A New Tissue Doppler Index in Predicting Future Atrial Fibrillation in Patients with Heart Failure

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Abstract

Background: Onset of atrial fibrillation (AF) in patients with heart failure (HF) is usually associated with a high occurrence of cardiovascular complications. E/(E'×S') ratio (E=early diastolic transmitral velocity, E'=early mitral annular diastolic velocity and S'=systolic mitral annulus velocity) has been shown to reflect left ventricular filling pressure.

Objetive: We investigate whether E/(E'×S') could be a predictor of new-onset AF in patients with HF.

Methods: We analyzed 113 consecutive hospitalized patients with HF, in sinus rhythm, after appropriate medical treatment. Patients with histories of AF, inadequate echocardiographic images, congenital heart disease, paced rhythm, significant primary valvular disease, acute coronary syndrome, coronary revascularization during follow-up, severe pulmonary disease or renal failure were not included. E/(E'×S') was determined using the average of septal and lateral mitral annular velocities. The primary study end-point was the new-onset AF.

Results: During the follow-up period (35.7 ± 11.2 months), 33 patients (29.2%) developed AF. Mean E/(E'×S') was 3.09 ± 1.12 in these patients, while it was 1.7 2 ± 1.34 in the other patients ($p < 0.001$). The optimal E/(E'×S') cut-off to predict new-onset AF was 2.2 (88% sensitivity, 77% specificity). There were 64 patients (56.6%) with E/(E'×S') ≤ 2.2 and 49 (43.4%) with E/(E'×S') > 2.2. New-onset AF was higher in patients with E/(E'×S') > 2.2 than in patients with E/(E'×S') ≤ 2.2 [29 (59.1%) *versus* 4 (6.2%), $p < 0.001$]. On multivariate Cox analysis including the variables that predicted AF on univariate analysis, E/(E'×S') was the only independent predictor of new-onset AF (hazard ratio = 2.26, 95% confidence interval = 1.25-4.09, $p = 0.007$).

Conclusions: In patients with HF, E/(E'×S') seems to be a good predictor of new-onset AF. (Arq Bras Cardiol 2011;97(6):468-477)

Keywords: Tissue doppler imaging, prognostic, heart failure, atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population[1,2] and its incidence increases with the severity of heart failure (HF)[3]. Mortality and morbidity after the onset of AF remains high despite recent progress in the management of this condition, even after adjustment for multiple variables including age, hypertension, ischemic heart disease and congestive HF[2,4-6]. Accordingly, practice guidelines for HF and AF have shifted their emphasis from treatment to prevention[1,7]. The identification of individuals at risk for AF remains a challenge, though. Therefore, risk stratification based on clinical, biomarkers and echocardiographic parameters to define patients who are at risk for AF has been studied extensively[8-18]. With its ability to identify or exclude abnormalities in cardiac structure and function, echocardiography could be useful for prediction of future development of AF[11-17]. Tissue Doppler Imaging (TDI), a new echocardiographic method, can predict AF[15-17]. The early diastolic transmitral velocity/early diastolic mitral annular velocity (E/E') ratio, reflecting left ventricular (LV) filling pressures, was proposed as a single Doppler parameter in prediction of new-onset AF[15-17]. These studies support the idea that increased intraventricular filling pressure correlates with the future development of AF. We have recently proposed a novel tissue Doppler index, E/(E'×S'), for the non-invasive assessment of LV end-diastolic pressure in a heterogeneous population of cardiac patients[19]. In this study, E/(E'×S') was the best predictor of LV end-diastolic pressure in sinus rhythm patients, and it was superior to E/E', E', S' or E, regardless of LV ejection fraction (LVEF), particularly in those with E/E' between 8 and 15 and in those with regional dysfunction. E/(E'×S') associates an index of diastolic function (E/E') and a parameter that explores LV systolic performance (S') and therefore could provide supplementary information compared to each component alone. We hypothesized that this novel TDI index, E/(E'×S'), may be more sensitive than traditional echocardiographic methods to predict future development of new-onset AF in patients with HF.

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Methods

Population studied

We analyzed 158 consecutive hospitalized patients with HF in sinus rhythm, diagnosed according to the guidelines[7,20]. Patients were excluded from the study if any of the following was present: history of AF, inadequate echocardiographic images, congenital heart disease, paced rhythm, significant primary valvular heart disease, acute coronary syndrome at inclusion, coronary artery bypass grafting during follow-up, severe pulmonary disease or renal failure. The other 113 patients formed our study group. The study was approved by the local research ethics committee.

Clinical variables recorded

The following clinical variables were recorded and included in the prognostic model: age, sex, body mass index, mean arterial pressure, heart rate, etiology of HF, New York Heart Association (NYHA) functional class, N-terminal pro-brain natriuretic peptide (NTproBNP) levels (determined simultaneously with echocardiography).

Echocardiography

Echocardiography was performed after appropriate medical treatment, within 24 hours of hospital discharge using a Vivid 7 ultrasonographic system (General Electric, Milwaukee, WI). Two-dimensional and M-mode measurements were performed according to the recommendations of the American Society of Echocardiography, working together with the European Association of Echocardiography[21]. The mechanism of mitral regurgitation (MR) was identified by transtoracic and/or transesophageal echocardiography[22]. The severity of MR was assessed from the apical views using the proximal convergence method; severe MR was considered if the regurgitant orifice area was $\geq$ 40 mm^2 and the regurgitant volume was $\geq$ 60 ml/beat[23]. Transmitral flow patterns were recorded from apical four-chamber windows with 3 to 5 mm pulsed-sample Doppler volume placed between the mitral valve tips. Maximal velocities of E and late diastolic transmitral flow (A) waves were measured during end-expiratory apnoea and E/A ratio calculated[24]; the velocities were recorded for five consecutive cardiac cycles, and the results were averaged. The global myocardial index (GMI) was determined using Doppler time intervals measured from mitral inflow and LV outflow Doppler tracings, as the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time[25].

The tissue Doppler program was set in pulsed-wave Doppler mode. Motion of mitral annulus was recorded in the apical four-chamber view at a frame rate of 80 to 140 frames per second. A 4 to 5 mm sample volume was positioned sequentially at the lateral and septal corners of the mitral annulus. The peak E' and S' were recorded for five consecutive cardiac cycles during end-expiratory apnoea, and the results were averaged. E/E' and E/(E'×S') were calculated using the average of septal and lateral mitral annular velocities (Figure 1)[19,24]. The restrictive LV filling pattern was defined accordingly to current guidelines[24]. All measurements were performed by an experienced echocardiographer.

Clinical outcome

The primary event consisted of new-onset AF. We established the occurrence of AF only when a physician confirmed the diagnosis by reviewing an electrocardiogram. We did not assess the duration of AF and made no distinction between paroxysmal, persistent, or permanent AF.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) for continuous variables and proportions for categorical variables. The mean values of continuous variables were compared by 2-independent sample t-tests, and differences in the prevalence between groups were compared via chi-square analyses. Receiver-operating characteristic (ROC) analysis was used to determine optimal cutoff values of continuous variables for the prediction of new-onset AF. Time-to-event analysis was performed using the Kaplan–Meier method. The relationship of parameters to the development of new AF was assessed with a Cox proportional hazards model. To test the independent predictor of new-onset AF, E/(E'×S') was entered into a multivariable Cox model that also included as covariates all significant variables by univariate analysis associated with new-onset AF. All analyses were performed with SPSS statistical software (version 15.0, SPSS Inc., Chicago, Illinois) and a value of $p < 0.05$ was considered for statistic significance. This work was supported by CNCSIS–UEFISCU, project number PN II/RU code PD 526/2010.

Results

This study included 113 consecutive hospitalized patients (the mean age was 61 ± 12 years; 54 women), with HF in sinus rhythm. Clinical variables were available for all patients. The mean LVEF was 41±15%; 77 patients had HF with reduced LVEF (68.1%) and 36 patients presented HF with normal LVEF (31.9%). Baseline clinical and echocardiographic data are summarized in Table 1. Mitral annular velocities from TDI were recordable at both sites in all 113 patients. After a mean follow-up of 35.7±11.2 months, new-onset AF developed in 33 patients (29.2%). As compared with patients who did not develop new AF, patients who developed new-onset AF had significantly higher NTproBNP levels and pulmonary artery systolic pressures, larger left atrial (LA) and LV volumes, lower LVEF, higher values for E, E/A, E/E' and GMI, lower E' and S' velocities, higher incidence of severe MR. In addition, there was no difference with regard to the distribution of age, gender, etiology, heart rate, mean arterial pressure, body mass index, NYHA class, medication (regarding beta blocker, angiotensin converting enzyme inhibitor/angiotensin receptor antagonist and diuretics) and E-deceleration time.

Figure 2 shows the ROC curves for the prediction of new-onset AF. The areas under ROC curves (AUC) are shown for the TDI parameters analyzed [E/(E'×S'), E/E' ratio, S', E'] and LA volume index (LAVI). The E/(E'×S') index was a significant predictor of new-onset AF (AUC= 0.83, 95% CI= 0.74–0.92, $p < 0.001$). The baseline E/E' ratio, S' and LAVI were also significant for predicting new-onset AF (AUC= 0.77, 95%CI= 0.68–0.86, $p < 0.001$; AUC= 0.76, 95%CI= 0.67–0.85, $p < 0.001$, and AUC= 0.68, 95%CI= 0.57–0.79, $p = 0.002$, respectively), whereas

the E' wave alone was an insignificant predictor (AUC = 0.61, 95%CI= 0.51–0.71, p = 0.056). A statistical comparison of the ROC curves demonstrates significant differences between E/(E'×S') and E/E' (p = 0.005), between E/(E'×S') and S' (p = 0.002), and between E/(E'×S') and LAVI (p < 0.001), respectively. The optimal cut-off value for E/(E'×S') ratio to predict new-onset AF was 2.2 with 88% sensitivity and 77% specificity.

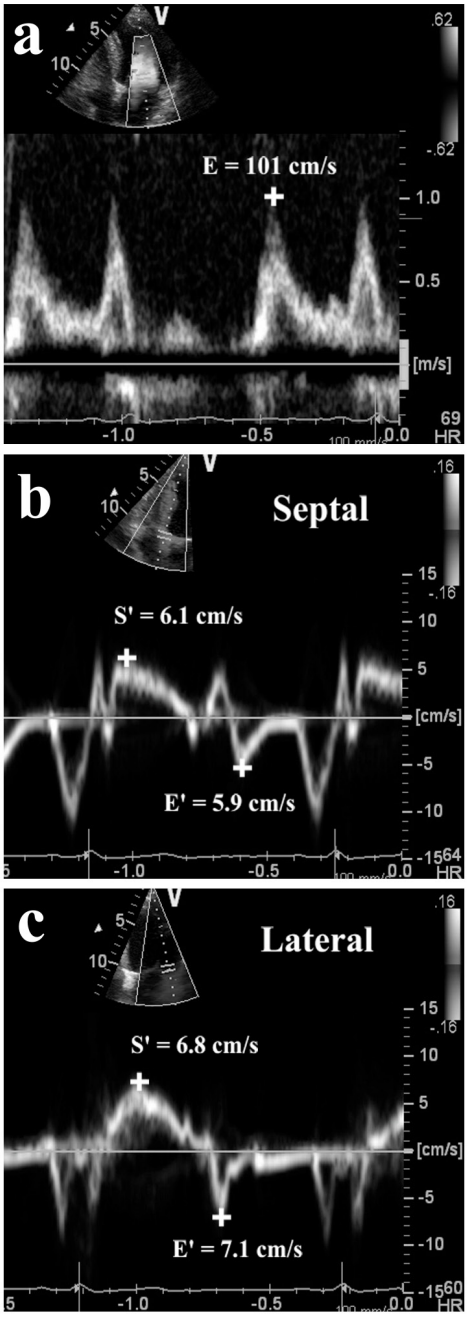

Figure 1 – *Bedside measurements of spectral Doppler peak early transmitral inflow (E) velocity (a) and spectral tissue Doppler peak early diastolic (E') velocities, respectively, peak systolic (S') velocities, at the septal (b) and lateral (c) corners of mitral annulus. E/(E'×S') and E/E' ratios were calculated (2.4 and respectively 15.5). The average of the velocities from septal and lateral mitral annulus was used.*

There were 64 patients (56.6%) with E/(E'×S')≤2.2 and 49 (43.4%) with E/(E'×S')>2.2. Mean E/(E'×S') was 3.34±0.98 in the group of patients with E/(E'×S')>2.2, while it was 1.19±0.47 in the others (p < 0.001). Patients with E/(E'×S')>2.2 presented significantly higher plasmatic NTproBNP levels (5379±4910 *vs.* 1265±1009 pg/ml, p < 0.001), larger LA and end–diastolic LV volumes (108±50 vs. 79±33 ml, p = 0.001, and 116±36 *vs.* 91±29 ml/m^2, p < 0.001, respectively), lower LVEF (34.8±13.2 *vs.* 46.2±13.3, p = 0.002), and higher incidence of severe MR [9 (18.3%) *vs.* 6 (9.3%), p = 0.01]. The incidence of new-onset AF was significantly higher in the group of patients with E/(E'×S')>2.2 than in the group with E/(E'×S')≤2.2 [29 (59.1%) *versus* 4 (6.2%), p < 0.001]. Figure 3 shows the Kaplan-Meier AF event-free curves for patients with E/(E'×S')≤2.2 and >2.2. During the follow-up period, cardiac death occurred in 18 patients (16%); new-onset AF was reported before the cardiac death in 14 of these patients. In the other group of 4 patients, cardiac death occurred between 28 and 41 months after the basal echocardiography. Non-cardiac death was not significantly different in the group of patients without AF compared to the group with new-onset AF [3 (3.75%) *vs.* 1 (3.03%), p = 0.16]. These patients were censored when we did new-onset AF analysis.

Table 2 shows the variables that predicted the new-onset AF on univariate Cox regression analysis. NTproBNP levels, severe MR, LVEF, LAV, LAVI, E/A, S', E', E/E', E/(E'×S'), LVEF≤40% combined with E/E'>15, and restrictive pattern emerged as predictors of AF in the patients studied. Age, sex, NYHA class, heart rate, mean arterial pressure, coronary artery disease, LV end-diastolic and end-systolic volume index, systolic pulmonary artery pressure, GMI, E and E-deceleration time, beta blocker, angiotensin converting enzyme inhibitor/angiotensin receptor antagonist or diuretics, were not significantly associated with new-onset AF in the univariate analysis.

Subsequently, all the variables that predicted the new-onset AF in the univariate analysis were entered into a forward multivariate Cox regression analysis. This analysis identified E/(E'×S') ratio as the only independent predictor of new-onset AF (HR= 2.26, 95% CI= 1.25-4.09, p =0.007) in the study population.

The additional benefit of E/(E'×S') to predict new-onset AF is shown in Figure 4. With regard to the incremental value, S' offers an additional benefit (p =0.003) over conventional parameters (LVEF, LAVI, E/A and E/E'). However, the addition of E/(E'×S') markedly improved the prognostic utility of the model containing LVEF, LAVI, E/A, E/E' and S' (p =0.001). We included in this model only the traditional echocardiographic parameters instead oft all of the variables that predicted the new-onset AF on univariate analysis.

To determine whether this effect was due to abnormal LV systolic function, we analyzed patients with preserved (LVEF≥50%) and those with reduced (LVEF<50%) LV

systolic function separately. In patients with LVEF<50%, the subgroup with E/(E'×S')≤2.2 (n =35) compared with the subgroup with E/(E'×S')>2.2 (n =42) had a significantly better event-free survival rate (91.4% vs. 42.8%, p <0.001). The benefit was more prominent in patients with LVEF≥50%. The patients with E/(E'×S')≤2.2 (n =29) and the patients with E/(E'×S')>2.2 (n =7) demonstrated a 96.5% and 28.5% event-free survival rate, respectively (p <0.001). Kaplan-Meier curves for AF event-free status in the two groups are shown in Figure 5.

Table 1 - Baseline characteristics of the study group

Variables	Total cohort (n = 113)	No AF (n = 80)	New-onset AF (n = 33)	p
Clinical characheristics				
Age, years	61 ± 12	60 ± 13	64 ± 10	NS
Male, n (%)	59 (52)	41 (51)	18 (54)	NS
Body mass index, kg/m²	27 ± 4.9	26 ± 5.6	29 ± 3.2	NS
Heart rate, beats/min	77 ± 16	75 ± 19	81 ± 9	NS
Mean arterial pressure, mmHg	95 ± 14	94 ± 15	98 ± 11	NS
Coronary artery disease, n (%)	74 (65)	52 (65)	22 (67)	NS
Non-ischemic cardiomyopathy, n (%)	29 (26)	21 (26)	8 (23)	NS
Systemic hypertension, n (%)	10 (9)	7 (9)	3 (9)	NS
NYHA functional class, n	2.57 ± 0.71	2.51 ± 0.67	2.92 ± 0.81	NS
NTproBNP, pg/ml	3,049 ± 2,835	2,297 ± 1,979	4,897 ± 4,408	0.001
Therapy in admission				
Beta blocker, n (%)	100 (88)	71 (89)	29 (87)	NS
ACEI/angiotensin receptor antagonist, n (%)	108 (95)	77 (96)	31 (94)	NS
Diuretics, n (%)	84 (74)	59 (73)	25 (76)	NS
Digoxin, n (%)	28 (25)	22 (27)	6 (18)	0.01
Nitrates, n (%)	75 (58)	56 (70)	19 (58)	0.03
Echocardiographic indices				
LV end-diastolic volume index, ml/m²	101 ± 32	96 ± 30	112 ± 35	0.008
LV end-systolic volume index, ml/m²	57 ± 18	55 ± 26	68 ± 30	0.01
LV ejection fraction, %	44 ± 14	43 ± 14	36 ± 13	0.02
Left atrial volume, ml	75±27	88±44	105 ± 39	0.03
Left atrial volume index, ml/m²	37±15	34±14	44 ± 18	0.01
Systolic pulmonary artery pressure, mmHg	34 ± 9	38 ± 13	45 ± 16	0.04
Global myocardial index	0.54 ± 0.37	0.58 ± 0.37	0.73 ± 0.41	0.01
Severe mitral regurgitation, n (%)	15 (13)	7 (9)	8 (24)	0.001
E-deceleration time, ms	169 ± 71	177 ± 74	150 ± 67	NS
E, cm/s	85 ± 27	80 ± 25	92 ± 26	0.001
E/A ratio	1.22 ± 0.79	1.05 ± 0.64	1.63 ± 1.09	0.002
E', cm/s	7.2 ± 2.7	7.56 ± 2.97	6.24 ± 1.75	0.04
S', cm/s	5.6 ± 2.6	6.1 ± 2.77	4.76 ± 1.28	0.02
E/E' ratio	11.8 ± 4.4	10.5 ± 4.2	14.7 ± 4.49	<0.001
E/(E'×S') ratio	2.12 ± 1.29	1.72 ± 1.34	3.09 ± 1.12	<0.001

Data are presented as mean ± standard deviation for continuous variables and number (proportion) for categorical variables. A - late transmitral flow velocity; ACEI - angiotensin converting enzyme inhibitor; E - early diastolic transmitral flow velocity; E' - early diastolic mitral annular velocity; LV - left ventricle; MR - mitral regurgitation; NTproBNP - N-terminal pro-brain natriuretic peptide; NYHA - New York Heart Association; S' - systolic velocity of mitral annulus.

Discussion

To the best of our knowledge, this is the first study investigating the value of a new tissue Doppler-derived index, E/(E'×S'), in predicting future development of AF. This parameter is useful to predict new-onset AF in patients with HF, in sinus rhythm, regardless of LVEF. The E/(E'×S') ratio was the strongest predictor of new-onset AF compared to several other echocardiographic parameters (conventional and TDI parameters), clinical variables and plasmatic NTproBNP levels.

AF is the most common arrhythmia in the general population[1,2]. Onset of AF in HF patients is usually associated with a high occurrence of cardiovascular complications[2,4-7]. In a large cohort of patients from the Framingham Heart Study, at first diagnosis of HF, 20% of patients later developed new AF after about 4 years[2]. In our study, the incidence of new-onset AF in HF was still high, even during optimal medical therapy, and occurred in 29.2% of the patients after a mean follow-up of 35.7±11.2 months. To enable the prevention of AF, risk stratification on the basis of large observational studies has shown that several parameters are associated with AF[8-18].

Conventional cardiovascular risk factors predict incident AF with reasonable accuracy[18]. A recent substudy of the AFFIRM trial demonstrated a statistically significant difference in NYHA functional class among HF patients who were able to maintain sinus rhythm throughout the trial vs. those who did not maintain it[5]. The incidence of AF is increased with the severity of HF[3]. In our study, NYHA functional class was a significant predictor of AF in the univariate analysis but it was eliminated in the multivariate analysis.

Coronary artery disease was highly prevalent in this series and one cannot rule out the occurrence of ischemic events contributing to the new-onset AF. When coronary disease causes regional hibernation of the myocardium, the E' velocity drops[17,26] and it has been shown to rise again after percutaneous coronary intervention[26]. In these patients, the E/E' ratio increase and S' decrease due to regional changes in the myocardium are often caused by subclinical coronary disease[17,26]. In our study, the

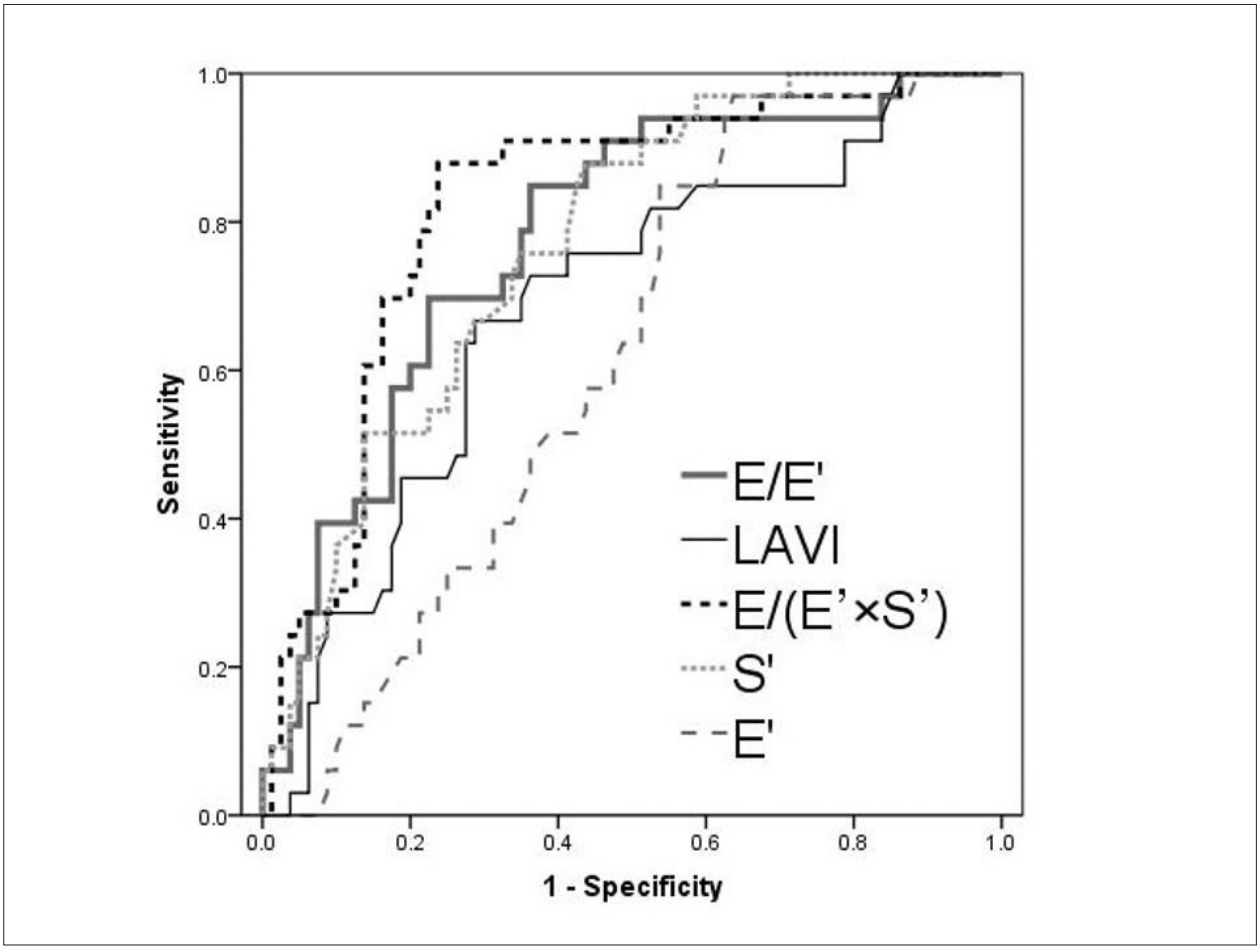

Figure 2 – *Receiver operating characteristic (ROC) curves for E/(E'×S'), E/E', S' and E' for prediction of new-onset atrial fibrillation in patients with heart failure. Area under the ROC curve (AUC) was 0.83 (95% CI = 0.74– 0.92, p <0.001) for E/(E'×S'), 0.77 (95% CI = 0.68 – 0.86, p <0.001) for E/E' ratio, 0.76 (95% CI = 0.67 – 0.85, p <0.001) for S', 0.68 (95%CI = 0.57–0.79, p =0.002) for LAVI, and 0.61 (95% CI = 0.51 – 0.71, p = 0.056) for E'. CI - confidence interval; E - peak early diastolic transmitral velocity; E' - peak early diastolic mitral annular velocity; LAVI - left atrial volume index; S' - peak systolic mitral annular velocity.*

Table 2 - Clinical, laboratory, and echocardiographic variables associated with new-onset atrial fibrillation in Cox univariate and multivariate analysis

Variables	Univariate HR (95% CI)	p -value	Multivariate HR (95% CI)	p -value
NTproBNP levels	1.04 (1.01 - 1.07)	0.001	1.01 (0.97 - 1.05)	0.43
Severe mitral regurgitation	1.03 (1.01 - 1.05)	0.003	0.97 (0.86 - 1.08)	0.48
LVEF	0.97 (0.94 - 1.00)	0.018	0.99 (0.95 - 1.04)	0.84
Left atrial volume	1.01 (1.00 - 1.02)	0.03	0.95 (0.91 - 0.99)	0.70
Left atrial volume index	1.04 (1.00 - 1.08)	0.02	0.98 (0.92 - 1.05)	0.61
E/A ratio	1.78 (1.31 - 2.42)	0.001	1.27 (0.75 - 2.13)	0.36
S' velocity	0.58 (0.45 - 0.76)	0.008	1.01 (0.97 - 1.04)	0.66
E' velocity	0.77 (0.64 - 0.93)	0.01	0.96 (0.71 - 1.29)	0.30
Restrictive pattern	2.06 (1.08 - 4.05)	0.029	0.80 (0.30 - 2.08)	0.65
E/E' ratio	1.26 (1.13 - 1.29)	<0.001	1.09 (0.91 - 1.29)	0.35
E/(E'×S') ratio	2.46 (1.87 - 3.23)	<0.001	2.26 (1.25 - 4.09)	0.007
LVEF≤40% and E/E'>15	2.21 (1.13 - 5.43)	0.009	0.30 (0.08 - 1.12)	0.08

A - late diastolic transmitral velocity; CI - confidence interval; E - early diastolic transmitral velocity; E' - mitral annular diastolic velocity; HR - hazard ratio; LV - left ventricle; LVEF - LV ejection fraction; S' - systolic velocity of mitral annulus; NTproBNP - N-terminal pro-brain natriuretic peptide.

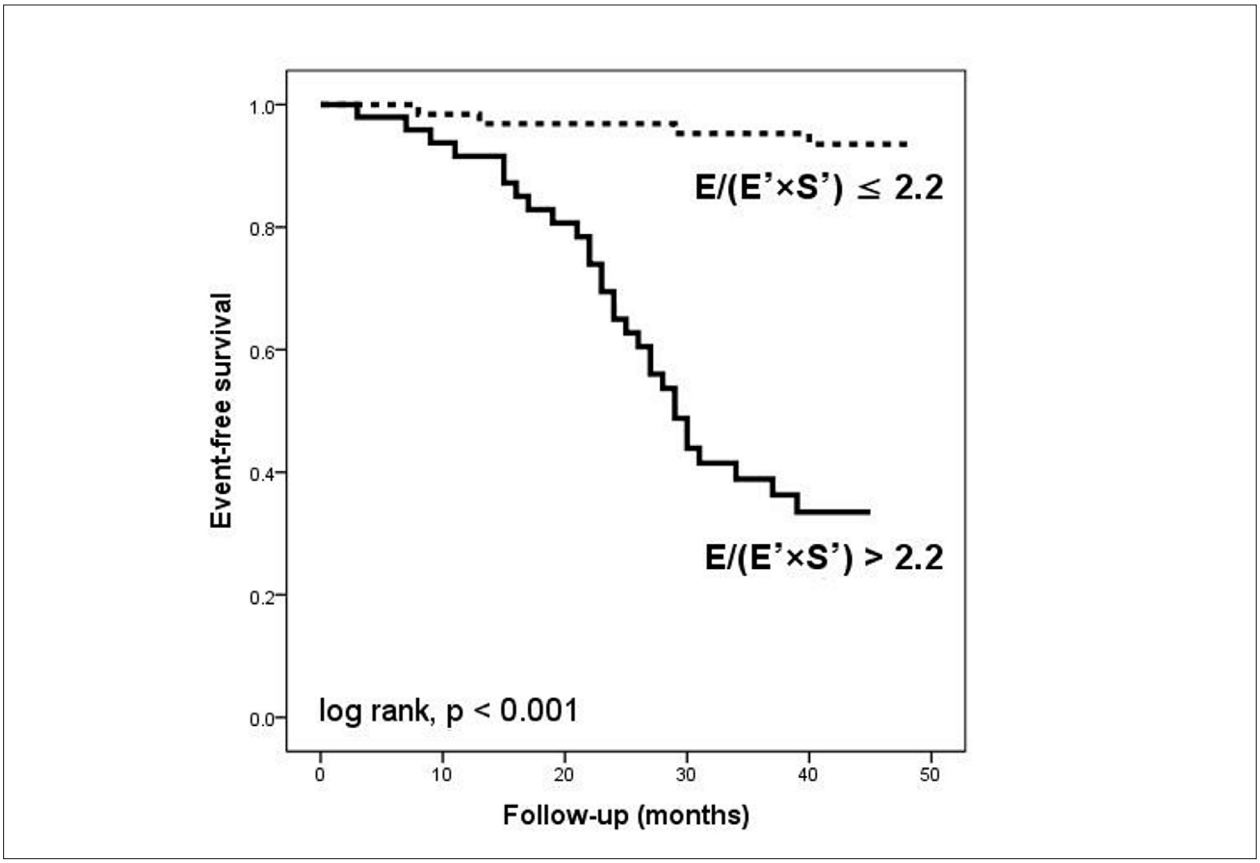

Figure 3 – *Kaplan-Meier curves of atrial fibrillation event-free survival in the 113 patients with heart failure according to E/(E'×S') ratio below and above 2.2. E - peak early diastolic transmitral velocity; E' - peak early diastolic mitral annular velocity; S' - peak systolic mitral annular velocity.*

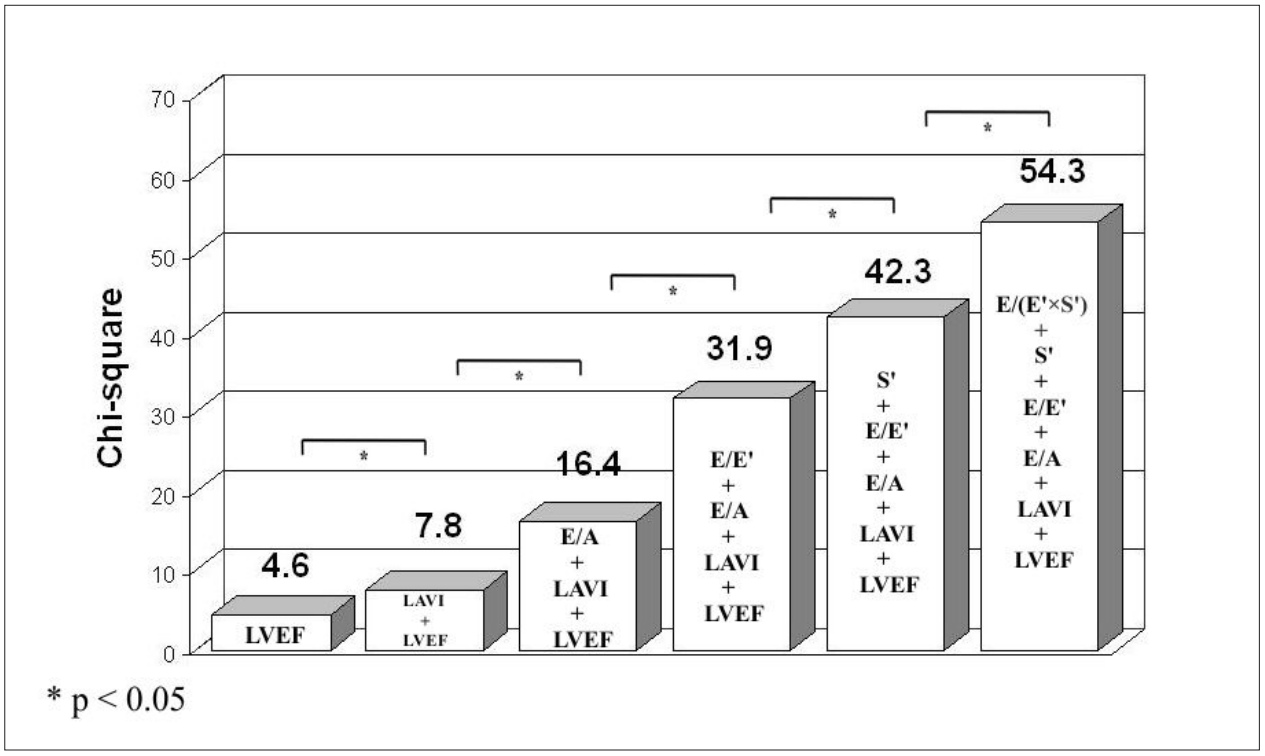

Figure 4 – *Prognostic value of echocardiographic parameters. Incremental prognostic value of the risk factors [left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), ratio of early to late transmitral flow velocity (E/A), ratio of early transmitral flow to early diastolic mitral annulus velocity (E/E'), systolic mitral annulus velocity (S') and E/(E'×S') ratio] by Cox proportional hazards model presented as a global chi-square value. The addition of E/(E'×S') index resulted in significant incremental improvement in the predictive value on the LVEF, LAVI, E/A, E/E' ratio and S' wave.*

presence of coronary artery disease was not an independent predictor of new-onset AF in the univariate analysis.

It has been suggested that biomarkers reflecting common pathophysiological processes may perform a better risk stratification[7,9,10,18]. A high NT-proBNP at baseline was associated with future development of AF, as recently reported[9]. Smith et al[18] demonstrated that natriuretic peptides, rather than other biomarkers, improve discrimination for new-onset AF. High natruretic peptides appear to identify patients at increased risk of paroxysmal AF in hypertensive patients[15] or after isolated coronary artery bypass grafting[10]. Univariate analysis of our data supports the observation that NTproBNP has prognostic value but differently from what is observed in the literature, NTproBNP was not a predictor in the multivariate Cox regression.

Several previous studies with echocardiographic imaging have suggested that a larger LA volume is associated with a higher risk of AF in patients with abnormal LV relaxation[8], in elderly patients[11,13] or in unselected patients[14]. Enlarged atria are best correlated with increased wall tension because of chronic elevation of ventricular filling pressures and reflect the remodeling process, representing a quantifiable surrogate of the arrhythmogenic substrate. Chronic myocyte stretch increases the intercellular matrix, collagen production, and fibrosis, mediated through the renin-angiotensin-aldosterone system[27]. Some authors demonstrated the incremental value of diastolic function (assessed with E-deceleration time, E/A, and LA volume) to clinical risk factors alone as predictor of AF[11,12]. These parameters are influenced by the volemic status, LA pressure, age and myocardial relaxation, and are associated with well recognized limitations[24]. In our study, LVEF, E/A, LA volume, LAVI, restrictive pattern, severe MR, predictors of outcome in the univariate analysis, were eliminated in the multivariate analysis.

TDI is a relatively new technique available on echocardiographic equipment of various manufacturers, which can detect subclinical longitudinal LV dysfunction[28]. Increased LV filling pressure is related to the enlargement of LA and to the future development of AF[27]. Reliable estimation of LV filling pressure is the most useful information from the echocardiographic assessment of diastole. Conceptually speaking, it is very difficult to separate relaxation from contraction, and it is better to consider them together as part of a continuous cycle, where systolic and diastolic abnormalities have a variable contribution to the failing LV[29]. Some authors consider that systolic function is in fact one of the most important determinants of diastolic function[28-30]. E/E' ratio has been proposed as the best single Doppler parameter in the prediction of AF[15-17]. Asymptomatic ventricular dysfunction often precedes HF or AF[18]. Hirata et al[31] showed that a parameter combining the diastolic index (E/E') with LVEF (a parameter that explores the systolic function) predicts outcomes in patients with HF (LVEF≤40% and E/E'>15). In a previous

study, we demonstrated that a new index, E/(E'×S'), is useful to assess the LV filling pressure, regardless of LVEF[19]. In this study, E/(E'×S') was the best predictor of LV end-diastolic pressure in a heterogeneous population of cardiac patients, and more closely related to LV filling pressure compared to E/E', E', S' or E. In terms of new-onset AF, E/(E'×S') was the only independent predictor in the multivariate analysis in this study. This novel parameter associates an index of diastolic function (E/E') and a marker that explores LV systolic performance (S') and therefore may provide supplementary information compared to each component considered separately. The superiority of E/(E'×S') over the combined index of Hirata can be attributed to the capacity of reduced S' to identify LV dysfunction in individuals with normal LVEF[28]. TDI does not require tracing of endocardial contours, unlike LV volumes and LVEF. Regarding the future development of AF, the complex E/(E'×S') index offers an additional benefit to more traditional echocardiographic parameters (LVEF, LAVI, E/A, S' and E/E').

Our results should be considered in the context of several limitations. The number of patients in this study was relatively small; however, we were able to reach several significant observations. We deliberately did not use more sophisticated Doppler parameters, such as pulmonary venous curves, the time interval between the onset of mitral inflow and early diastolic annular velocity by ($T_{E'-E}$) and mitral inflow during a Valsalva maneuver; these Doppler parameters are difficult to record and, thus, are not suitable for daily practice. We have limited TDI measurements at two sites (septal and lateral mitral annulus) and we did not examine anterior and posterior velocities that could have provided additional information. Our study is a single center study and its reproduction in other centers or by multicenter studies would argue for its validity.

In conclusion, in this group of patients with HF in sinus rhythm, the novel tissue Doppler-derived index, E/(E'×S'), seems to be a good independent long-term predictor of new-onset AF. The E/(E'×S') ratio >2.2 can be a simple, effective tool for assessing high risk patients for future development of new-onset AF, regardless of LVEF.

Acknowledgements

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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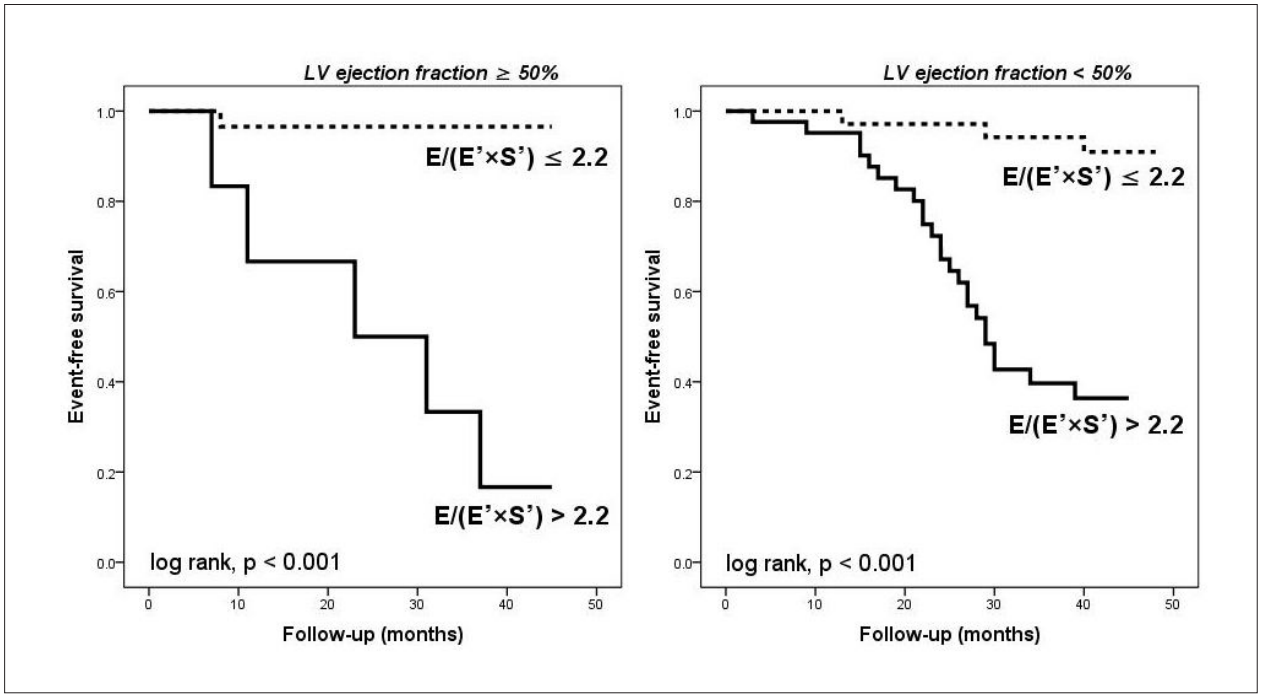

Figure 5 – *Kaplan-Meier curves of atrial fibrillation event-free survival in patients with heart failure with preserved left ventricular ejection fraction (a) and with reduced ejection fraction (b), according to E/(E'×S') ratio below and above 2.2. E - peak early diastolic transmitral velocity; E' - peak early diastolic mitral annular velocity; LV - left ventricle; S' - peak systolic mitral annular velocity.*

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