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Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement

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Aims To evaluate myocardial multidirectional strain and strain rate (S-and-SR) in severe aortic stenosis (AS) patients with preserved left ventricular (LV) ejection fraction (EF), using two-dimensional speckle-tracking strain imaging (2D-STI). The long-term effect of aortic valve replacement (AVR) on S-and-SR was also evaluated.

Methods and results Changes in LV radial, circumferential, and longitudinal S-and-SR were evaluated in 73 severe AS patients (65 ± 13 years; aortic valve area 0.8 ± 0.2 cm^2) with preserved LVEF ($61 \pm 11\%$), before and 17 months after AVR. Strain and strain rate data were compared with data from 40 controls (20 healthy individuals and 20 patients with LV hypertrophy) matched by age, gender, body surface area, and LVEF. Compared with controls, severe AS patients had significantly decreased values of LV S-and-SR in the radial ($33.1 \pm 14.8\%$, $P = 0.2$; 1.7 ± 0.5 s^{-1}, $P = 0.003$), circumferential ($-15.2 \pm 5.0\%$, $P = 0.001$; -0.9 ± 0.3 s^{-1}, $P < 0.0001$), and longitudinal ($-14.6 \pm 4.1\%$, $P < 0.0001$; -0.8 ± 0.2 s^{-1}, $P < 0.0001$) directions. At 17 months after AVR, LV S-and-SR significantly improved in all the three directions, whereas LVEF remained unchanged ($60 \pm 12\%$, $P = 0.7$).

Conclusion In severe AS patients, impaired LV S-and-SR existed although LVEF was preserved. After AVR, a significant S-and-SR improvement in all the three directions was observed. These subtle changes in LV contractility can be detected by 2D-STI.

Keywords Aortic stenosis • Speckle tracking • LV ejection fraction

Introduction

Aortic stenosis (AS) is the most common native valve heart disease.[1] The therapeutic management of patients with AS depends on the haemodynamic severity of the stenosis and the presence of symptoms (angina, syncope, dyspnoea), since the onset of symptoms and the left ventricular (LV) systolic function determines a poor prognosis.[2–4] Aortic valve replacement (AVR) is the only treatment option that can interrupt the natural course of the valve disease. In patients with preserved LV ejection fraction (EF), outcome after surgical AVR is excellent, but patients with reduced LVEF have significantly worse outcome.[5–7]

The chronic LV pressure overload induced by AS results in LV geometry and performance changes; in order to compensate the elevated mid-wall stress, the LV wall thickness increases, maintaining normal LVEF.[8] However, when LV pressure exceeds the LV hypertrophy, the increased mid-wall stress results in an impairment in LV performance, although LV volumes and EF may be still within the normal range.[8] At that stage, AVR can reverse the LV hypertrophy and improve LV systolic performance and clinical outcome.[9] Detection of subtle changes in LV systolic function (when LVEF is still preserved) may help in an earlier patient referral for AVR.

Strain imaging has demonstrated to be the most appropriate method to evaluate LV myocardial contractility properties and,[10,11] accordingly, may enable a better characterization of subtle changes in LV performance in severe AS patients. Two-dimensional speckle-tracking strain (2D-STI) imaging allows the angle-independent evaluation of myocardial strain and strain rate

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(S-and-SR) in the three directions (radial, circumferential, and longitudinal), providing comprehensive information on LV myocardial contractility.[12,13] Aim of the present study was to detect abnormalities in multidirectional myocardial S-and-SR in patients with severe AS and preserved LVEF, using 2D-STI. In addition, improvement in strain after AVR is currently unknown, and the effect of AVR on changes in these strain parameters at long-term follow-up was also evaluated.

Methods

Study population and study protocol

The study population comprised 73 selected patients with severe AS (aortic valve area $<1\ cm^2$) treated with surgical AVR. The patients were selected from a cohort of patients with severe AS referred for surgical AVR to our institution. Exclusion criteria included concomitant moderate-to-severe aortic regurgitation, subvalvular AS, mitral stenosis or moderate-to-severe mitral regurgitation, depressed LVEF ($<50\%$), and previous valve replacement.

Clinical evaluation prior to AVR included the assessment of symptoms (angina, syncope, and dyspnoea) and a physical examination. In addition, demographic data and cardiovascular risk factors were recorded. All patients underwent coronary angiography before AVR. Significant coronary artery disease was defined by the presence of lumen stenosis $\geq 50\%$ in at least one of the major epicardial coronary arteries. In all patients, 2D transthoracic echocardiography and 2D-STI were performed before AVR and at long-term follow-up (median 17 months). Clinical and echocardiographic data were retrospectively analysed.

Echocardiographic data

Conventional 2D echocardiography was performed using commercially available equipment (Vivid-7, General Electric Vingmed, Milwaukee, WI, USA). Patients were imaged in the left lateral decubitus position and data were acquired with a 3.5 MHz transducer at a depth of 16 cm in the parasternal (long- and short-axis views) and apical views (two- and four-chamber and apical long-axis views). Left ventricular dimensions were calculated from the standard M-mode images at the parasternal long-axis views and included LV diameters and end-diastolic thickness of the interventricular septum and posterior wall. Left ventricular mass was calculated using the formula proposed by Devereux *et al.*[14] and corrected by the body surface area to derive LV mass index. According to previous criteria, LV hypertrophy was defined when LV mass index was $>110\ g/m^2$ for women and $>134\ g/m^2$ for men.[14] The LV end-diastolic and end-systolic volumes were measured from the apical two- and four-chamber views, and LVEF was calculated using the Simpson's rule.[15]

Left ventricular diastolic function was evaluated using early (E-wave) and late (A-wave) transmitral velocities, the *E/A* ratio, and the *E*-deceleration time obtained from the spectral pulsed-wave Doppler recordings.[16] In addition, tissue Doppler echocardiography was performed, adjusting gain and frame rate to get an appropriate tissue characterization. The peak early diastolic velocity (E') was measured at the basal myocardial segments on the apical four-chamber view and E/E' ratio was calculated.[17]

The aortic valve area was calculated by the continuity equation, and the maximum pressure gradient across the restrictive orifice was estimated by the modified Bernoulli equation ($4v^2$).[2] Mean transaortic pressure gradient was calculated averaging the instantaneous gradients over the ejection period on the continuous-wave Doppler recordings. As a measurement of global LV afterload, the valvulo-arterial impedance was calculated with the formula proposed by Briand *et al.*[18] Finally, colour Doppler echocardiography was performed after optimizing gain and Nyquist limit in order to evaluate the presence of regurgitant valve disease. The severity of valvular regurgitation was determined on a qualitative scale (mild, moderate, and severe), according to the current guidelines for the management of patients with valvular heart disease.[2] Patients with moderate-to-severe mitral or aortic regurgitation were excluded from the study.

Strain and strain rate analysis with speckle-tracking strain imaging

Comprehensive assessment of LV myocardial S-and-SR was performed using 2D-STI. For this purpose, standard 2D grey-scale images of the LV were acquired at parasternal mid-ventricular short-axis view and at conventional apical two- and four-chamber and apical long-axis views, with a mean frame rate of 71 ± 7 frames/s. Data were stored in cine-loop format and transferred to a workstation for further off-line analysis.

Two-dimensional speckle-tracking strain imaging enables angle-independent myocardial deformation analysis by tracking frame-to-frame natural acoustic markers, or speckles, that appear equally distributed within the myocardial wall.[12,19,20] This novel imaging method provides reliable and accurate information on myocardial strain in the three spatial directions: radial, circumferential, and longitudinal.[12,19,20] Applying the strain Lagrangian formula $(L-L_0/L_0)$,[21] the percentage change in myocardial length (L) relative to the initial length (L_0) derives myocardial strain (expressed in percentage). The temporal derivation of myocardial strain results in strain rate and is a measure of the rate of deformation (expressed in s^{-1}).[21] The radial deformation relates to the thickening (positive strain) and thinning (negative strain) of the myocardial wall. The circumferential deformation relates to the shortening (negative strain) and lengthening (positive strain) of the myocardial wall along the curvature of the LV in the short-axis view. Finally, the longitudinal deformation relates to motion from mitral annulus to the LV apex in the apical views and results in shortening (negative strain) and lengthening (positive strain).[12,21]

Strain and strain rate quantification was performed by using a commercially available software (EchoPAC version 7.0.0, General Electric-Vingmed), as described previously.[13,19,20] In brief, the endocardial contour was manually traced at an end-systolic frame. The software then automatically traced a concentric region of interest including the entire myocardial wall. The myocardial tracking was verified, and the region-of-interest width was adjusted to optimize the tracking, if needed. Next, segmental strain analysis was performed by dividing each LV image into six segments. Peak systolic radial and circumferential S-and-SR values were calculated averaging the peak systolic values of the six segments from the LV mid-ventricular short-axis view. Peak systolic longitudinal S-and-SR was calculated averaging the peak systolic values of the 18 segments, derived from the 6 segments of the 3 apical views (two- and four-chamber and apical long-axis views) (*Figure 1*).

Finally, S-and-SR data of severe AS patients were compared with data obtained from 20 healthy controls and 20 hypertensive patients with LV hypertrophy. The group of healthy controls comprised individuals matched for age, gender, body surface area, and LVEF who were referred for echocardiography with atypical chest pain, palpitations, or syncope without murmur. Those individuals who showed LV dilatation, had known hypertension, or were referred for echocardiographic evaluation of known valvular disease, murmur, or heart failure were

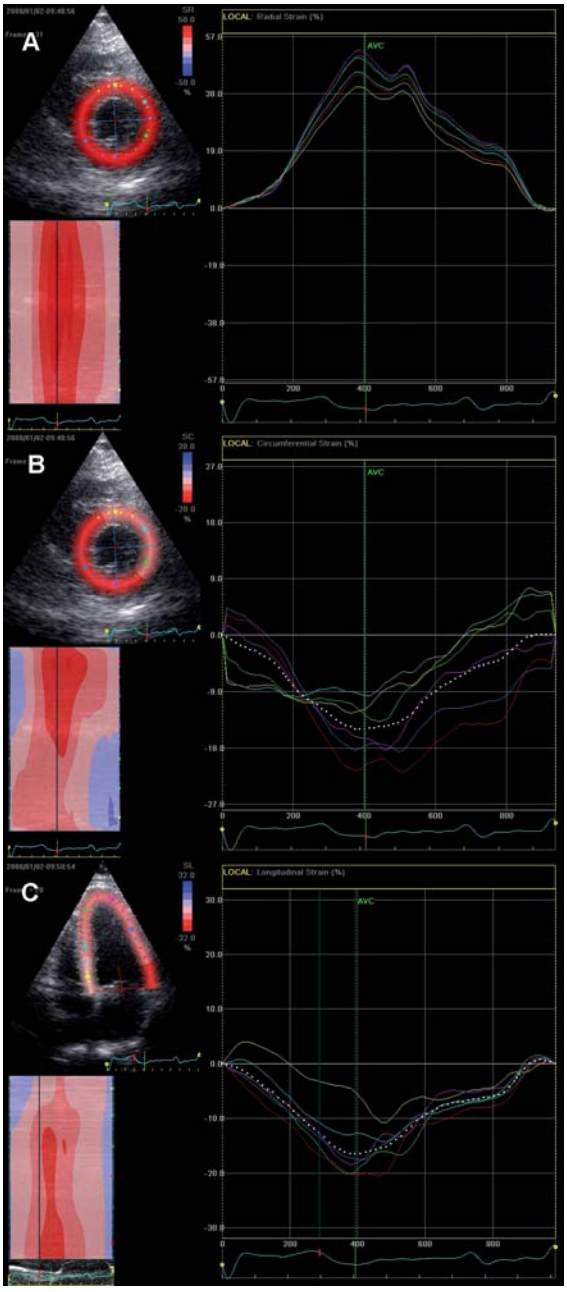

Figure 1 Assessment of left ventricular myocardial strain patterns by using speckle-tracking strain imaging. Radial and circumferential strain (*A* and *B*) are calculated from mid-ventricular short-axis views of the left ventricle. Longitudinal strain (*C*) is calculated from apical views of the left ventricle.

excluded. Accordingly, all individuals included in the control group had normal echocardiography. The group of patients with LV hypertrophy comprised hypertensive patients matched for age, gender, body surface area, LV mass index, and LVEF. Those patients with hypertrophic cardiomyopathy, significant LV outflow tract obstruction (at rest or after Valsalva manoeuvres), any clinical significant valvular heart disease, and coronary artery disease were excluded from this group.

Statistical analysis

Normal distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Continuous variables are expressed as mean ± standard deviation unless otherwise noted. Categorical data are expressed as numbers and percentages. Comparisons between baseline and follow-up were performed with two-sided Student's *t*-test and Wilcoxon signed rank test for paired continuous data (normal and skewed data, respectively) and McNemar test for paired categorical data. Comparisons between healthy controls, hypertensive patients with LV hypertrophy, and AS patients at baseline were performed by one-way analysis of the variance (ANOVA) and Kruskal–Wallis test, as appropriate. Afterwards, *post hoc* analysis was applied to adjust for inflation of the type I error with multiple tests. In addition, S-and-SR data in AS patients (before and at follow-up after AVR) and in controls were compared using the two-sided Student's *t*-test for unpaired data. Linear regression analysis was used to test the relationship between changes in LV S-and-SR and changes in LV mass and LV afterload.

Intra- and interobserver reproducibility of S-and-SR measurements by 2D-STI analysis was determined by intraclass correlation coefficient and Bland–Altman analysis.[22] Intraobserver reproducibility was determined by repeating the S-and-SR measurements by one experienced reader in 25 randomly selected patients. A second, blinded experienced reader performed the strain analysis in the same 25 patients, providing the interobserver reproducibility data.

All statistical analyses were performed with SPSS software (version 15.0, SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant.

Results

Study population

A total of 73 patients with severe AS, defined by an aortic valve area <1 cm^2, were studied (*Table 1*). The majority of the patients (86%) presented with at least one symptom, whereas 10 patients (14%) were asymptomatic. Coronary angiography performed prior to AVR demonstrated coronary artery disease in 26 patients (37%); all had normal LVEF (mean 61 ± 11%), without regional wall motion abnormalities. In patients with severe AS but asymptomatic, indication for AVR was based on the presence of concomitant significant coronary artery disease.

Bioprostheses were implanted in 48 patients (67%), and the 25 remaining patients (33%) received mechanical prostheses. Additional coronary artery bypass graft surgery was performed in 21 patients (29%).

Median echocardiographic follow-up after AVR was 17 months [inter-quartile range (25–75): 6–34 months]. At follow-up, no significant changes in medical treatment were observed: 34 (47%) patients were treated with beta-blockers ($P = 0.189$ vs. baseline), 36 (49%) patients were under angiotensin-converting enzyme-inhibitors/angiotensin-receptor antagonists-II ($P = 0.383$ vs. baseline), 12 (16%) patients were under Ca antagonists ($P = 0.581$ vs. baseline), and 20 (27%) patients received diuretics ($P = 0.648$ vs. baseline).

Baseline echocardiography

The echocardiographic characteristics of the study population at baseline are summarized in *Table 2*. All patients had normal LV

Table 1 Clinical characteristics of the severe aortic stenosis patients

	Healthy controls ($n = 20$)	LV hypertensive patients ($n = 20$)	AS patients ($n = 73$)
Age (years)	65 ± 8	66 ± 9	65 ± 13
Gender, M/F	7/13	10/10	41/32
Systolic blood pressure (mmHg)	122 ± 10	155 ± 21	145 ± 22
Diastolic blood pressure (mmHg)	70 ± 12	87 ± 11	80 ± 11
Cardiovascular risk factors, *n* (%)			
Hypertension	—	20 (100)	38 (52)
Diabetes mellitus	—	0 (0)	10 (14)
Hypercholesterolaemia	—	7 (35)	25 (34)
Current smoking	—	8 (40)	23 (32)
Peripheral vascular disease	—	0 (0)	11 (15)
Family history of coronary artery disease	—	4 (20)	16 (22)
AS symptoms, *n* (%)			
Angina	—	—	23 (32)
Syncope	—	—	10 (14)
Dyspnoea	—	—	42 (58)
Asymptomatic	—	—	10 (14)
Medication, *n* (%)			
Beta-blockers	—	11 (55)	41 (56)
Ca-receptor antagonists	—	4 (20)	9 (12)
ACE-I/ARA-II	—	13 (65)	31 (43)
Diuretics	—	8 (40)	17 (23)
Statins	—	8 (40)	28 (38)

ACE-I/ARA-II, angiotensin-converting enzyme-inhibitors/angiotensin-receptor antagonists-II; AS, aortic stenosis.

Table 2 Baseline multidirectional left ventricular strain and strain rate values in severe aortic stenosis patients, healthy controls, and hypertensive patients with left ventricular hypertrophy

	Healthy controls ($n = 20$)	LV hypertensive patients ($n = 20$)	AS patients ($n = 73$)	ANOVA *P*-value
Age (years)	65 ± 8	66 ± 9	65 ± 13	0.95
BSA (m^2)	1.9 ± 0.1	1.9 ± 0.1	1.9 ± 0.2	0.56
LV mass index (g/m^2)	109 ± 28*,§	144 ± 33	157 ± 49	<0.0001
LVEF (%)	62 ± 7	61 ± 7	61 ± 11	0.91
Radial strain (%)	38.9 ± 6.4	34.4 ± 10.7	33.1 ± 14.8	0.2
Radial strain rate (s^{-1})	2.2 ± 0.6†	1.8 ± 0.5	1.7 ± 0.5	0.003
Circumferential strain (%)	−19.5 ± 2.9†	−17.0 ± 3.0	−15.2 ± 5.0	0.001
Circumferential strain rate (s^{-1})	−1.3 ± 0.3*,§	−1.1 ± 0.3‡	−0.9 ± 0.3	<0.001
Longitudinal strain (%)	−20.3 ± 2.3*,‖	−17.2 ± 3.7‡	−14.6 ± 4.1	<0.001
Longitudinal strain rate (s^{-1})	−1.1 ± 0.2*	−0.9 ± 0.2‡	−0.8 ± 0.2	<0.001

AS, aortic stenosis; BSA, body surface area; EF, ejection fraction; LV, left ventricle/ventricular.
*$P < 0.0001$ vs. AS patients.
†$P < 0.005$ vs. AS patients.
‡$P < 0.01$ vs. AS patients.
§$P = 0.03$ vs. LV hypertensive patients.
‖$P = 0.005$ vs. LV hypertensive patients.

cavity diameters and volumes and preserved LVEF (*Table 2*). The mean end-diastolic thickness of the interventricular septum and the posterior wall were 15 ± 4 and 13 ± 2 mm, respectively. Mean LV mass index was 157 ± 49 g/m^2, and, according to previous criteria,[14] LV hypertrophy was observed in 55 patients (75%). Mild aortic regurgitation was present in 31 patients (43%);

Table 3 Echocardiographic characteristics of the severe aortic stenosis patients

	Baseline	Follow-up	*P*-value
Heart rate (b.p.m.)	71 ± 12	72 ± 13	0.7
Systolic blood pressure (mmHg)	145 ± 22	143 ± 18	0.06
LV end-diastolic diameter (mm)	50 ± 8	49 ± 8	0.3
LV end-systolic diameter (mm)	31 ± 8	30 ± 8	0.8
Interventricular septum thickness (mm)	15 ± 4	12 ± 3	<0.001
Posterior wall thickness (mm)	13 ± 2	12 ± 2	<0.001
LV mass index (g/m^2)	157 ± 49	124 ± 38	<0.001
LV end-diastolic volume (mL)	108 ± 37	99 ± 35	0.007
LV end-systolic volume (mL)	44 ± 25	41 ± 26	0.2
LVEF (%)	61 ± 11	60 ± 12	0.7
Aortic valve area (cm^2)	0.8 ± 0.2	1.6 ± 0.5	<0.001
Maximum transaortic Δ*P* (mmHg)	71 ± 21	23 ± 9	<0.001
Mean transaortic Δ*P* (mmHg)	45 ± 15	12 ± 6	<0.001
Global LV afterload ($mmHg/mL/m^2$)	5.9 ± 1.3	4.3 ± 0.8	<0.001
E/A ratio	0.9 ± 0.5	0.9 ± 0.5	0.9
E-wave deceleration time (ms)	254 ± 92	237 ± 78	0.2
E/E′ ratio	20 ± 9	17 ± 13	<0.001

EF, ejection fraction; LV, left ventricular; Δ*P*, pressure gradient.

according to the exclusion criteria, no patients showed moderate or severe aortic regurgitation. The LV diastolic function was characterized by an inverted *E/A* ratio (mean 0.9 ± 0.6), prolonged E-wave deceleration time (mean 254 ± 92 ms), and a mean *E/E′* ratio of 20 ± 9.

Baseline multidirectional left ventricular myocardial strain and strain rate values

The echocardiographic image quality was sufficient to analyse myocardial S-and-SR with 2D-STI in all patients. Strain and strain rate data obtained in severe AS patients were compared with the group of 20 normal controls and 20 patients with LV hypertrophy.

One-way ANOVA analysis demonstrated that the patients with severe AS had significantly reduced strain values in the circumferential and longitudinal directions and significantly reduced strain rate values in all the three directions compared with the group of healthy controls and the group of hypertensive patients with LV hypertrophy. The *post hoc* analysis showed that these differences were statistically significant in the longitudinal direction (*Table 2*).

Changes in left ventricular dimensions and function after aortic valve replacement

At long-term follow-up (median 17 months) after AVR, the mean aortic valve area increased from 0.8 ± 0.2 to 1.6 ± 0.5 cm^2 ($P < 0.001$), together with a significant decrease in transaortic pressure gradients (maximum pressure gradient from 71 ± 21 to 23 ± 9 mmHg, $P < 0.001$; mean pressure gradient from 45 ± 15 to 12 ± 6 mmHg, $P < 0.001$). At follow-up, a significant reduction in the thickness of the interventricular septum (from 15 ± 4 to 12 ± 3 mm, $P < 0.001$) and posterior wall (from 13 ± 2 to 12 ± 2 mm, $P < 0.001$) was observed, together with a significant reduction in LV mass index (from 157 ± 49 to 124 ± 38 g/m^2, $P < 0.001$). In addition, global LV afterload significantly reduced at long-term follow-up (from 5.9 ± 1.3 to 4.3 ± 0.8 $mmHg/mL/m^2$, $P < 0.001$). Importantly, LV cavity dimensions and LVEF remained unchanged (*Table 3*). Regarding LV diastolic function, no significant changes were noted (*Table 3*).

Changes in left ventricular myocardial strain and strain rate at after aortic valve replacement

Changes in LV myocardial S-and-SR were evaluated in a subgroup of patients with severe AS and without potential confounding factors such as hypertension or coronary artery disease ($n = 23$) and in the entire study cohort ($n = 73$). In the subgroup of patients with severe AS and without hypertension or coronary artery disease, significant improvements in LV multidirectional S-and-SR were observed at long-term follow-up after AVR (median 17 months) (*Table 4*). Similarly, the entire study cohort showed significant improvements in myocardial strain values in all the three directions: radial (from 33.1 ± 14.8 to 37.2 ± 13.4%; $P = 0.02$), circumferential (from −15.2 ± 5.0 to −18.0 ± 5.3; $P < 0.001$), and longitudinal (from −14.6 ± 4.1 to −16.4 ± 4.5%; $P < 0.001$) (*Figure 2*). In addition, myocardial strain rate increased significantly in the three directions: radial (from 1.7 ± 0.5 to 2.0 ± 0.8 s^{-1}, $P = 0.01$), circumferential (from −0.9 ± 0.3 to −1.2 ± 0.3 s^{-1}; $P < 0.001$), and longitudinal (from −0.8 ± 0.2 to −0.9 ± 0.2 s^{-1}; $P < 0.001$) directions (*Figure 2*). Importantly, at long-term follow-up after AVR, radial and circumferential

Table 4 Changes in left ventricular multidirectional strain and strain rate in the subgroup of patients with severe aortic stenosis and without hypertension or coronary artery disease ($n = 23$)

	Baseline	Follow-up	*P*-value
Heart rate (b.p.m.)	69 ± 8	72 ± 12	0.4
LV end-diastolic volume (mL)	119 ± 43	107 ± 41	0.2
LV end-systolic volume (mL)	48 ± 28	46 ± 31	0.7
LVEF (%)	61 ± 11	60 ± 10	0.6
LV mass index (g/m^2)	168 ± 57	128 ± 47	<0.001
Aortic valve area (cm^2)	0.7 ± 0.1	1.6 ± 0.2	<0.001
Maximum transaortic ΔP (mmHg)	74 ± 19	20 ± 8	<0.001
Mean transaortic ΔP (mmHg)	44 ± 13	11 ± 8	<0.001
Global LV afterload ($mmHg/mL/m^2$)	5.9 ± 1.5	4.4 ± 0.6	0.0001
Radial strain (%)	34.6 ± 16.0	41.6 ± 11.2	0.014
Radial strain rate (s^{-1})	1.7 ± 0.5	2.1 ± 0.6	0.027
Circumferential strain (%)	−17.6 ± 4.6	−19.8 ± 4.8	0.018
Circumferential strain rate (s^{-1})	−1.0 ± 0.3	−1.3 ± 0.3	0.048
Longitudinal strain (%)	−15.1 ± 3.8	−16.9 ± 4.8	0.026
Longitudinal strain rate (s^{-1})	−0.8 ± 0.2	−0.9 ± 0.2	0.019

ΔP, pressure gradient; EF, ejection fraction; LV, left ventricular.

S-and-SR values normalized (without significant differences between severe AS patients and the normal controls), whereas longitudinal S-and-SR improved after AVR, but remained reduced compared with the normal controls ($P < 0.001$) (*Figure 2*). A representative example of changes in LV myocardial strain in the three directions after AVR is shown in *Figure 3*.

Relationship between changes in left ventricular strain and strain rate and changes in left ventricular mass index and left ventricular afterload

The relationship between changes in LV S-and-SR parameters and changes in LV end-diastolic volume, LV mass index reduction, and LV afterload was evaluated by linear regression analysis. Changes in LV S-and-SR parameters were not related to LV end-diastolic volume or mass index reduction (*Table 5*). However, significant relations were observed between changes in LV S-and-SR parameters and changes in aortic valve area. When the relationship between changes in LV S-and-SR parameters and changes in global LV afterload was evaluated (taking into account the double resistance that the LV faces: valvular and arterial), significant relations were observed only for changes in circumferential and longitudinal S-and-SR but not for radial S-and-SR (*Table 5*).

Intraobserver and interobserver reproducibility

Reliability analysis demonstrated good intra- and interobserver agreement for the measurement of S-and-SR in the three orthogonal directions. In addition, Bland–Altman analysis showed small bias, with no significant trend for all S-and-SR measurements performed by the same observer (*Table 6*).

Discussion

The present study demonstrated that patients with severe AS and preserved LVEF already exhibited decreased LV S-and-SR in all the three directions (radial, circumferential, and longitudinal), illustrating subclinical systolic LV dysfunction despite normal LVEF. Importantly, at long-term follow-up after AVR, a significant improvement in these parameters was observed, whereas LVEF remained unchanged. These findings highlight that 2D-STI enables early detection of subtle changes in LV systolic function despite a normal LVEF in severe AS patients. Moreover, a significant improvement in strain was noted after AVR (despite an unchanged LVEF), further underscoring the value of strain imaging to detect changes in these patients and the characterization of the improvement in myocardial deformation after AVR.

Left ventricular myocardial strain in severe aortic stenosis

Aortic stenosis results in LV systolic pressure overload and elevated wall stress.[8,23] Consequently, LV wall thickness increases (as confirmed in the current study), in an attempt to maintain adequate wall stress.[8,23] With increasing severity of the AS, LV hypertrophy progresses in order to minimize LV wall stress and preserve LV systolic function. However, at a certain point in time, LV hypertrophy cannot compensate the increased LV pressure, resulting in afterload mismatch. This afterload mismatch represents the first step of the LV dysfunction in severe AS.[8] Eventually, LV volumes will increase and LVEF decreases.[8] Once LVEF is decreased, outcome after surgical AVR is worse,[6] and it may thus be preferred to detect subclinical systolic LV dysfunction before LVEF becomes reduced. In severe AS, the exceeded LV afterload co-exists with a reduced mid-wall shortening, even when LVEF is still preserved.[8] Several studies based on Doppler-derived strain data have

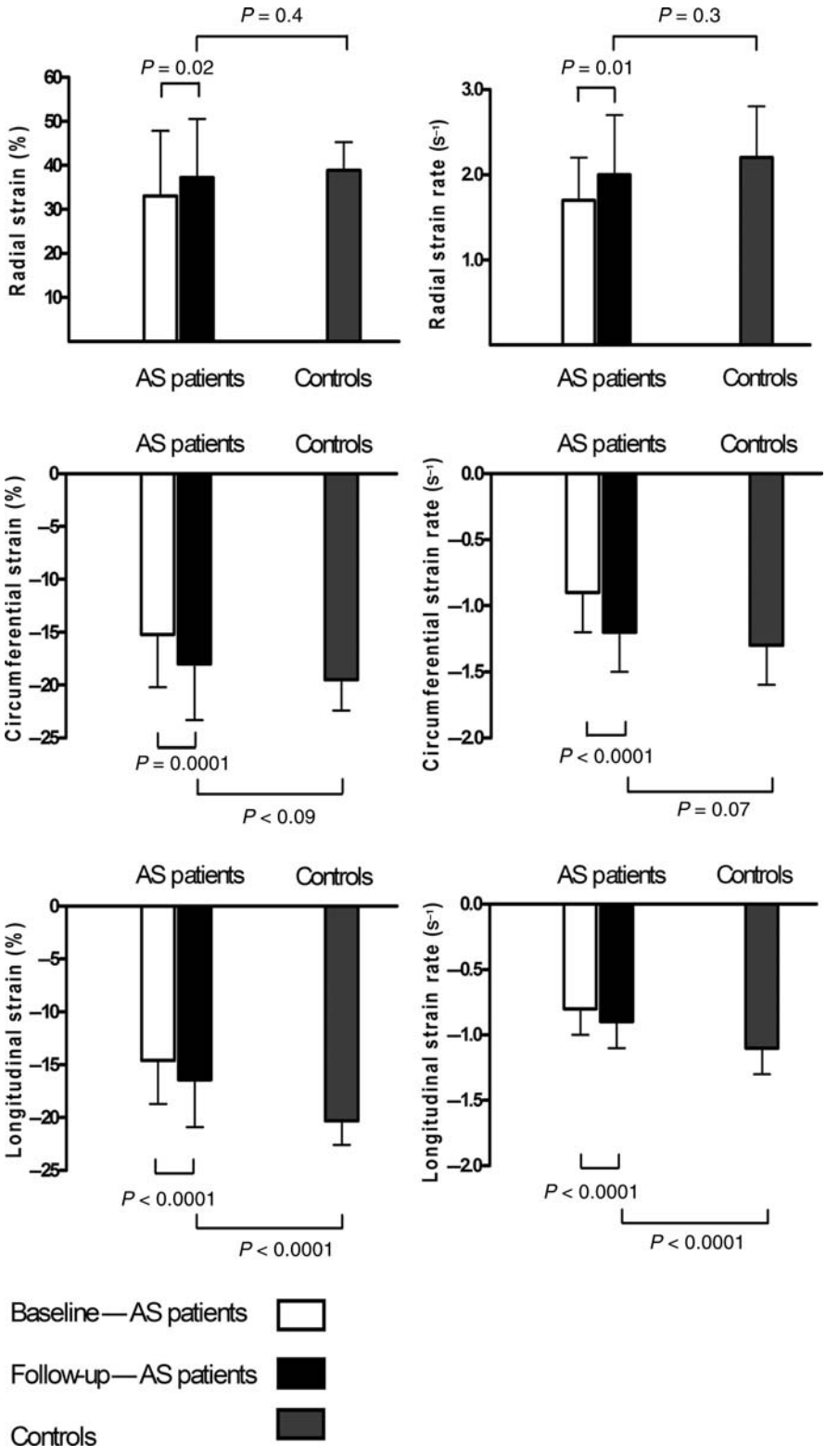

Figure 2 Changes in left ventricular myocardial strain and strain rate in radial, circumferential, and longitudinal directions. Strain and strain rate values of aortic stenosis patients are presented in white bars at baseline and in black bars at follow-up. Strain and strain rate values obtained in the group of healthy controls are presented in grey bars. In aortic stenosis patients, significant increases in all the three different types of strain and strain rate were observed at long-term follow-up after aortic valve replacement. The increase in strain and strain rate values was more pronounced in the radial and circumferential directions, reaching almost the normal reference values (without differences compared with healthy controls).

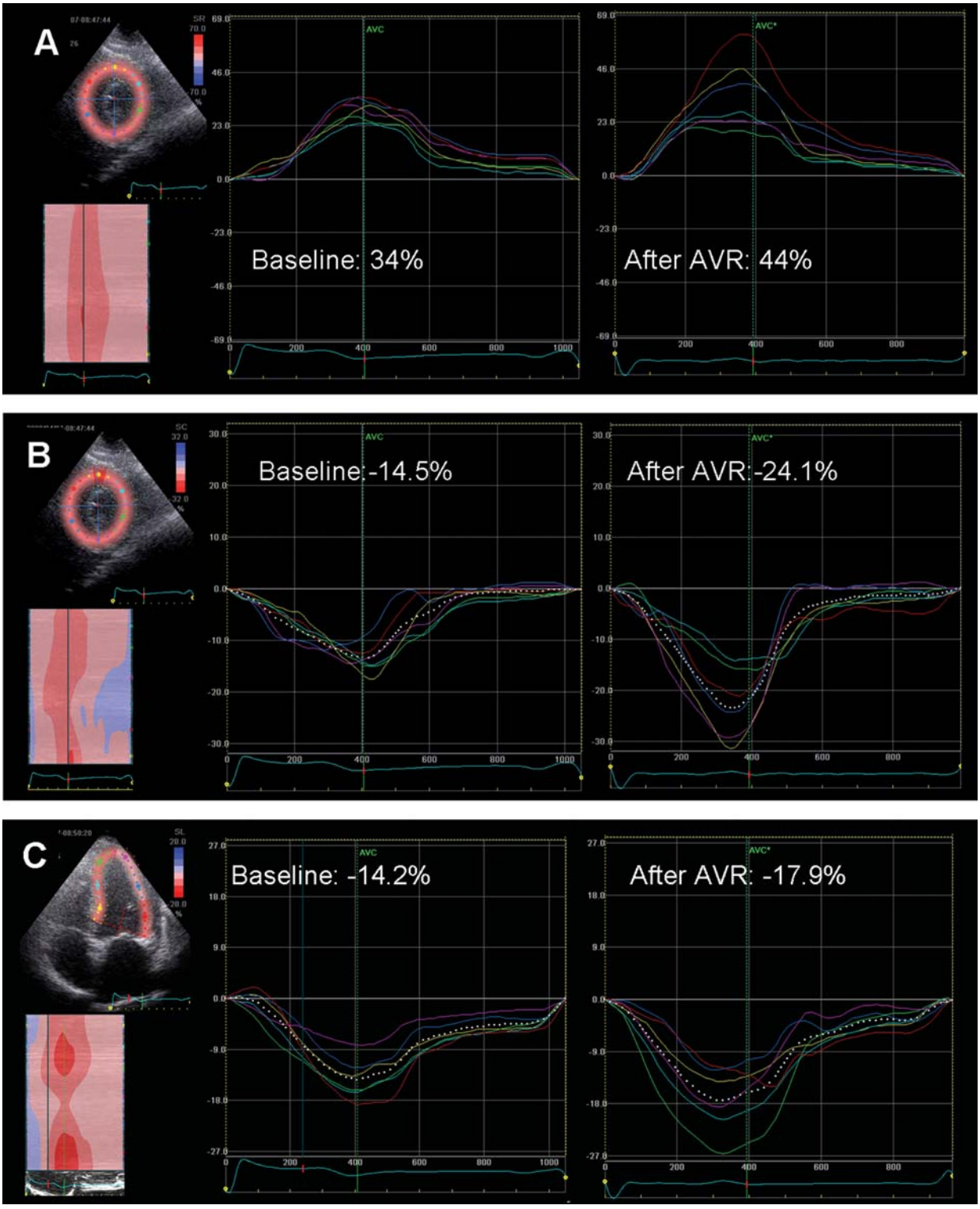

Figure 3 Example of strain analysis in radial (*A*), circumferential (*B*), and longitudinal (*C*) directions before and after aortic valve replacement. At long-term follow-up after aortic valve replacement (AVR), left ventricular myocardial strain increased in all the three directions, as indicated in the panels, whereas left ventricular ejection fraction remained unchanged (53–55%).

Table 5 Relationship between changes in left ventricular strain and strain rate parameters and changes in left ventricular end-diastolic volume, mass index, and left ventricular afterload

	ΔLV end-diastolic volume		ΔLV mass index		ΔAortic valve area		ΔGlobal LV afterload	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Radial strain (%)	0.051	0.667	0.004	0.970	0.283	0.034	0.166	0.198
Radial strain rate (s^{-1})	0.229	0.051	0.018	0.883	0.302	0.024	0.221	0.085
Circumferential strain (%)	0.201	0.088	0.015	0.897	0.461	<0.001	0.403	0.001
Circumferential strain rate (s^{-1})	0.014	0.908	0.136	0.250	0.549	<0.001	0.327	0.009
Longitudinal strain (%)	0.059	0.621	0.035	0.766	0.524	<0.001	0.426	0.001
Longitudinal strain rate (s^{-1})	0.104	0.383	0.165	0.163	0.366	0.006	0.269	0.034

LV, left ventricular.

Table 6 Intraobserver and interobserver reproducibility of myocardial strain and strain rate assessed by two-dimensional speckle-tracking imaging

	Intraobserver			Interobserver		
	Mean difference ± 2SD	ICC	*P*-value	Mean difference ± 2SD	ICC	*P*-value
Radial strain (%)	0.79 ± 10.28	0.97	<0.001	2.03 ± 17.63	0.81	0.007
Radial strain rate (s^{-1})	−0.08 ± 0.88	0.92	<0.001	0.02 ± 1.22	0.85	0.003
Circumferential strain (%)	0.18 ± 3.66	0.96	<0.001	−0.28 ± 4.6	0.90	0.001
Circumferential strain rate (s^{-1})	0.11 ± 0.62	0.86	<0.001	−0.02 ± 0.25	0.96	<0.001
Longitudinal strain (%)	−0.21 ± 2.48	0.98	<0.001	0.99 ± 3.39	0.90	0.001
Longitudinal strain rate (s^{-1})	−0.01 ± 0.28	0.95	<0.001	0.05 ± 0.26	0.93	<0.001

ICC, intraclass correlation coefficient; SD, standard deviation.

reported reduced values of myocardial deformation (thickening or shortening) in severe AS patients.[24–26] However, the inherent limitation of Doppler-based imaging (angle insonation dependency) precludes an accurate assessment of global LV myocardial strain.[12] Importantly, 2D-STI allows a multidirectional approach of myocardial strain measurement and overcomes the limitation of the angle insonation dependency.[12] Preliminary work by Becker *et al.*[27] evaluated LV myocardial strain in 22 patients with symptomatic severe AS and preserved LVEF. By applying 2D-STI to mid-ventricular short-axis images, global radial and circumferential S-and-SR were assessed. Significant decreases in all parameters were noted ($22.7 \pm 2.0\%$ and $1.3 \pm 0.07\ s^{-1}$ for radial S-and-SR, respectively; $-14.9 \pm 1.0\%$ and $-1.29 \pm 0.07\ s^{-1}$ for circumferential S-and-SR, respectively).[27] The findings of the present study extend these findings in a larger cohort, but also evaluated myocardial strain in three different directions. In line with the previous work,[24–27] impairment in global LV myocardial strain was noted, whereas LVEF was still preserved. Of note, this impairment was present in all the three directions of cardiac deformation (radial, circumferential, and longitudinal). More important, patients with severe AS showed more decreased values of S-and-SR compared with individuals with the same amount of LV hypertrophy (hypertensive patients) and healthy controls. In patients with severe AS, the haemodynamic severity of the valve stenosis rather than the amount of LV hypertrophy may contribute to impair the LV S-and-SR by reducing the coronary flow reserve, as demonstrated previously.[28,29] When the effective orifice area is 1 cm^2, the coronary flow reserve reduces dramatically, leading to repetitive ischaemic injury of the myocardium.[28,29] As a consequence, the amount of fibrotic areas may increase substantially.[30] Schwartzkopff *et al.*[30] described a higher amount of peri-myocytic fibrosis in patients with AS compared with hypertensive patients. This higher degree of myocardial fibrosis may impact negatively on LV performance, resulting in more impaired LV S-and-SR.

Accordingly, the present study highlights the deleterious effects of AS on global LV performance and confirms the presence of subtle LV systolic dysfunction in all the three strain directions despite normal LVEF. These subtle abnormalities in LV systolic function can be assessed using 2D-STI.

Changes in left ventricular strain and strain rate at long-term follow-up after aortic valve replacement

Left ventricular loading conditions change acutely after AVR with a dramatic decrease in LV pressure overload. Over time, the LV adapts to this new situation with a regression of LV hypertrophy and an improvement in LV performance.[31,32] In the present

study, the changes in LV geometry and function after AVR were evaluated at long-term follow-up. Together with a significant decrease in LV afterload (with a significant increase in aortic valve area and a significant decrease in global LV afterload index) and a significant reduction in LV mass index, improvements in radial, circumferential, and longitudinal S-and-SR were observed. The impact of AVR on LV S-and-SR at long-term follow-up has not been studied extensively.[27,33] Poulsen *et al.*[33] evaluated the changes in Doppler-derived longitudinal strain after AVR in 40 severe AS patients and preserved LVEF. The authors observed a sustained improvement of longitudinal strain (from -9 ± 4 to $-12 \pm 3\%$ at 3 months and $-14 \pm 4\%$ at 12 months; $P = 0.0001$) without significant changes in LVEF.[33] In addition, LV mass index decreased significantly from 184 ± 48 to 127 ± 31 g/m^2 ($P = 0.0001$).[33] Furthermore, in the previously mentioned study of Becker *et al.*,[27] the changes in radial and circumferential S-and-SR after AVR were evaluated at 6-month follow-up. The authors reported a significant increase in radial and circumferential S-and-SR [from 22.7 ± 2.0 to $24.9 \pm 2.1\%$ for radial strain ($P < 0.001$) and from -14.9 ± 1.0 to $-17.3 \pm 1.5\%$ for circumferential strain ($P < 0.001$)], whereas LVEF also remained unchanged.[27] Of note, the meridional wall stress reduced inversely, reflecting the decrease in LV pressure.[27]

The present study demonstrates that changes in LV myocardial S-and-SR are related more to changes in LV afterload rather than LV mass reduction or LV dimensions. The increase in the effective orifice area was related to an improvement in LV performance with an increase in multidirectional LV myocardial S-and-SR. Previous work demonstrated a direct relation between impaired coronary flow reserve and the haemodynamic severity of the valve stenosis but not with the amount of LV mass.[28,29] The improvement in coronary flow reserve after AVR, secondary to the increased effective orifice area,[29] results in a more efficient myocardial arterial supply and in an LV S-and-SR improvement. At follow-up, the LV hypertrophy regression may help to further improve LV performance, by improving the transmural myocardial perfusion. However, similar to the previous work, the present study shows that the reduction in LV afterload and LV mass do not determine significant changes in LVEF.[29] Accordingly, 2D-STI may provide a sensitive tool to detect the improvement in LV systolic function after AVR.

Study limitations

The heterogeneous study population, including patients with coronary artery disease and hypertension, may yield different results from what could be obtained if pure severe AS patients were studied. However, coronary artery disease and hypertension are two frequent associated co-morbidities in AS, and the exclusion of severe AS patients with those conditions would introduce a selection bias that could mask the clinical spectrum of the disease. The inclusion of those patients yields a more reliable view of what in daily clinical practice can be observed. However, additional studies evaluating selected subpopulations could provide more specific insight into the LV mechanics. Particularly, in patients with severe AS and concomitant coronary artery disease, the presence of pathological post-systolic strain can be observed. The changes in LV strain pattern in this subgroup of patients may differ from those patients with isolated severe AS, having important implications in LV performance and clinical outcome. Finally, diastolic function improved after AVR. Unfortunately, the patients studied did not undergo right cardiac catheterization to confirm the presence of elevated LV filling pressures.

Clinical implications

At present, the timing of intervention in patients with severe AS is determined by the presence of symptoms (angina, syncope, or heart failure) and the haemodynamic severity of the AS.[2] However, the deleterious effects of severe AS on LV performance may precede the onset of symptoms or the impairment in LVEF.[8,26] Therefore, an early intervention could be desirable in order to prevent the effects of the chronic pressure overload on LV geometry (LV dilatation) and performance (reduction in LVEF). In addition, since the long-term outcome after AVR is worse when LVEF is reduced,[6,7] it may be of importance to identify patients with subtle systolic LV dysfunction with yet preserved LVEF, who could then be referred at an earlier stage to surgical AVR. Additional prospective studies are needed to determine the onset of subtle systolic LV dysfunction and to correlate it with the onset of AS related symptoms.

The findings of the present study demonstrated the presence of impaired LV systolic S-and-SR in severe AS patients, although LVEF was still normal, and that improvement in S-and-SR in all the three directions occurred after AVR. Two-dimensional speckle-tracking imaging allows for an early detection of impaired LV S-and-SR and for monitoring the improvement in S-and-SR after AVR. It should be stated that the repeated echocardiographic analysis was obtained at a median of 17 months and that it thus remains unclear when the improvement in S-and-SR occurred (immediately or late after AVR). Finally, additional studies are needed to elucidate the prognostic implications of LV S-and-SR changes after AVR.

Conclusions

Severe AS patients have impaired multidirectional LV myocardial S-and-SR, although LVEF is still preserved. Importantly, at long-term follow-up after AVR, a significant improvement in LV myocardial S-and-SR was observed in all the three directions. These subtle changes in LV systolic function can be adequately detected by 2D-STI.

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