.002$ ), higher brachial PP ( $r = -0.25$ ,  $P = 0.009$ ), and with symptoms ( $r = -0.34$ ,  $P < 0.001$ ). No association between hypertension and EF1 was detected ( $P = 0.123$ ). In multivariable linear regression, lower EF1 was associated with lower strain rate independent of age, peak aortic jet velocity, LV mass index, diastolic dysfunction, and LVEF (Table 3, Model 1). In Model 2, lower EF1 was associated with higher PP/SVi independent of age, peak aortic jet velocity, LVEF, and global longitudinal strain (Table 3). Replacing PP/SVi by Zva did not change the results. In Model 3, we included all



significant variables from the univariable analyses in a stepwise procedure. Lower strain rate, higher peak aortic jet velocity and higher PP/SVi all remained as significant and independent covariates of EF1 (all  $P < 0.05$ ) (Table 3). Higher acceleration time was also associated with lower EF1 in univariable analysis ( $\beta = -0.46$ ,  $P < 0.001$ ). Due to a strong collinearity between peak aortic jet velocity and acceleration time, these two variables were not included in the same multivariable model. However, replacing peak aortic jet velocity with acceleration time in secondary models, did not change the results, and the association between EF1 and acceleration time remained significant in all multivariable models (data not shown). When restricting analyses only to moderate and severe AS groups, the association between PP/SVi and EF1 in multivariable stepwise regression became stronger ( $\beta = -0.35$ ,  $P < 0.001$ ), the association between peak velocity and EF1 slightly attenuated ( $\beta = -0.27$ ,  $P = 0.006$ ), while the association between EF1 and strain rate remained unchanged ( $\beta = -0.39$ ,  $P < 0.001$ ).

In univariable logistic regression analysis, EF1  $< 25\%$  was associated with higher mechanical dispersion (OR = 1.03,  $P = 0.022$ ), but after multivariable adjustment the association was attenuated ( $P > 0.05$ ). In multivariable logistic regression analysis, EF1  $< 25\%$  shared the same covariates as for EF1 in a continuous scale (Table 4).

## Discussion

The detection of early myocardial dysfunction in AS may be challenging. After the development of symptoms, there is a sharp increase in the risk of irreversible myocardial damage and mortality. Irreversible myocardial damage is often referred to as midwall fibrosis on late gadolinium enhanced cardiac magnetic resonance imaging, which is common in AS and reduces the survival benefit of aortic valve

replacement.<sup>21</sup> EF1, a measure of peak systolic LV function, has been shown to predict outcome more precisely than the traditional markers of end-systolic LV function like LVEF and global longitudinal strain in patients with AS.<sup>12</sup> The present study adds to previous knowledge by demonstrating that EF1 progressively declined with increasing AS severity, and that lower EF1 was associated with lower global longitudinal strain rate and higher PP/SVi independent of AS severity.

### The association between EF1 and strain rate

Cardiomyocyte contraction occurs predominantly in the first part of systole and peaks approximately at the time of peak aortic jet velocity. It has been demonstrated that strain rate and peak aortic jet velocity are almost simultaneous events in the cardiac cycle,<sup>22</sup> and their respective timing intervals in early systole corresponds well with peak force development in individual cardiomyocytes.<sup>23</sup> In line with these findings, we observed a closer association between EF1 and peak strain rate than with global longitudinal strain and EF1 in the present study.

Even though strain rate does not directly measure peak myocardial contraction *per se*, the relationship between strain rate and contractility has been shown in an experimental pig model.<sup>24</sup> Weidemann *et al.* demonstrated that while strain rate was related to contractility, global longitudinal strain was more closely related to SV and LVEF.<sup>25</sup> EF1 and strain rate are measures of peak systolic performance, and are therefore less load dependent, and more closely related to contractility, which is in line with our findings. In contrast, end-systolic measures, such as LVEF and global longitudinal strain, are more associated with maximal LV load which is reached in late systole. As demonstrated by our results, EF1 showed a progressive reduction from mild to severe AS while LVEF remained within the normal range across all grades of AS severity. Similarly, EF1 was also closely related to peak  $S'$ , a reliable marker of systolic function that has been closely related to contractility.<sup>26</sup>

Peak systolic indices are also better markers of changes in inotropic alterations.<sup>26</sup> Strain rate often remains constant during an increase in heart rate, suggesting that it is relatively independent of heart rate variations.<sup>25</sup> Similarly, no correlation between heart rate and EF1 was detected in this study.

Strain rate has been shown to be affected by both preload and afterload, but to a lesser degree than end-systolic markers.<sup>27</sup> In this regard, it is inevitable that EF1 to a certain degree is load dependent due to its close correlation with strain rate. This is reflected by our findings, as EF1 remained associated with peak strain rate independent of both PP/SVi and AS severity, together representing the total arterial- and valvular load on the LV. Thus, lower EF1 is not just a consequence of afterload excess, but reflects impairment in intrinsic myocardial systolic contractility. These results are in line with previous research demonstrating that in severe AS patients, the ratio between wall stress and LVEF is significantly reduced, indicating reduced contractility.<sup>28</sup> This highlights the fact that watchful waiting for spontaneous symptoms in some patients with severe AS may lead to irreversible damage in LV myocardium. As recommended by the guidelines, valve replacement is recommended in patients with asymptomatic very severe AS (peak jet velocity  $> 5.5$  m/s).<sup>3,29</sup> We

**Table 3** Linear regression analyses of covariates of first-phase ejection fraction

	Univariable		Multivariable model 1		Multivariable model 2		Multivariable model 3	
	Standardized $\beta$ coefficient	P value	Standardized $\beta$ coefficient	P value	Standardized $\beta$ coefficient	P value	Standardized $\beta$ coefficient	P value
Global longitudinal strain rate ( $s^{-1}$ )	-0.50	<0.001	-0.38	<0.001			-0.40	<0.001
PP/SVi (mmHg/mL/m <sup>2</sup> )	-0.29	0.002			-0.27	0.003	-0.28	<0.001
Peak aortic jet velocity (m/s)	-0.41	<0.001	-0.26	0.003	-0.36	<0.001	-0.33	<0.001
Age (years)	-0.28	0.003	-0.20	0.021	-0.11	0.241	NS	NS
Global ejection fraction (%)	0.18	0.059	0.13	0.106	0.15	0.059	NS	NS
Left ventricular mass index (g/m <sup>2.7</sup> )	-0.24	0.011	-0.02	0.833			NS	NS
Diastolic dysfunction (yes/no)	-0.29	0.002	-0.09	0.284			NS	NS
Filling pressure ( $E/e'$ )	-0.27	0.004					NS	NS
Global longitudinal strain (%)	-0.40	<0.001			-0.28	0.001	NS	NS
Peak $S'$ (cm/s)	0.46	<0.001					NS	NS
End-systolic wall stress (dyne/cm <sup>2</sup> )	-0.26	0.005					NS	NS
Acceleration time (ms)	-0.46	<0.001					NS	NS
Body mass index (kg/m <sup>2</sup> )	0.18	0.060					NS	NS
Heart rate (bpm)	-0.07	0.469					NS	NS
Hypertension (yes/no)	-0.15	0.123					NS	NS
Mechanical dispersion (ms)	-0.15	0.127					NS	NS
Systolic blood pressure (mmHg)	-0.15	0.077					NS	NS
Zva (mmHg/mL/m <sup>2</sup> )	-0.33	<0.001					NS	NS
Relative wall thickness ratio	-0.12	0.188					NS	NS
Posterior wall thickness (mm)	-0.20	0.033					NS	NS
Septal wall thickness (mm)	-0.21	0.027					NS	NS
Acceleration/ejection time ratio	-0.38	<0.001					NS	NS

Model 1, multiple  $R^2$  0.37,  $P < 0.001$ ; Model 2, multiple  $R^2$  0.37,  $P < 0.001$ ; Model 3, multiple  $R^2$  0.40,  $P < 0.001$ . Model 1: multivariable model of the association between EF1 and global longitudinal strain rate. Model 2: multivariable model of the association between EF1, global longitudinal strain and PP/SVi. Model 3: multivariable stepwise regression model, including all significant variables from univariable analyses.

ms, milliseconds; NS, not significant; bpm, beats per minute; PP/SVi, pulse pressure/stroke volume index; Zva, valvulo-arterial impedance.

hypothesize that EF1 could be particularly useful in this setting as a sensitive and prognostically validated tool to guide treatment decisions in patients with asymptomatic severe AS and normal LVEF in the future.

## The association between EF1 and arterial stiffness

In AS, increased LV load is caused by combined arterial and valvular resistance. Increased arterial load in AS is commonly caused by hypertension and/or increased arterial stiffness.<sup>19,30</sup> Interestingly, in this study higher PP/SVi, a surrogate of arterial stiffness, was identified as an important covariate of EF1. In patients with arterial stiffness, the reflected-wave reaches the proximal aorta in early systole, boosting systolic BP and increasing myocardial oxygen demand.<sup>20</sup> Early wave reflections increase the pulsatile load in mid-systole, and may occur at the time corresponding to EF1. This underlines the importance of time-varying systolic load on LV function. The increased tension in early systole might prolong contraction, preserving LVEF at the expense of an impaired early systolic function and diastolic relaxation. We corroborate previous findings by demonstrating a significant univariable relationship between EF1 and filling pressure.<sup>11</sup>

In our data, EF1 correlated better with the estimated central PP than with brachial PP. This is in line with previous findings which showed that central aortic PP was a better predictor of target organ damage.<sup>31</sup> Higher PP/SVi has also been demonstrated as an independent predictor of cardiovascular events and all-cause mortality in hypertensive patients.<sup>32</sup> Furthermore, one could speculate that the arterio-ventricular coupling demonstrated in the current study, could contribute to the observed impaired prognosis in AS patients with reduced arterial compliance.<sup>18</sup>

## Limitations

This study was small and performed in AS patients with acceptable image quality, and assessment may be less feasible and reproducible in patients with poor acoustic windows. In addition, cause-effect relations cannot be determined due to the cross-sectional study design. PP/SVi is an echocardiographic surrogate of arterial stiffness. The relationship between EF1 and a more direct and accurate measure of arterial stiffness, such as the gold standard pulse wave velocity, should be tested in larger outcome studies in the future.

EF1 was significantly associated with self-reported symptoms. However, the true prevalence of symptoms in our study cohort may have been underestimated since a treadmill exercise test was not

**Table 4** Uni- and multivariable logistic regression analyses of covariates of first-phase ejection fraction <25%

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
PP/SVi (mmHg/mL/m <sup>2</sup> ) (per 1SD)	1.61 (1.05–2.48)	0.029	1.89 (1.08–3.31)	0.026
Strain rate (s <sup>-1</sup> ) (per 1SD decline)	2.74 (1.59–4.77)	<0.001	2.56 (1.57–5.54)	0.003
Peak aortic jet velocity (m/s)	3.08 (1.74–5.44)	<0.001	2.95 (1.57–5.54)	0.001
Diastolic dysfunction (yes/no)	4.36 (1.74–10.90)	0.002	NS	NS
Left ventricular mass index (g/m <sup>2.7</sup> )	1.04 (1.01–1.07)	0.014	NS	NS
Global longitudinal strain (%)	1.32 (1.09–1.60)	0.004	NS	NS
Mechanical dispersion (ms)	1.03 (1.04–1.05)	0.022	NS	NS
Age (per year)	1.09 (1.04–1.15)	0.001	NS	NS
Ejection fraction (%)	0.94 (0.86–1.03)	0.172	NS	NS
Relative wall thickness (per 0.01)	1.05 (1.00–1.09)	0.048	NS	NS
Systolic blood pressure (mmHg)	1.01 (0.99–1.03)	0.262	NS	NS

CI, confidence interval; ms, milliseconds; NS, not significant; OR, odds ratio; PP/SVi, pulse pressure/stroke volume index; SD, standard deviation.

performed to assess revealed symptoms. In our study, there was some overlap in EF1 across mild, moderate and severe AS, which might limit its application in patients with less severe AS. This needs to be studied in larger studies with less severe AS. Coronary artery disease is common in AS patients. Although known coronary artery disease was an exclusion criterion by design, we cannot exclude that asymptomatic coronary artery disease may have been present in some participants with reduced EF1. In severe AS, higher serum B-type natriuretic peptide has been independently associated with lower global longitudinal strain.<sup>33</sup> However, B-type natriuretic peptide was not measured in the present study, and the relation to EF1 could therefore not be assessed. Lastly, both EF1 and strain rate values were derived from the B-mode frame rate. This could lead to inaccuracies in the measurement of EF1 and underestimation of strain rate. However, we have carefully optimized the frame rate and achieved an acceptable frame rate which is above the recommended frame rate threshold for strain rate measurements.

## Conclusions

In patients with varying degree of AS, severity, lower myocardial contractility and higher arterial stiffness were both associated with lower EF1, a marker of peak systolic function, independent of AS severity.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

**Conflict of interest:** none declared.

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