Ratio of Transmitral Early Filling Velocity to Early Diastolic Strain Rate Predicts All-Cause Mortality in Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Aims: The ratio of early mitral inflow velocity to global diastolic strain rate (E/e'sr) has recently emerged as a novel measure of left ventricular (LV) filling pressure. This new measure has demonstrated to have prognostic value superior to E/e'. This study aimed to investigate the prognostic value of E/e'sr in a large cohort of patients with heart failure with reduced ejection fraction (HFrEF) in relation to all-cause mortality.

Methods: We retrospectively studied 897 HFrEF (mean age 66 ± 12 years, 73% male, 59% ischemic cardiomyopathy) patients who underwent speckle tracking echocardiography where E/e'sr along with novel and conventional echocardiographic parameters were obtained. The primary endpoint was defined as all-cause mortality.

Results: During follow-up (median: 40 months IQR: 22-57), 137 (15.3%) patients died. Both E/e'sr and E/e' were significantly associated with mortality (E/e'sr: HR 1.03 95%CI [1.02-1.04], $p<0.001$, per 0.10m increase) and (E/e': HR 1.04 95%CI [1.02-1.06], $p = 0.001$, per 1unit increase). E/e'sr remained an independent predictor in a multivariable model after adjusting for age, gender, mean arterial pressure, heart rate, BMI, total cholesterol, diabetes mellitus, ischemic cardiomyopathy, LVEF, LVIDd, LVMI, LAVI, TAPSE and LV-GLS (HR 1.02 95%CI [1.01-1.03], $p = 0.007$) whereas E/e' did not (HR 1.01 95%CI [0.98-1.04], $p = 0.57$). Furthermore, E/e'sr provided incremental prognostic information beyond a model including known risk factors: age, gender, total cholesterol, mean arterial pressure, heart rate, BMI, smoking status and E/e' (Harrell's C-statistics: 0.72 (0.68-0.77) vs 0.70 (0.66-0.75), $p = 0.047$).

Conclusions: In HFrEF patients, E/e'sr provides independent and incremental prognostic information regarding all-cause mortality superior to E/e'. (*J Cardiac Fail 2019;25:877−885*)

Key Words: Two-dimensional speckle tracking echocardiographic, early diastolic strain rate, global longitudinal strain, systolic heart failure, HFrEF, long-term outcome, filling pressures.

Introduction

Heart failure (HF) is a global pandemic and there is currently 5.7 million people in the US diagnosed with HF and the prevalence is rising.[1] Patients suffering from HF with reduced ejection fraction (HFrEF) have a general lowered functional level and higher morbidity and mortality than people without HF.[2,3]

Identification of high-risk patients is key to improve the prognosis by initiating more intensive monitoring and treatment. Previous studies have shown that both impaired left ventricular (LV) systolic and diastolic function were associated with a poor outcome in patients with HF.[4,5] Elevated filling pressure is a diagnostic hallmark of HF. Information regarding filling pressure is important in quantifying severity of HF and in monitoring effect of treatment. The ratio of transmitral early filling velocity (E) to the early relaxation tissue velocity (e') is an important diastolic function parameter and is known to correlate well with LV filling pressure in patients with reduced LV ejection fraction (LVEF).[6,7] However, tissue Doppler derived E/e' is subject to certain technical limitations including high sensitivity to sample location and transverse motion, angle dependency with a significant risk of errors with angulations $>20°$[8] and the risk of missing regional disturbances as e' is obtained at the basal segments of the heart.[9,10] The ratio of transmitral early filling velocity to early diastolic strain rate (E/e'sr) has recently emerged as a novel measure of LV filling

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pressure and is able to circumvent the limitations of E/e'. A strong correlation has previously been found between E/e'sr and invasively measured LV filling pressure.[11,12,13] Furthermore, E/e'sr has shown to be superior to E/e' in several studies as e'sr is measured from the entire LV and therefore reflects global LV relaxation better than E/e'.[14,15,16,17] The purpose of this study was to assess the prognostic value of E/e'sr in predicting mortality in a large cohort of patients suffering from HF with reduced LVEF and whether it was superior to E/e'.

Methods

Study Population

This retrospective study identified 1,102 consecutive nonacute patients referred to the HFrEF clinic at Gentofte Hospital from 2003-2013. All patients had LVEF $\leq$ 45% at referral. All patients had HFrEF diagnosed by an experienced clinician and a history of angiography to assess coronary artery status. Each patient had an echocardiographic examination retrieved from the hospital's database. Only patients with an echocardiographic examination performed within 1 year of admittance were included (median 30 days prior to admittance; IQR: 6-56 days before admittance). Twenty-two patients were excluded as they did not have an echocardiographic examination within 1 year of admittance. Furthermore, 183 patients were excluded due to poor image quality or inadequate image quality for determining E/e'sr, leaving 897 patients with image quality sufficient to measure E/e'sr. Clinical baseline data was obtained upon admittance to the HFrEF clinic and included previous procedures performed, relevant status of medication initiated at admission date and history of diseases. Ischemic cardiomyopathy was defined as patients with a history of myocardial infarction and/or had undergone percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass graft (CABG) surgery. Follow-up was 100% and mortality status was retrieved from the Danish National Registry of Mortality.

Echocardiography

Echocardiography was performed using Vivid 7 or 9 ultrasound systems (GE Healthcare, Horten, Norway) and stored on a GE Healthcare image vault. All echocardiograms were analyzed offline using commercially available post-processing software (Echopac version 12) by a trained investigator blinded to all other information.

Conventional Echocardiography

LV end-diastolic dimensions were measured in the parasternal long-axis view at the tip of the mitral leaflets according to existing recommendations.[18] LV end-diastolic dimensions include: interventricular septum thickness, LV internal dimension and LV posterior wall dimension. LVEF was measured using the modified Simpson's biplane method. LV mass index (LVMI) was calculated as the anatomical mass (estimated by the Devereux formula) divided by body surface area (estimated by the Du Bois formula). Left atrial volume was measured with the area length method and divided by body surface area to obtain left atrial volume index (LAVI). Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode echocardiography in the apical 4-chamber view.

Mitral valve inflow patterns were assessed using pulsed-wave Doppler in the apical 4-chamber view and peak velocities of transmitral early filling (E) and transmitral late filling (A) along with E/A ratio and deceleration time (DT) of the E-wave. Pulsed-wave Doppler was further used to measure the peak longitudinal early diastolic tissue velocity (e') with the sample volume placed at the septal and lateral mitral annular sites in the apical 4-chamber view and the mean was calculated and used for E/e'.

Speckle Tracking Echocardiography

The apical 4-chamber, 2-chamber and 3-chamber views were used for two-dimensional speckle tracking analysis with an average of 74 $\pm$ 18 frames per second. A semi-automated function was used to place the region of interest (ROI) to cover the thickness of the myocardial wall at end-systole. The ROI was adjusted manually by the investigator in cases of inaccurate tracking of the myocardial motion. A segment was excluded if untraceable due to shadow/artifact or if it did not cover the entire myocardial wall. Left ventricular Global longitudinal strain (LV-GLS) was calculated as the average of the 3 views and in cases of unsuccessful tracking of a chamber, the remaining 2 chambers were averaged to obtain LV-GLS (percentage of chambers available: 4-chamber views: 95.1%; 2-chamber views: 96.0% and 3-chamber views: 94.3%). Peak global systolic and diastolic strain rates were calculated using the same method and an example of the measurement is displayed (Figure 1). E was indexed to peak early diastolic strain rate (e'sr) to obtain E/e'sr. Reproducibility was found good when testing intra- and interobserver variability for strain rate e with a small bias (mean difference $\pm$1.96 SDs was -0.06 $\pm$ 0.27 for the intraobserver analysis and 0.07 $\pm$ 0.31 for the interobserver analysis).

Statistics

STATA Statistics/Data analysis, SE 12.0 (StataCorp, Texas, USA) was used for all analyses. Statistical significance was defined as a two-tailed $p \leq 0.05$. Baseline demographic, clinical and echocardiographic data stratified according to tertiles of E/e'sr were compared with trend tests using linear regression for continuous Gaussian distributed variables, non-Gaussian distributed variables were tested using an extension of the Wilcoxon rank-sum test[19], and by χ^2 test for trend for proportions. Histograms and normal Q-Q plots were used to assess if the variables were distributed as a Gaussian. The association between E/e'sr and the primary outcome was tested using Cox proportional hazards regression models including multivariable models adjusting for baseline and echocardiographic parameters. Parameters included in the multivariable model were the statistically significant variables from Table 1 and additionally variables which were deemed clinically relevant to include in

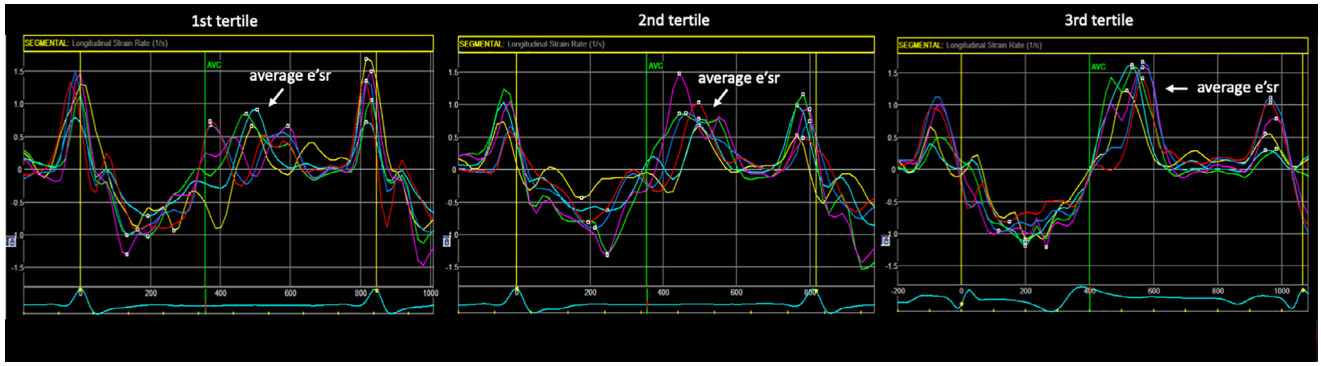

Fig. 1. Methodological example of strain rate measurement. An example of how strain rates (strain rate s, e and a) are measured using post-processing software. Colored lines represent regional curves and the white dotted line represents the average values.

the model even though they were not statistically significant in Table 1 *(gender, mean arterial blood pressure, BMI, total cholesterol and ischemic cardiomyopathy)*. Information regarding mitral regurgitation was missing in 330 (37%) patients and was therefore not included in the primary analysis. However, a sensitivity analysis with the variable included was fit. Rates of events were calculated by dividing events with person-time at risk. A Poisson model was used to estimate incidence rates and the association between E/e'sr and outcome was investigated using restricted cubic splines with the number of knots chosen according to the lowest Akaike information criterion value (Figure 3). Harrell's C-statistics were obtained from uni- and multivariable Cox proportional hazards regression models to evaluate the prognostic value of E/e'sr in relation to existing risk factors for predicting the outcome.

E/e' and E/e'sr were assessed individually in the multivariable regression model to avoid multicollinearity and E, DT and E/A ratio were not included in the model for the same reason. An exemption was made in the incremental analysis in which it was tested if E/e'sr had prognostic value beyond that of E/e'.

Ethics

This study was approved by the Danish Data Protection Agency, journal no. 03240 (I-suite), ID: GEH-2014-047

Results

During a median follow-up of 40 months (IQR: 22-57 months), 137 (15.3%) patients died. The mean E/e'sr was 164.7 ± 104.3cm. Elevated E/e'sr was significantly associated with higher age, higher heart rate, diabetes mellitus, a history of coronary bypass surgery, percutaneous transluminal coronary angioplasty, angina pectoris. Furthermore, E/e'sr was associated with echocardiographic measures: lower LVEF, larger LVIDd, increased LVMI, higher peak A-wave velocity, shorter DT of early mitral inflow, average peak early diastolic mitral annular velocity, lower TAPSE, increased index LAVI and lower LV-GLS (Table 1). Type of medication was not associated with higher E/e'sr.

Relationship Between E/e'sr and Mortality

The risk of dying increased with increasing tertiles of E/e'sr (Figure 2) and was found to be more than 3 times higher in the highest tertile of E/e'sr as compared to patients in the lowest tertile of E/e'sr (tertile 1 vs tertile 3: HR: 3.21 95%CI [2.08-4.96], $p < 0.001$). A model was fitted with an interaction term between atrial fibrillation and E/e'sr in which it was found that atrial fibrillation did not modify the relationship between E/e'sr and outcome (p for interaction = 0.177), and it was therefore not included in the models.

In univariable Cox regression analysis, E/e'sr was significantly associated with all-cause mortality (HR: 1.03 95%CI [1.02-1.04], $p < 0.001$, per 0.1m increase). In the restricted cubic spline model, the relationship between E/e'sr and the outcome was close to being linear but with a best fit with 3 knots. This suggests a slightly non-linear relationship (Figure 3). E/e' was also significantly associated with the outcome in a univariable model (HR: 1.04 95%CI [1.02-1.06], p = 0.001, per 1unit increase). Univariable and multivariable Cox regression analysis for all variables included are displayed in Table 2. In multivariable Cox regression after adjusting for age, gender, mean arterial pressure (MAP), heart rate, BMI, total cholesterol, diabetes, ischemic cardiomyopathy, LVEF, LVIDd, LVMI, LAVI, TAPSE and LV-GLS, E/e'sr remained an independent predictor of the outcome (HR: 1.02 95%CI [1.01-1.03], p = 0.007). The only other variables to remain independent in this model were age, MAP, diabetes, LAVI and LV-GLS (Table 2). E/e' did not remain a significant predictor when included in the same multivariable model instead of E/e'sr (HR: 1.01 95%CI [0.98-1.04], p = 0.57). Adding information regarding mitral regurgitation did not change the prognostic value of E/e'sr in the model (HR 1.02 95%CI [1.01-1.03], p = 0.007). A sensitivity analysis was performed using a cut-off of LVEF<40% for HFrEF (97 patients in total had LVEF>40%). In this analysis, E/e'sr remained an independent predictor of the outcome (HR: 1.02 95%CI [1.01-1.03], p = 0.020). Furthermore, E/e'sr remained significant after adding medication to the multivariable model: RAS blockade, beta-blocker, spironolactone, diuretic, anticoagulants, antiarrhythmics and calcium channel blocker (HR: 1.02 95%CI [1.01-1.03], p = 0.004).

Table 1. Baseline characteristics according to tertiles of E/e'sr

E/e'sr, cm	All	1st tertile	2nd tertile	3rd tertile	*P Value for trend*
		< 114	114 - 173	> 173	
Number	897	299	299	299	
Baseline characteristics					
Age, years	66.4 ± 11.5	63.6 ± 12.9	66.9 ± 10.4	68.9 ± 10.4	*<0.001*
Male gender, n (%)	657 (73.2)	227 (75.9)	204 (68.2)	226 (75.6)	*0.056*
Mean Arterial Pressure, mmHg	94 ± 13	95 ± 13	94 ± 14	93 ± 13	*0.24*
Heart rate, beats per minute	73 ± 15	73 ± 13	71 ± 15	76 ± 16	*<0.001*
BMI, kg/m^2	26.5 ± 4.8	26.2 ± 4.7	26.9 ± 5.0	26.6 ± 4.9	*0.21*
Total cholesterol mmol/L	4.5 ± 1.1	4.5 ± 1.1	4.4 ± 1.1	4.4 ± 1.1	*0.33*
Diabetes mellitus, n (%)	110 (12.3)	24 (8.0)	39 (13.0)	47 (15.7)	*0.014*
Atrial fibrillation /atrial flutter, n (%)	106 (11.8)	39 (13.0)	34 (11.4)	33 (11.0)	*0.72*
Pacemaker, n (%)	41 (4.6)	12 (4.0)	16 (5.4)	13 (4.3)	*0.72*
Implantable cardioverter-defibrillator, n (%)	23 (2.6)	5 (1.7)	6 (2.0)	12 (4.0)	*0.15*
CABG, n (%)	189 (21.1)	48 (16.1)	62 (20.7)	79 (26.4)	*0.008*
PTCA, n (%)	266 (29.7)	110 (36.8)	89 (29.8)	67 (22.4)	*<0.001*
History of MI	429 (47.8)	151 (50.5)	146 (48.8)	132 (44.1)	*0.27*
History of angina pectoris	212 (23.6)	88 (29.4)	59 (19.7)	65 (21.7)	*0.013*
Ischemic cardiomyopathy, n (%)	528 (58.9)	184 (61.5)	174 (58.2)	170 (56.9)	*0.49*
Mitral regurgitation, n (%)					*<0.001*
-No information		110 (37)	105 (34)	85 (29)	
-None/discrete		117 (39)	91 (31)	75 (25)	
-Mild		68 (22)	98 (33)	128 (43)	
-Moderate		4 (2)	5 (2)	10 (3)	
-Severe		0 (0)	0 (0)	1 (0)	
Medication					
RAS blockade	518 (57.7)	167 (55.9)	178 (59.5)	173 (57.9)	*0.66*
Beta-blocker	597 (66.6)	209 (69.9)	196 (65.6)	192 (64.2)	*0.31*
Spironolactone	139 (15.5)	48 (16.1)	54 (18.1)	37 (12.4)	*0.15*
Diuretic	464 (51.7)	153 (51.2)	165 (55.2)	146 (48.8)	*0.29*
Anticoagulants	171 (19.1)	61 (20.4)	56 (18.7)	54 (18.1)	*0.75*
Antiarrhythmics	44 (4.9)	9 (3.0)	17 (5.7)	18 (6.0)	*0.17*
Calcium channel blocker	7 (0.8)	2 (0.7)	4 (1.3)	1 (0.3)	*0.36*
Echocardiography					
E/e'sr (cm)	164.8 ± 104.3	86.8 ± 17.0	141.0 ± 17.0	266.5 ± 123.0	
LVEF (%)	28.0 ± 9.2	33.6 ± 7.5	27.8 ± 8.1	22.5 ± 8.5	*<0.001*
LVIDd (cm)	5.6 ± 1.1	5.3 ± 0.8	5.5 ± 1.0	6.1 ± 1.0	*<0.001*
LVMI (g/m^2)	119.7 ± 38.6	107.0 ± 37.2	115.1 ± 32.0	136.9 ± 39.8	*<0.001*
E, cm/s	7.7 [6.1-9.5]	6.5 [5.3-7.8]	7.9 [6.4-9.4]	9.2 [7.5-11.4]	*<0.001*
A, cm/s	7.1 [5.0-8.8]	6.8 [5.4-8.2]	7.7 [5.5-9.2]	6.6 [4.1-9.0]	*<0.001*
E/A-ratio	1.0 [0.8-1.6]	0.9 [0.7-1.2]	0.9 [0.7-1.4]	1.4 [0.9-2.4]	*<0.001*
DT (ms)	180.2 [143.8-229.8]	186.5 [152.5-236.5]	187.6 [148.9-232.0]	166.9 [129.3-217.7]	*<0.001*
e' (cm/s)	6.7 ± 2.5	7.7 ± 2.5	6.7 ± 2.4	5.8 ± 2.0	*<0.001*
e'sr (s^{-1})	0.6 ± 0.3	0.8 ± 0.2	0.6 ± 0.2	0.4 ± 0.1	*<0.001*
E/e'	11.7 [9.0-15.9]	8.9 [6.9-10.6]	12.0 [9.6-15.0]	16.0 [12.3-21.9]	*<0.001*
TAPSE (cm)	1.9 ± 0.6	2.0 ± 0.5	1.9 ± 0.6	1.8 ± 0.6	*<0.001*
LAVI (mL/m^2)	27.5 [21.0-35.8]	24.0 [18.1-30.3]	27.2 [21.4-34.9]	31.7 [24.6-40.3]	*<0.001*
LV-GLS (%)	-9.7 ± 3.3	-12.1 ± 2.9	-9.8 ± 2.6	-7.3 ± 2.4	*<0.001*

E/e'sr = ratio of peak transmitral early diastolic inflow velocity to global early diastolic strain rate; BMI = Body Mass Index; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; MI=mypcardial infarction; RAS=renin-angiotensin system; LVEF=Left Ventricular Ejection Fraction; LVIDd = Left Ventricular Internal Diameter at end-diastole; LVMI = Left Ventricular Mass Index; E = peak transmitral early diastolic inflow velocity; A = peak transmitral late diastolic inflow velocity; DT = deceleration time of early diastolic inflow; e' = average peak early diastolic longitudinal mitral annular velocity determined by color TDI; TAPSE=tricuspid annular plane systolic excursion; LAVI=left atrial volume index; LV-GLS= left ventricular global longitudinal strain;

Incremental Value of E/e'sr in Relation to Predicting Mortality in HFrEF

Harrell's C-statistics was obtained for all univariable Cox regression models (Table 2) in order to evaluate their individual prognostic value. Only LV-GLS had a higher Harrell's C-statistics than E/e'sr, however, the difference was not statistically significant (0.69 [0.65-0.74] vs 0.66 [0.61-0.71], p = 0.078).

To assess the prognostic value of E/e'sr compared to E/e' these two variables were included in a step-wise fashion to a multivariable model (model 1) consisting of known cardiovascular risk-factors: age, gender, total cholesterol, MAP, heart rate, BMI and smoking status. Model 2 included the same risk factors as model 1 and additionally E/e'. Model 3 contained the same variables as model 2 and additionally E/e'sr. E/e' did not significantly improve model 1 (0.69 [0.65-0.74] vs 0.70 [0.66-0.75], p = 0.11)

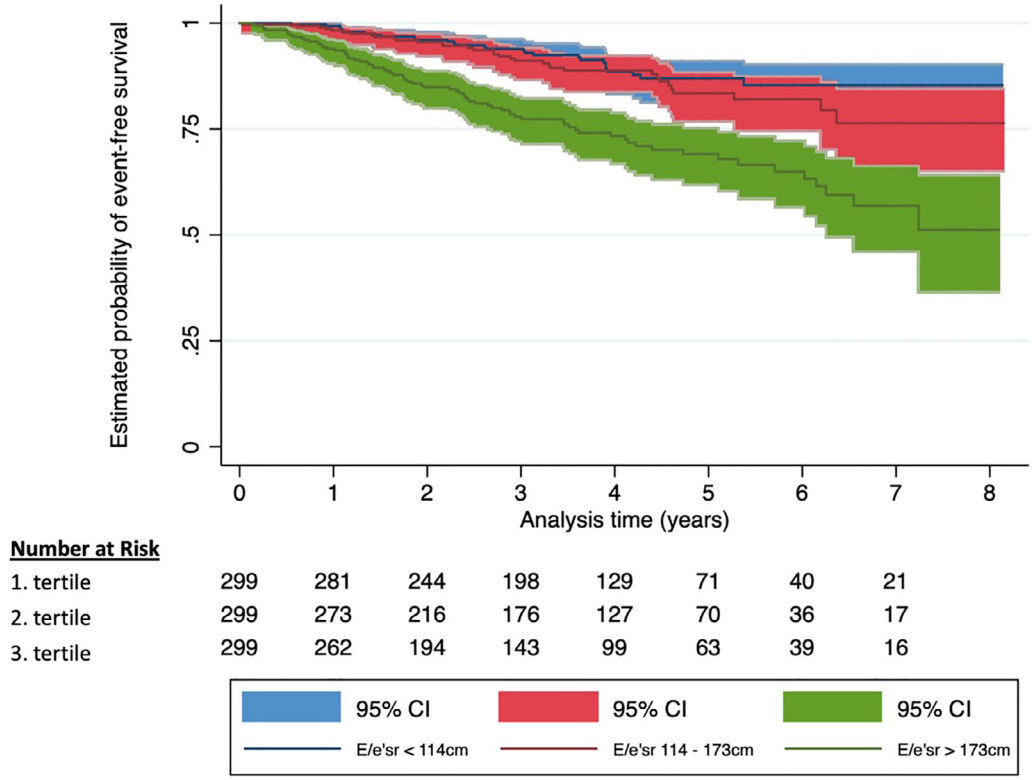

Fig. 2. Kaplan Meier curves stratified according to tertiles of E/e'sr in patients. Kaplan Meier survival estimates stratified according to tertiles of E/e'sr (with 95% confidence intervals). Risk table is displayed at timepoints 0, 1, 2, 3, 4, 5, 6 and 7 years. Abbreviations: CI = confidence interval, E/e'sr = Ratio of transmitral early filling velocity to early diastolic strain rate.

whereas E/e'sr did significantly improve model 1 (0.69 [0.64-0.73] vs 0.71 [0.67-0.78], p = 0.010). Furthermore, model 2 was significantly improved by adding E/e'sr (0.70 [0.66-0.75] vs 0.72 [0.68-0.77], p = 0.047) (Figure 4).

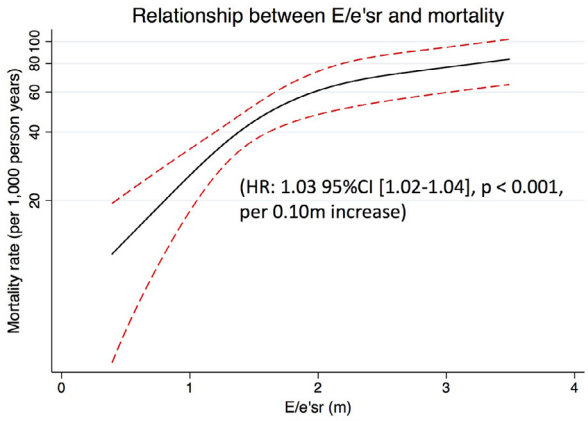

Fig. 3. Relationship between of E/e'sr and mortality. Displaying the unadjusted incidence rate of all-cause mortality (with 95% confidence intervals) per 1,000 person years for the population. E/e'sr is displayed in meters (m). The HR is calculated from a univariable Cox proportional hazard regression model of E/e'sr. HRs are calculated per 10cm increase of E/e'sr. Abbreviations: CI = confidence interval, HR = Hazard rate, E/e'sr = Ratio of transmitral early filling velocity to early diastolic strain rate.

Discussion

This is currently the largest study to investigate the predictive value of E/e'sr in patients suffering from heart failure with reduced ejection fraction. We were able to demonstrate that: (1) E/e'sr as a measure of LV filling pressure is a significant predictor of mortality independent of demographic, clinical and echocardiographic parameters, (2) E/e'sr provides incremental prognostic value in predicting mortality over and above known cardiovascular risk factors including E/e' and (3) E/e'sr is superior to E/e' as a predictor of mortality in HFrEF patients.

Prognostic Value of E/e'sr in Relation to Mortality Compared to E/e'

Several studies have previously found E/e' to be a useful non-invasive measure of LV filling pressure.[20,21,22] However, conflicting results has been reported. In some studies E/e' > 15 has a high sensitivity and specificity for predicting elevated LV filling pressure[20,23], but in other studies E/e' has been found to lack accuracy.[24,25] These inconsistencies may be explained by the known limitations of Doppler-derived e.g. the high susceptibility to sample location[8]. The ratio of transmitral early filling velocity to early diastolic strain rate has recently emerged as novel measure of LV filling pressure avoiding the technical limitations of the Doppler-based method and seems to better reflect LV filling pressures. [13,14,16,26] Early diastolic

Table 2. Uni- and multivariable Cox proportional hazard models

	Univariable analysis				*Multivariable analysis**		
	HR	95%CI	*p-value*	C-statistic	HR	95%CI	*p-value*
Age, per 1-yr increase	1.04	1.03-1.06	*<0.001*	0.63	1.04	1.02-1.06	*<0.001*
Male gender	1.24	0.83-1.85	*0.28*	0.52	1.17	0.76-1.81	*0.47*
MAP, per 1mmHg increase	0.97	0.96-0.98	*<0.001*	0.62	0.98	0.96-0.99	*0.001*
Heart rate, per 1 beat/min decrease	1.02	1.01-1.03	*0.003*	0.56	1.01	0.99-1.02	*0.35*
BMI, per 1-kg/m^2 increase	0.97	0.93-1.01	*0.12*	0.55	0.97	0.93-1.02	*0.24*
Total cholesterol, per 1mmol increase	0.85	0.72-0.99	*0.046*	0.55	0.91	0.76-1.08	*0.28*
Diabetes mellitus	1.95	1.27-2.98	*0.002*	0.54	2.03	1.23-3.34	*0.006*
Ischemic cardiomyopathy	1.12	0.79-1.58	*0.52*	0.51	0.88	0.61-1.27	*0.49*
LVEF, per 1% increase	0.95	0.93-0.96	*<0.001*	0.65	0.99	0.96-1.02	*0.49*
LVIDd, per 1cm increase	1.22	1.04-1.44	*0.017*	0.57	0.86	0.68-1.10	*0.24*
LVMI, per 1-g/m^2 decrease	1.01	1.00-1.01	*0.002*	0.58	1.00	0.99-1.01	*0.71*
LAVI, per ml/m^2 decrease	1.03	1.02-1.04	*<0.001*	0.60	1.02	1.00-1.03	*0.02*
TAPSE, per 1-cm increase	0.53	0.39-0.71	*<0.001*	0.60	0.82	0.59-1.14	*0.24*
E/A ratio, per 1 unit increase**	1.15	0.98-1.35	*0.080*	0.54	-	-	-
DT, per 1-ms decrease**	1.00	0.995-1.00	*0.057*	0.56	-	-	-
LV-GLS, per 1% decrease	1.24	1.16-1.31	*<0.001*	0.69	1.12	1.03-1.23	*0.010*
E/e', per 1 unit increase***	1.04	1.02-1.06	*0.001*	0.59	1.01	0.98-1.04	*0.57*
E/e'sr per 0.1m increase	1.03	1.02-1.04	*<0.001*	0.66	1.02	1.01-1.03	*0.007*

*The multivariable model includes age, gender, MAP, heart rate, BMI, total cholesterol, diabetes mellitus, ischemic cardiomyopathy, LVEF, LVIDd, LVMI, LAVI, TAPSE, LV-GLS and E/e'sr. Only significant predictors are displayed.

**E/A ratio and DT were not included in the multivariable model due to multicollinearity.

***E/e' was analyzed separately from E/e'sr in a multivariable model with the same variables.

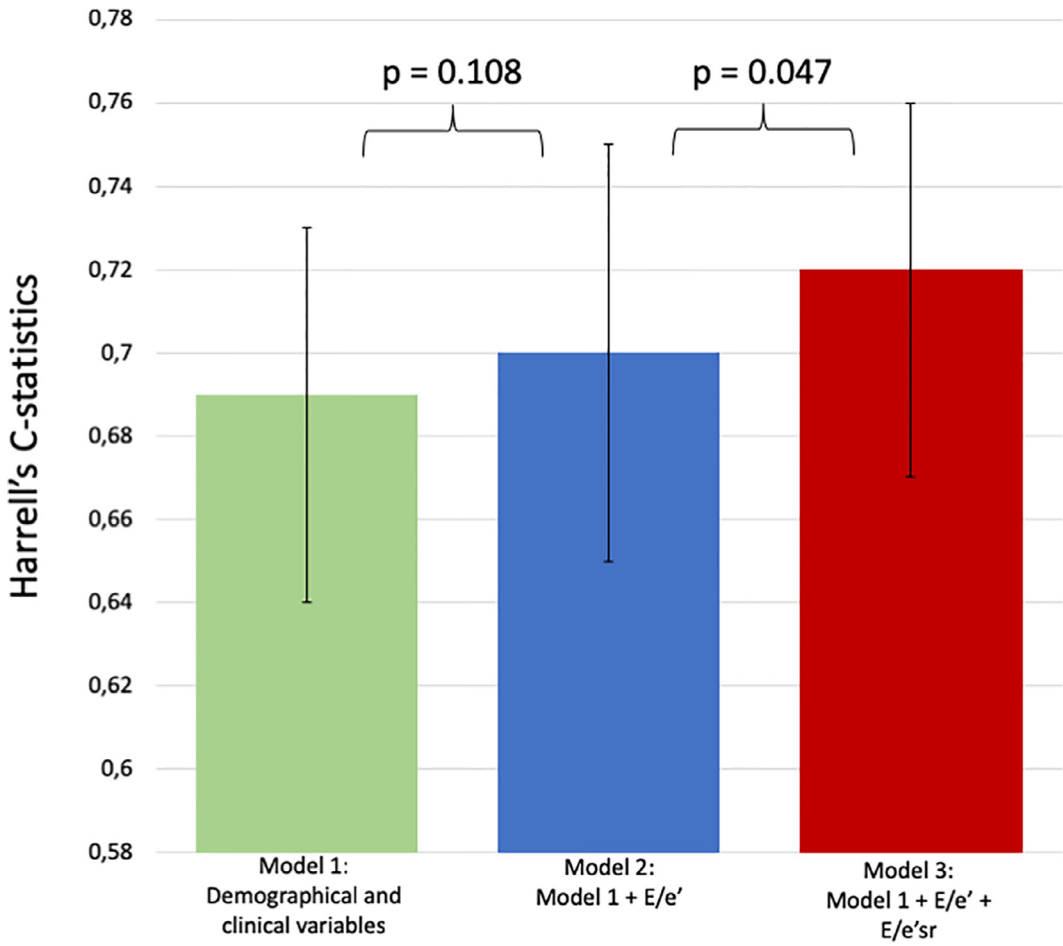

Fig. 4. Incremental value of E/e'sr assessed by differences in Harrell's C-statistics. Harrell's C-statistics for risk models; model 1: age, gender, total cholesterol, mean arterial pressure, heart rate, BMI and smoking status, model 2: same as model 1 and additionally E/e' and model 3: same as model 2 and additionally E/e'sr. Confidence intervals (95%) are displayed as capped bars.

strain rate may better reflect the global LV relaxation as it is a global measurement taking the entire LV into account in contrast to e' which only measures velocity at the basal segments of the heart. In E/e', it is assumed that the local peak velocities of the mitral annulus reflect the global LV relaxation. However, this may not be true in cases with regional dysfunction and mechanical dyssynchrony as can often be observed in HFrEF, bundle branch block and ischemic heart disease. Furthermore, e' has been shown to be affected by pre-load[27] whereas e'sr is less load-dependent. Both indexes have E-wave as a component which is known to be load-dependent meaning that even though E/e'sr may be less load-independent than E/e', it is still load-dependent to a certain degree. In HFrEF patients, changes in loading conditions due to volume overloading are often seen and can exaggerate E-wave velocity and thus affect E/e'sr. However, our results show that E/e'sr was independent of diuretics usage which suggests that E/e'sr was not profoundly affected by volume overloading.

Our findings suggest that E/e'sr has good value as a predictor of mortality in which diastolic dysfunction may play a role. Similar results were found in a smaller cohort of systolic heart failure patients by Chan et al, in which they were also able to demonstrate the superiority of E/e'sr compared to E/e' as predictor of adverse outcome.[28] Their findings were limited compared to ours in that they chose to include few echocardiographic parameters in their multivariable models thereby not assessing the prognostic strength of E/e'sr compared to conventional echocardiographic measurements. Hsu et al further showed the strength of E/e'sr as a predictor of all-cause mortality in HF in patients suffering from atrial fibrillation.[17] Ersbøll et al showed in their cohort of AMI patients that E/e'sr was a stronger predictor of HF, stroke, atrial fibrillation and all-cause mortality than E/e' and, similar to our findings, that E/e'sr has prognostic value beyond that of E/e'.[14] Interestingly, these findings were contradicted by the discoveries in a study by Shanks et al in STEMI patients in which they did not find E/e'sr to have significant prognostic value. However, their study was limited by a smaller population size (n=371) and a shorter follow-up period (17.3 ± 12.2 months) compared to our study and the study by Ersbøll et al. Our group has recently been able to demonstrate E/e'sr to be superior to E/e' and other echocardiographic measures in a large general population study, thereby underscoring that E/e'sr is a reliable predictor of outcome in patients with preserved systolic function as well as in patients with impaired systolic function.[15]

To summarize, E/e'sr has been found to have important prognostic information in various patient populations in relation to a wide spectrum of outcomes including HF, AMI, atrial fibrillation and mortality. With the increasing usage of two-dimensional speckle tracking in our field globally, E/e'sr may be a fast, accurate and non-invasive way of estimating LV filling pressure in patients undergoing echocardiographic examination. As estimation of LV filling pressure is useful in diagnosis and monitoring of treatment in HF patients, E/e'sr may serve as an important tool in the clinical setting. Additionally, our results suggest that E/e'sr provides prognostic information on mortality both in patients with and without atrial fibrillation.

Correct evaluation of the diastolic function is important in almost all patients suffering from cardiac pathology, underlining the importance of having reliable and accurate measurements at hand. Being able to estimate LV filling pressure is especially important in monitoring HFrEF patients, which is why our results are interesting as E/e'sr improved, though marginally, the multivariable risk models when the clinically used E/e' did not. As the current literature on E/e'sr is limited, future studies of large cohorts are important to determine the clinical usefulness and implications of E/e'sr along with establishing cut-offs to be used in clinic and guidelines. Additionally, larger studies evaluating the accuracy of E/e'sr in estimating invasively measured LV filling pressure are needed in order to validate E/e'sr as a good surrogate of LV filling pressure.

Limitations

This study is subject to certain limitations. The echocardiographic examination in some of the patients was performed relatively late (up to a year) compared to their admittance to the HFrEF clinic. Under ideal circumstances, the echocardiographic examination should be performed on the day of admittance to most correctly reflect in-clinic cardiac performance. However, most patients had their echocardiogram performed close to the day of admittance (median 30 days prior to admittance; IQR: 6-56 days before admittance). Furthermore, information regarding the patients' medication were registered at admission to the HFrEF clinic and this study could therefore not account for later changes in medication even though these could affect both E/e'sr and mortality. As this was a retrospective study under clinical conditions, we were only able to obtain a single cardiac cycle and lacked information on QRS duration along with cardiac re-synchronization therapy. Additionally, the study did not have information on eGFR and NT-pro-BNP, which are both known to be important when assessing the the prognosis in patients with HFrEF.

Conclusions

In patients suffering from HFrEF, E/e'sr is an independent predictor of all-cause mortality. E/e'sr provides incremental prognostic information beyond E/e' and known cardiovascular risk factors in relation to mortality. Additionally, E/e'sr demonstrated to be a stronger predictor of mortality when compared to E/e' in this study of patients with HFrEF.

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Declaration of Competing Interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.07.007.

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