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Early Diastolic Strain Rate in Relation to Systolic and Diastolic Function and Prognosis in Aortic Stenosis

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ABSTRACT

OBJECTIVES This study examined the impact of early mitral inflow velocity-to-early diastolic strain rate (E/SRe) ratio on long-term outcome after aortic valve replacement (AVR) in aortic stenosis (AS).

BACKGROUND In AS, increased filling pressures are associated with a poor prognosis and can be estimated using the early diastolic mitral inflow velocity-to-early diastolic velocity of the mitral annulus (E/e′) ratio. Recent studies suggest that the E/SRe ratio surpasses the E/e′ ratio in estimating outcome.

METHODS Pre-operative evaluation was performed in 121 patients with severe AS (aortic valve area <1 cm^2) and left ventricular ejection fraction (LVEF) of >40% who were scheduled for AVR. Patients were divided according to E/SRe median and followed for 5 years. The primary endpoint was overall mortality.

RESULTS LVEF was lower (53 ± 7% vs. 56 ± 7%, respectively; $p = 0.03$) and a restrictive filling pattern more common (28% vs. 8%, respectively, $p = 0.005$) in patients with increased E/SRe ratio. Five-year overall mortality was increased in patients with high E/SRe (40% vs. 15%, respectively; $p = 0.007$). In univariate Cox regression analysis, E/SRe, age, European System for Cardiac Operative Risk Evaluation (EuroSCORE), LV mass index, left atrial volume index, LVEF, global longitudinal strain, E/e′ ratio, and N-terminal pro-B-type natriuretic peptide level were univariate predictors of overall mortality, although when we adjusted for the predefined variables age, history of diabetes mellitus and LVEF, only E/SRe and left atrial volume index remained associated with overall mortality. Even when we included left atrial volume index in the multivariate model, E/SRe was significantly associated with overall mortality (hazard ratio [HR]: 2.2; 95% confidence interval [CI]: 1.1 to 4.4; $p < 0.05$); additionally, in a model with forward selection, E/SRe was the sole predictor (HR: 2.9; 95% CI: 1.6 to 5.5; $p = 0.001$. The overall log likelihood chi-square analysis of the predictive power of the multivariate model containing E/SRe was statistically superior to models based on the E/e′ ratio.

CONCLUSIONS Pre-operative E/SRe ratio was significantly associated with long-term post-operative survival and was superior to the E/e′ ratio in patients with severe AS undergoing AVR. (Effect of Angiotensin II Receptor Blockers (ARB) on Left Ventricular Reverse Remodelling After Aortic Valve Replacement in Severe Valvular Aortic Stenosis; NCT00294775) (J Am Coll Cardiol Img 2016;9:519–28) © 2016 by the American College of Cardiology Foundation.

Aortic stenosis (AS) is characterized by left ventricular (LV) pressure overload leading to LV hypertrophy and fibrosis. The consequence is increased chamber stiffness and delayed active LV relaxation, which will cause LV diastolic dysfunction, increased filling pressure, and worsening prognosis (1–3). A cornerstone in assessing diastolic function and estimating filling pressure noninvasively is assessment of the early diastolic mitral inflow velocity-to-early diastolic velocity of

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AUC = area under the curve

AVR = aortic valve replacement

GLS = global longitudinal strain

LA = left atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SRe = early diastolic strain rate

the mitral annulus (E/e′) ratio (3,4). Recent studies, however, have raised some important concerns about the E/e′ ratio (4-6), some of which are related to angle dependency and the effect of passive tethering of e′.

Measurement of the early mitral inflow velocity-to-early diastolic strain rate (E/SRe) ratio has recently been proposed as a novel marker of elevated LV filling pressure (7,8). The potential advantage of this marker is that the regional early velocity of diastolic deformation (strain rate) more accurately reflects diastolic performance of all myocardial segments. Moreover, based on 2-dimensional (2D) speckle tracking echocardiography, diastolic deformation is less depending on insonation angle. In a recent paper, the E/SRe ratio was superior to E/e′ in predicting cardiovascular events among patients with myocardial infarction (9). Whether this also is the case among patients with AS is not known. We thus hypothesized that E/SRe would be associated with adverse outcome after aortic valve replacement (AVR) among patients with severe symptomatic AS and that the E/SRe ratio would provide incremental information to E/e′.

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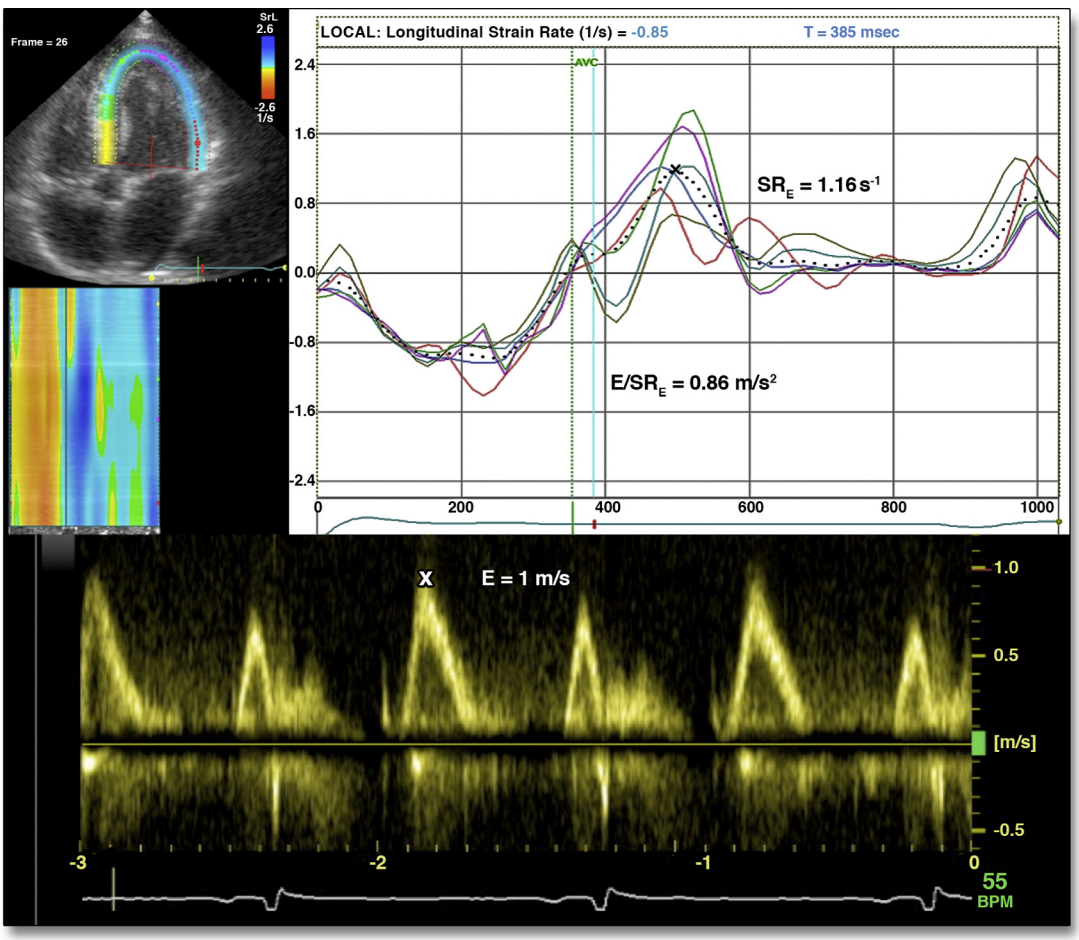
METHODS

The present investigation was a post-hoc analysis of a prospective, single-center, randomized study conducted to evaluate the effect of candesartan in addition to conventional treatment on reverse remodelling in consecutive patients undergoing AVR

FIGURE 1 Example of Measurement of E/SRe



Measurements are shown of early mitral inflow velocity (E) using pulse-wave Doppler and early diastolic strain rate (SRe) from 2D speckle tracking. AVC = aortic valve closure.

for symptomatic AS. The study was registered with the National Board of Health and Danish Data Protection Agency, approved by the local ethics committee, and registered with (NCT00294775). All patients gave written informed consent. The study design and effect of candesartan on regression of LV hypertrophy was published previously (10). Briefly, we enrolled patients >18 years if age with symptomatic severe AS (Doppler-derived aortic valve area <1 cm^2) scheduled for AVR at Odense University Hospital, Denmark, between February 2006 and April 2008. Patients with left ventricular ejection fraction (LVEF) <40%, s-creatinine concentration >220 μmol/l, previous aortic valve surgery, planned additional valve repair/replacement, infective endocarditis, predominant aortic valve regurgitation, or ongoing treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker were excluded.

Ischemic heart disease was defined as a history of myocardial infarction, previous revascularization with percutaneous coronary intervention, or coronary artery bypass grafting or, if pre-operative coronary angiography demonstrated, significant stenosis requiring coronary artery bypass grafting in addition to AVR.

ECHOCARDIOGRAPHY. All echocardiograms were performed by a single experienced operator using a Vivid 5 ultrasonography system (GE Medical System, Horten, Norway) on the day prior to surgery. Images were obtained with a minimum frame rate of 70 frames/s. For all Doppler recordings, a horizontal sweep of 100 mm/s was used; for patients in sinus rhythm, the average of 5 consecutive beats were measured; for patients with atrial fibrillation, 10 beats were averaged. Echocardiograms were digitally stored and later analyzed completely blinded for all clinical and survival data. Aortic valve area was estimated by quantitative Doppler ultrasound using the continuity equation. Peak and mean flow velocity across the valve was determined in the window where the highest velocity could be recorded using continuous wave Doppler with the cursor as parallel as possible with the flow across the valve. Peak and mean transvalvular gradient was estimated using the modified Bernoulli equation. Finally, the peak systolic flow velocity in the outflow tract was estimated with pulsed wave Doppler (11).

Left ventricular mass was estimated according to the joint recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging, using Devereux's formula (12). LV mass index of >116 g/m^2 in males or >100 g/m^2 in females was considered indicative of LV hypertrophy.

TABLE 1 Patient Characteristics

	E/SRe <0.93 (n = 60)	E/SRe ≥0.93 (n = 61)	p Value
Age, yrs	71 ± 10	74 ± 8	0.11
Number of males	40 (66)	37 (61)	0.49
Atrial fibrillation occurrence	9 (15)	10 (16)	0.83
Hypertension occurrence	27 (45)	26 (43)	0.79
Diabetes mellitus occurrence	6 (10)	12 (18)	0.14
Ischemic heart disease occurrence	17 (28)	20 (33)	0.60
Number of subjects with NYHA functional class shown (I/II/III)	10/35/15	13/29/19	0.53
6-min walk test, m	360 ± 116	332 ± 127	0.26
EuroSCORE	5.4 ± 1.9	6.0 ± 2.0	0.08
Logistic EuroSCORE	4.7 ± 3.1	6.1 ± 4.5	0.04
BSA, m^2	1.8 ± 0.3	1.9 ± 0.5	0.39
Systolic blood pressure, mm Hg	145 ± 21	147 ± 20	0.66
Number of types of treatment shown			
Diuresis	16 (27)	26 (43)	0.07
Beta-blocker therapy	12 (20)	15 (25)	0.54
Calcium channel blocker therapy	11 (18)	14 (23)	0.53
Candesartan therapy	30 (50)	31 (51)	0.93
Number of surgery types			
Concomitant CABG	16 (27)	20 (33)	0.46
Mechanical prosthesis	10 (17)	9 (15)	0.74
Prosthesis size, mm	23.1 ± 4.7	22.7 ± 4.7	0.68
Creatinine concentration, μmol/l	102 ± 24	99 ± 19	0.35
Biomarkers concentration			
NT-proBNP, pmol/l	315 (148–664)	805 (259–5,868)	0.0002
Fibulin-1, μg/ml	76 (61–100)	90 (72–108)	0.05

Values are mean ± SD, n (%), or median (interquartile range).
BSA = body surface area; CABG = coronary artery bypass graft; NYHA = New York Heart Association.

Relative wall thickness was calculated using the formula: [2 × posterior wall thickness / LV internal diameter in diastole] (13). LVEF was estimated using Simpson's biplane method. Longitudinal LV systolic function was assessed using peak systolic mitral annular motion assessed with tissue Doppler imaging, with the Doppler sample volume placed in the septal and lateral mitral valve annulus, and the average was calculated.

Mitral inflow was assessed in the apical 4-chamber view, using pulsed-wave Doppler with the sample volume paced at the tips of mitral leaflets during diastole. From the mitral inflow profile, the E- and A-wave peak velocities and deceleration times were measured. Doppler tissue imaging of the mitral annulus was used in the aforementioned sampling sites to measure the early diastolic velocity, e′, from each site, and an average was calculated.

The E/e′ ratio was used as a noninvasive marker of LV filling pressures (4). Because the E/e'_{sep} ratio correlates better with invasively estimated wedge pressures than the E/e'_{lat} ratio in AS (4), we used E/e'_{sep} in our study. Diastolic filling pattern and

TABLE 2 Echocardiographic Data

	E/SRe <0.93 (n = 60)	E/SRe ≥0.93 (N = 61)	p Value
Aortic valve area, cm^2	0.85 ± 0.28	0.79 ± 0.27	0.21
AV maximum velocity, m/s	3.7 ± 0.7	4.1 ± 0.8	0.01
V_{LVOT}, m/s	0.92 ± 0.22	0.98 ± 0.27	0.22
AV mean gradient, mm Hg	35 ± 12	42 ± 17	0.01
Valvulo-arterial impedance, mm Hg/ml/m^2	4.8 ± 1.7	5.0 ± 1.4	0.35
LV ejection fraction (%)	56 ± 7	53 ± 7	0.03
LV ejection fraction >50%	44 (73)	55 (90)	0.02
Stroke volume index, ml/m^2	42 ± 14	40 ± 12	0.46
Cardiac index, l/m^2	2.8 ± 1.1	2.8 ± 1.0	0.90
LV end diastolic volume, ml	97 ± 28	122 ± 33	<0.0001
LV end systolic volume, ml	43 ± 14	57 ± 19	<0.0001
LV mass index, g/m^2	120 ± 32	141 ± 46	0.005
Interventricular septum thickness, mm	13 ± 2	13 ± 2	0.17
LV posterior wall, mm	13 ± 2	14 ± 2	0.01
Relative wall thickness	0.59 ± 0.12	0.62 ± 0.16	0.29
E, m/s	0.69 ± 0.18	0.91 ± 0.22	<0.0001
A, m/s	0.89 ± 0.25	1.00 ± 0.29	0.03
Deceleration time, ms	204 ± 51	196 ± 66	0.46
Diastolic function grade I/II/III/IV	3/32/12/5	1/25/15/17	0.038
Restrictive filling pattern	5 (8)	17 (28)	0.005
Propagation velocity Vp, cm/s	62 ± 27	51 ± 28	0.02
e'_{sep}, cm/s	6.1 ± 1.8	5.4 ± 1.5	0.02
e'_{lat}, cm/s	7.1 ± 2.4	7.3 ± 2.6	0.61
$e'_{average}$, cm/s	6.6 ± 1.8	6.4 ± 1.8	0.48
Left atrial volume index, ml/m^2	42 ± 16	55 ± 19	0.0001
E/e'_{sep}	11.7 ± 3.5	17.7 ± 4.9	<0.0001
$s'_{average}$, cm/s	6.6 ± 1.3	5.8 ± 1.5	0.003
% of global longitudinal strain	−17.4 ± 2.9	−13.6 ± 3.5	<0.0001
E/SRe (range), m	0.74 (0.64–0.85)	1.26 (1.15–1.52)	-

Values are mean ± SD

A = mitral inflow A velocity; AV = aortic valve; E/e'_{sep} = early diastolic mitral inflow velocity-to-early diastolic velocity of the septal mitral annulus ratio; E/SRe = early mitral inflow velocity-to-early diastolic strain rate ratio; e'_{lat} = early diastolic velocity of the lateral mitral annulus; LV = left ventricular; s′ = systolic velocity of the mitral annulus; V_{LVOT} = Doppler-velocity at the LV outflow tract.

restrictive filling pattern was categorized according to guidelines (14). Left atrial (LA) volume was assessed using the area length method (12) from the apical 4- and 2-chamber views and was indexed for body surface area.

Two-dimensional speckle tracking analysis was performed by a single investigator in the 3 apical views by, first, manually tracking the endocardium at the onset of systole, after which the software tracked the myocardial speckle pattern frame by frame. The region of interest was adjusted to cover the thickness of the myocardium, and adequate tracking was verified and corrected if necessary. Strain analysis was performed only if software was able to track more than 4 of 6 segments. Aortic valve closure was identified on continuous wave Doppler recording through the aortic valve. The LV was subsequently divided by the software into 18 segments. Global longitudinal strain (GLS) was calculated for each of the 3 apical views and for mean GLS as the average of all 3 views. Global systolic strain rate and global early diastolic SR (SRe) were calculated from the average of 18 segments: for patients in sinus rhythm, the average of 3 consecutive beats was measured; for patients with atrial fibrillation, 5 beats were averaged The E/SRe ratio was calculated as the E velocity divided by the global SRe value (Figure 1). Patients were divided according to median E/SRe ratio.

BIOMARKER ANALYSIS. Blood samples were collected immediately after the echocardiogram, when the subjects had been resting in a recumbent position for at least 30 min. Samples were collected in EDTA tubes and centrifuged. Plasma samples were stored at −80°C for later analysis. A sandwich immunoassay was used for measuring fibulin-1 levels (15,16). N-terminal pro-B-type natriuretic peptide (NT-proBNP) and creatinine concentrations were analyzed using a Modular Analytics P unit (Roche Diagnostics, Indianapolis, Indiana).

CLINICAL EXAMINATION AND FOLLOW-UP. All patients underwent coronary angiography and a thorough clinical examination prior to AVR. Operative risk was estimated using the EuroSCORE (17). By September 2012, outcome data were collected from the Danish Central Population Registry (survival status) and from discharge notes available in the Danish National Patient Registry. In case of ambiguous information, local hospitals were contacted, and the patient's medical records were reviewed.

The primary endpoint of this study was overall mortality, and the secondary endpoint was cardiovascular mortality. Endpoints were assessed by one of the investigators, who was blinded to all echocardiographic measurements. No patients were lost to follow-up.

STATISTICAL ANALYSIS. Data are mean ± SD or numbers and percentages. Differences between groups were tested by Student *t* test; non-Gaussian distributed variables were tested by Wilcoxon rank sum test; categorical variables were tested by Fisher exact test. Due to a non-Gaussian distribution, the E/SRe ratios and fibulin-1 concentrations are presented as median and interquartile ranges (IQRs), whereas NT-proBNP concentration was logarithm transformed. Correlations were obtained using the Spearman rank test. Mortality rates were calculated using the product limit method and plotted according to the Kaplan-Meier method; rates were compared using the log-rank test. Further estimation of risk was performed using Cox proportional hazard models. All

significant variables were tested in different multivariate Cox regression analyses, adjusting for the predefined variables LVEF, history of diabetes, and age. In addition to hazard ratios (HR), HR adjusted for ±1 SD were calculated, dividing the variable by the SD of the measurement. Finally, a model with forward selection of all variables except GLS and s′ (due to colinearity with E/SRe) was constructed with entry and retention in the model set to 0.05. Overall differences between models were tested by calculating overall differences in log likelihood chi-square analysis between models. In addition, the area under curve (AUC) of the model was calculated using the generalized U statistic proposed by DeLong et al. (18). The assumptions (proportional hazard assumption, linearity of continuous variables, and lack of interaction) were tested and found to be valid. Interobserver variability was assessed in 20 randomly selected patients, with the calculation of mean differences and 95% limits of agreement. Receiver-operator characteristic curves were generated to determine the cutoff values that best distinguished patients who died during follow-up. A p value of <0.05 was considered significant. STATA/SE version 9.0 software (StataCorp LP, College Station, Texas) was used for statistical analysis.

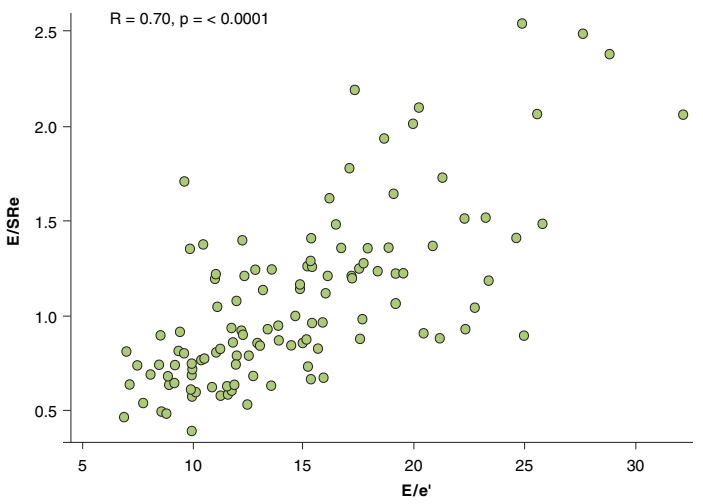
RESULTS

Of 125 patients included, the E/SRe ratio was obtainable in 121 patients (97%). In 4 patients >3 segments were not possible to analyze and were thus excluded. Median E/SRe was 0.93 (IQR: 0.74 to 1.26). Intraobserver and interobserver mean differences and 95% limits of agreement for E/SRe were 0.05 ± 0.24 and 0.06 ± 0.27, respectively, compared to 1.0 ± 4.6 and 0.9 ± 6.6, respectively for E/e′ (Online Figures 1 and 2).

Clinical characteristics of the groups divided according to E/SRe above and below this median are shown in **Table 1**, and echocardiographic characteristics are shown in **Table 2**. Clinical characteristics were similar in both groups, although logistic EuroSCORE was higher among patients with increased E/SRe (6.1 ± 4.5 vs. 4.7 ± 3.1, respectively; p = 0.04).

Despite no differences in effective aortic valve area, the transvalvular velocity was higher among patients with increased E/SRe (4.1 ± 0.8 m/s vs. 3.7 ± 0.7 m/s, respectively; p = 0.01) (**Table 2**). E/SRe correlated positively with LV mass index (r = 0.30; p = 0.0009), LA volume index (r = 0.48, p < 0.0001), left ventricular end diastolic volume (r = 0.45; p < 0.0001), E/e′ (r = 0.70; p < 0.0001) (**Figure 2**), and

FIGURE 2 Scatter Plot for E/e′ and E/SRe



Scatter plot shows the association between E/e′ and E/SRe. Analysis revealed a significant correlation between these 2 parameters. E/e′ = early diastolic mitral inflow velocity-to-early diastolic velocity of the mitral annulus ratio; E/SRe = early mitral inflow velocity-to-early diastolic strain rate ratio.

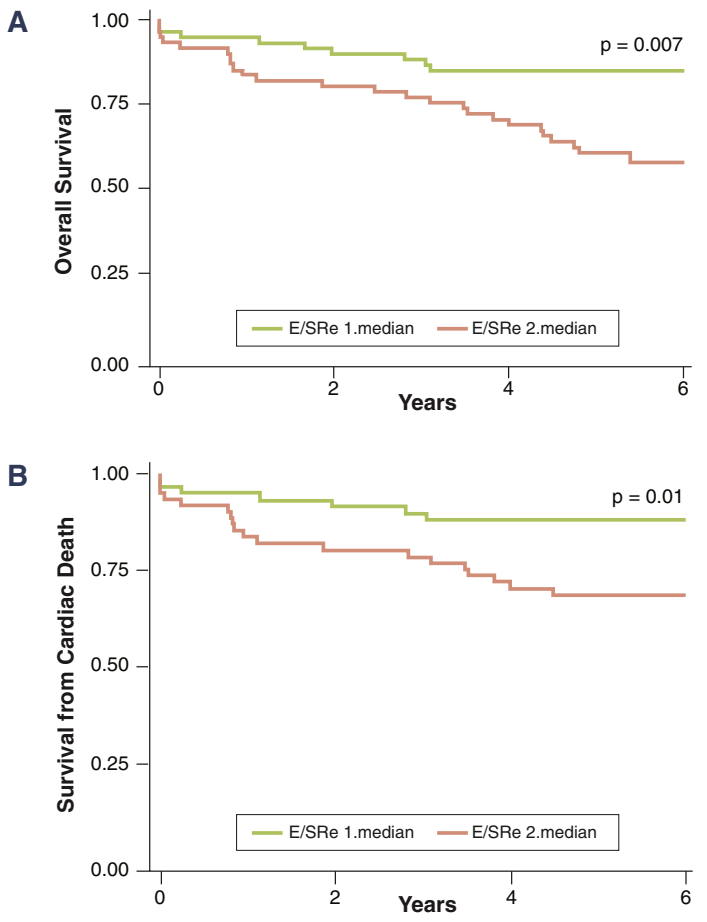
NT-proBNP (r = 0.43; p < 0.0001) (Online Figures 1 and 2). Higher fibulin-1 levels were present in patients with increased E/SRe (76 [61 to 100 μg/ml] vs. 90 [72 to 108 μg/ml], respectively; p < 0.05). Both systolic and diastolic functions were reduced among patients with increased E/SRe as LVEF was reduced (53 ± 7 vs. 56 ± 7, respectively p = 0.03), and a restrictive filling pattern was more common (28% vs. 8%, respectively; p = 0.005).

CLINICAL OUTCOME. The median follow- up duration for the total cohort was 5.0 years (IQR: 4.3 to 6.0 years). Death occurred in 37 patients (31%) due to a cardiac cause in 26 patients (n = 15 sudden cardiac death, n = 7 post-operative death, n = 3 congestive heart failure, and n = 1 aortic aneurysm) and a noncardiac cause in 11 patients (7 from cancer, 3 from infectious disease, and 1 from subarachnoid hemorrhage). All-cause and cardiac mortality rates were increased in patients with E/SRe greater than the median (estimated 5-year overall mortality of 40% vs. 15%, respectively, p = 0.007, and an estimated 5-year cardiac mortality rate of 32% vs. 12%, respectively; p = 0.01) (**Figure 3A**).

Thirty-day mortality was similar between groups (6.5% [n = 4] vs. 3.3% [n = 2] high E/SRe median and low E/SRe median, respectively; p = 0.68).

In univariate Cox regression analysis, E/SRe, age, EuroSCORE, LV mass index, LA volume index, LVEF, GLS, E/e′, and NT-proBNP were univariate predictors

FIGURE 3 Event-Free Survival as a Function of E/SRe



Kaplan-Meier curves show **(A)** overall survival and **(B)** cardiac survival according to median E/SRe ratio. Abbreviations as in Figure 2.

of overall mortality (Table 3), although when we adjusted for the predefined variables age, history of diabetes mellitus, and LVEF, only E/SRe ratio and LA volume index remained associated with overall mortality. Even when we included LA volume index or treatment with candesartan in the multivariate model, E/SRe was significantly associated with overall mortality (HR: 2.2; 95% confidence interval [CI]: 1.1 to 4.4; $p < 0.05$ models not demonstrated). Testing the multivariate model in the subset of patients with sinus rhythm led to consistent findings (HR: 2.2; 95% CI: 0.9 to 5.0; $p = 0.06$). In addition, all variables were tested in a stepwise Cox model with forward selection; the E/SRe ratio was the sole predictor of mortality (HR: 2.9; 95% CI: 1.6 to 5.5; $p = 0.001$; data not demonstrated).

In a univariate Cox regression analysis, E/SRe, age, EuroSCORE, history of diabetes mellitus, LV mass index, LA volume index, LVEF, s′, GLS, E/e′, and NT-proBNP were associated with cardiac mortality. When we adjusted for age, history of diabetes mellitus, and LVEF, this association was still significant for E/SRe, LV mass index, E/e′, GLS, and LA volume index (Table 4). In a multivariate model containing LVEF, LV mass index, and E/SRe, E/SRe ratio was the sole predictor of cardiac mortality (HR: 2.7: 95% CI: 1.1 to 6.7; $p = 0.04$; data not demonstrated).

In the subset of patients with LVEF >50% ($n = 99$), we demonstrated a similar association between overall mortality and E/SRe (HR: 3.3; 95% CI: 1.6 to 6.8); $p = 0.001$, while neither E/e'_{sep} nor NT-proBNP significantly associated with mortality (HR = 1.07 (95% CI: 0.99 to 1.14); $p = 0.08$, and HR: 1.29; 95% CI: 0.95 to 1.73; $p = 0.10$, respectively).

Comparing the overall log likelihood chi-square analysis of the predictive power of 3 nested models, each including EuroSCORE, history of diabetes, and LVEF, the model including E/SRe was statistically superior to models based on E/e′ or NT-proBNP, as shown in Figure 4. Consistent with these findings, the model including E/SRe and the aforementioned variables provided a larger AUC (0.71 ± 0.05) than the model based solely on EuroSCORE, history of diabetes, and LVEF (AUC: 0.67 ± 0.05). Replacing E/SRe in the model with E/e′ or NT-proBNP resulted in an AUC of 0.69 ± 0.05. The rate of correct classification for the model containing E/SRe was 74%, compared to 70% in the models including E/e′ or NT-proBNP.

Using receiver-operating characteristic curve analysis, an E/SRe ratio ≥1.04 (AUC: 0.64), an E/e′ ratio ≥14.9 (AUC: 0.60), and an NT-proBNP concentration of ≥367 pmol/l (AUC: 0.62) were the best cutoff values with which to identify nonsurviving patients during follow-up, although these differences were not statistically significant. Similar best cutoff values were identified when we performed the analysis with cardiac death as endpoint: an E/SRe ratio ≥1.14 (AUC: 0.67), an E/e′ ratio ≥15.2 (AUC: 0.62), and an NT-proBNP concentration ≥471 pmol/l (AUC: 0.67).

In the subset of patients without LV hypertrophy, overall mortality was 37% and 14% ($p = 0.07$) in the high- and low-E/SRe group, respectively. Similarly, in patients with LV hypertrophy, mortality was increased in the group of patients with high E/SRe (43% vs. 25% in the group with low E/SRe, $p = 0.11$) (Figure 5).

DISCUSSION

The main finding in the present study of patients with LVEF >40% undergoing AVR for severe AS is that the pre-operative early mitral inflow velocity-to-early

TABLE 3 Univariate Pre-Operative Predictors of Overall Mortality

	Univariate			Univariate*	
	HR	$HR_{adjusted/SD}$	p Value	HR	p Value
E/SRe, per unit	2.80 (1.50–5.30)	1.59	0.001	2.30 (1.10–4.50)	0.02
Age, per yr	1.05 (1.00–1.09)	1.54	0.03		
EuroSCORE, per unit	1.17 (1.00–1.37)	1.37	0.047		
Sex	0.80 (0.40–1.60)		0.51		
Diabetes mellitus	2.00 (0.90–4.30)		0.10		
Ischemic heart disease	1.21 (0.60–2.60)		0.64		
Atrial fibrillation	1.10 (0.50–2.60)		0.25		
LV mass index, per g/m^2	1.01 (1.00–1.02)	1.44	0.009	1.01 (0.99–1.01)	0.08
Relative wall thickness, per %	1.02 (0.99–1.04)	1.30	0.12		
Left atrial volume index, per ml/m^2	1.02 (1.00–1.03)	1.43	0.01	1.02 (1.00–1.03)	0.04
LV ejection fraction, per %	0.95 (0.91–1.00)	0.70	0.05		
$s'_{average}$, per cm/s	0.79 (0.61–1.01)	0.71	0.06		
Global longitudinal strain, per %	1.11 (1.02–1.22)		0.02	1.07 (0.97–1.18)	0.20
Deceleration time, per 10 ms	1.03 (0.98–1.09)	1.22	0.23		
E/e'_{sep}, per unit	1.07 (1.01–1.13)	1.43	0.02	1.06 (0.99–1.12)	0.07
log NT-proBNP, per pmol/l	1.33 (1.04–1.69)	1.44	0.02	1.20 (0.90–1.59)	0.21
Candesartan treatment	1.20 (0.63–2.30)		0.58		

*6 different models adjusted for age, diabetes, and LV ejection fraction.
$HR_{adjusted/SD}$ = hazard ratio adjusted for 1 SD; other abbreviations are as in Table 1.

diastolic strain rate ratio was an independent predictor of long-term post-operative survival. Although E/SRe and E/e′ were correlated, E/SRe was superior to E/e′ in predicting outcome, with a nearly 3-fold increase in mortality per unit and correctly categorizing 4% more patients than E/e′.

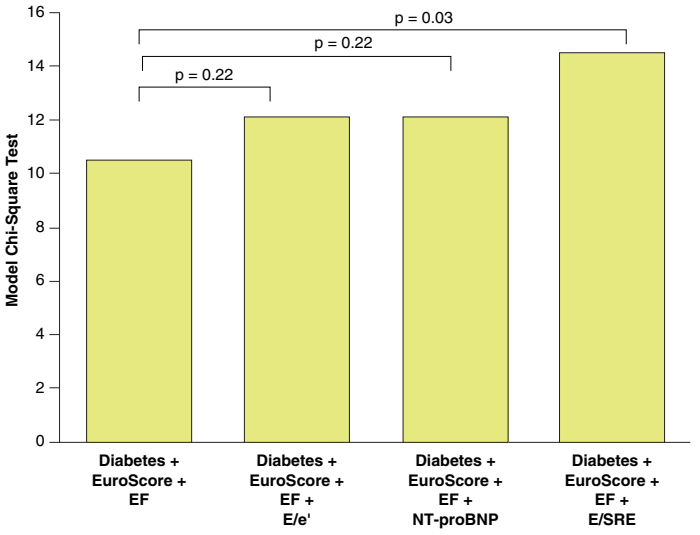
The severity of diastolic dysfunction and severity of increased filling pressure before valve replacement has in noninvasive and invasive studies been demonstrated to predict exercise intolerance (2), and clinical outcome (1,3). Thus, it is likely that LV pressure overload in combination with coexisting LV hypertrophy and myocardial fibrosis leads to increased LV and LA filling pressures which eventually will cause a transition from an asymptomatic state to a symptomatic state.

TABLE 4 Univariate Pre-Operative Predictors of Cardiac Mortality

	Univariate			Univariate*	
	HR	$HR_{adjusted\ pr\ SD}$	p Value	HR	p Value
E/SRe, per unit	3.60 (1.80–7.40)	1.77	<0.001	2.90 (1.30–6.40)	0.007
Age, yrs	1.06 (1.00–1.11)	1.52	0.04		
EuroSCORE, per unit	1.26 (1.05–1.53)	1.45	0.02		
Sex	0.71 (0.30–1.50)		0.31		
Diabetes mellitus	3.10 (1.30– 7.10)		0.008		
Ischemic heart disease	0.83 (0.30–2.40)		0.74		
Atrial fibrillation	1.70 (0.70–4.30)		0.25		
Left ventricular mass index, per g/m^2	1.01 (1.00–1.02)	1.40	0.007	1.01 (1.00–1.02)	0.047
Relative wall thickness, per %	1.03 (1.00–1.06)	1.30	0.02	1.03 (1.00–1.06)	0.03
Left atrial volume index, per ml/m^2	1.03 (1.00–1.04)	1.46	0.004	1.02 (1.01–1.05)	0.01
LV ejection fraction, per %	0.94 (0.89–0.99)	0.65	0.047		
$s'_{average}$, per cm/s	0.71 (0.53–0.95)	0.70	0.02	0.81 (0.59–1.12)	0.21
Global longitudinal strain, per %	1.24 (1.11–1.38)	2.22	<0.001	1.20 (1.06–1.36)	0.005
Deceleration time, per 10 ms	1.02 (0.96–1.09)	1.26	0.49		
E/e'_{sep}, per unit	1.08 (1.01–1.15)	1.32	0.02	1.07 (1.00–1.15)	0.046
log NT-proBNP, per pmol/l	1.47 (1.09–1.97)	1.64	0.01	1.33 (1.30–6.99)	0.10
Candesartan treatment	1.20 (0.55–2.59)		0.65		

*7 different models adjusted for age, diabetes, and LV ejection fraction.
Abbreviations as in Table 2.

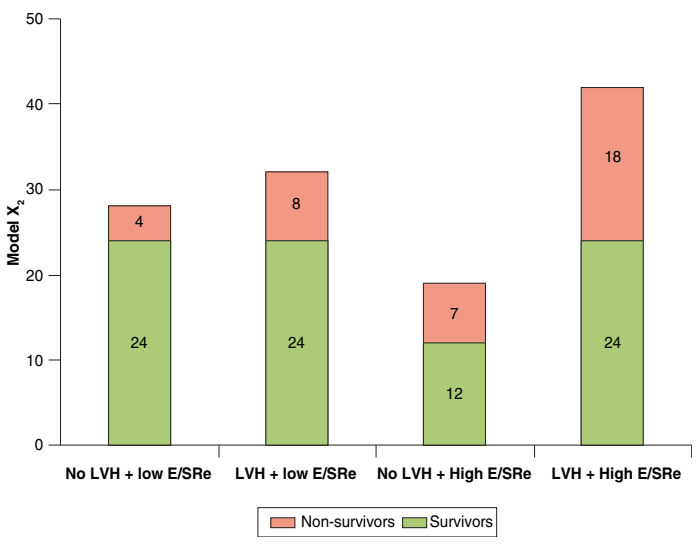
FIGURE 4 Comparison of Multivariate Models



Incremental prognostic comparison among the E/e′ ratio, NT-proBNP, and the E/SRe ratio in predicting overall mortality. E/SRe ratio provided incremental information for diabetes, EuroSCORE, and EF. EF = ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Figure 2.

Recently the ratio of E/SRe has been proposed as a novel marker of elevated LV filling pressures (7,8). The ratio was investigated in a large population with myocardial infarction, where Ersbøll et al. (9) demonstrated that E/SRe was superior to E/e′ in predicting outcome. The present study extends this finding to patients with severe AS, where we demonstrated that E/SRe outperformed E/e′ and NT-proBNP. This may reflect that although e′ correlates with the LV relaxation coefficient tau (19), and the ratio of E/e′ associates to LV filling pressures in AS (4), the association with tau in patients with normal LVEF is, at best, moderate (19). Furthermore, tissue Doppler imaging-assessed e′ has still some important limitations. First, TDI-estimated velocities may be inaccurate as a consequence of the Doppler-related angle dependency. Second, early diastolic relaxation is an active energy-dependent process initiated in the basal segments of the LV that propagates toward the apex. This base-to-apex gradient creates a wave of relaxation that, together with untwisting and myocardial thinning due to its incompressible nature, results in chamber enlargement (20). TDI-based assessment of early relaxation using e′ obtained in the basal medial and lateral annulus may not accurately reflect regional alterations in relaxation or alterations in the mid-wall/apical segments. This may be particularly important among patients with AS, as both basal and mid-wall segments are affected (21). Both animal (22) and human (23) models have demonstrated that the suction effect and elastic recoil of the LV depend on the early-diastolic base to apex interventricular pressure gradient, and that this gradient correlates to Doppler derived deformation parameters (24). As strain rate during early diastole estimated by speckle-tracking reflects the sum of all gradients it is likely that SRe identifies patients with reduced interventricular gradients and as consequence patients with reduced elastic recoil and impaired relaxation. Further strengthening this view, propagation velocity was reduced among patients with increased E/SRe ratio, implying that they had reduced suction effect of the LV.

FIGURE 5 Overall Mortality as a Function of LVH and E/SRe



Overall mortality among 4 groups stratified according to the presence of LVH and median E/SRe ratio. LVH = left ventricular hypertrophy; other abbreviations as in Figure 2.

In addition, our study finding confirms those of other studies (25) demonstrating that increased filling pressures are most prominent in patients with marked LV hypertrophy, although interestingly, our data suggest that differences in LV mass index most likely reflect increased LV cavity rather than increased wall thickness. We similarly demonstrate an association between E/SRe and fibulin-1, a novel biomarker associated with markers of LV filling pressure (16), myocardial stiffness (26) that has been suggested to reflect myocardial fibrosis. Both findings further strengthen the view that excessive LV remodeling in AS is unfavorable and is associated with a poor post-operative outcome. No prospective studies have determined whether early surgery

before severe hypertrophy has developed is beneficial, but it seems intuitive, and the most recent European guidelines (27) have proposed that surgery should at least be considered in patients with excessive LV hypertrophy in the absence of hypertension. We demonstrated that the presence of increased filling pressures was associated with an increased mortality regardless of LV hypertrophy, and thus, it seems that filling pressure rather than the mechanism for increased filling pressures is the key prognostic factor. Finally, because E/SRe is associated with remodeling and filling pressure, we speculate that E/SRe could be used to monitor patients with ambiguous symptoms, to distinguish symptomatic from truly asymptomatic patients.

STUDY LIMITATIONS. The sample size was small, which makes our models unstable with a potential risk of overfitting the models. In addition this was a post hoc analysis, and the present study should only be considered hypothesis generating. Clearly, larger studies also including patients with depressed LVEF, are warranted. The entry criterion for the study was symptomatic AS referred for AVR. Thus, the applicability to asymptomatic patients is unknown. Future studies should be performed in asymptomatic patients to clarify whether our findings also apply to a general population with AS. E/SRe had a very good feasibility, but it was not possible in all patients. We have no data for mitral annular calcification or conduction abnormalities, a factor known to affect diastolic and systolic functions; data should therefore be interpreted cautiously.

LV structure was assessed by echocardiography, and no histologic examinations were performed; thus, we can only speculate on the degree of myocardial fibrosis.

CONCLUSIONS

The present study demonstrates that the pre-operative early mitral inflow velocity -to-early diastolic strain rate (E/SRe) ratio is significantly associated with long-term post-operative survival, with a nearly 3-fold increase in risk of mortality per unit, and is superior to the velocity-based E/e′ ratio in patients with severe AS undergoing AVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Evaluation of early diastolic filling by using pulsed wave and tissue Doppler echocardiography has proven to be important but the limitations of that method may be overcome in part by using the early mitral inflow velocity-to-global diastolic strain rate ratio (E/SRe). We report the use of this index in a population with severe symptomatic aortic stenosis undergoing aortic valve replacement. E/SRe proved to be robust and reproducible and was able to predict long-term post-operative outcome better than other markers of left ventricular filling pressure. Thus, this index seems to provide incremental information about hemodynamic burden to conventional indices in the pressure-overloaded heart.

TRANSLATIONAL OUTLOOK: Future studies should be conducted in larger populations that include asymptomatic patients in order to assess whether the index ultimately could stratify risk in even asymptomatic patients who could benefit from early referral for valve replacement.

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APPENDIX For supplemental figures, please see the online version of this article.