Original Article

Prognostic Value of a Tissue Doppler Index of Systodiastolic Function in Patients with Asymptomatic Heart Failure

Nicola Riccardo Pugliese, Iacopo Fabiani, Salvatore La Carrubba[1], Scipione Carerj[2], Lorenzo Conte, Paolo Colonna[3], Pio Caso[4], Frank Benedetto[5], Francesco Antonini-Canterin[6], Maria Francesca Romano[7], Rodolfo Citro[8], Vitantonio Di Bello, on behalf of Italian Society of Cardiovascular Echography (SIEC)

Cardio Thoracic and Vascular Department, University of Pisa, Pisa, [1]Villa Sofia Hospital, Palermo, [2]"San Giovanni di Dio e Ruggiero d'Aragona" Hospital, Salerno, [3]Cardiology University Department, Bari, [4]Monaldi Hospital, Napoli, [5]"Bianchi-Melacrino-Morelli" Hospital, Reggio Calabria, [6]"S.Maria degli Angeli" Hospital, Pordenone, [7]"Sant'Anna School of Advanced Studies, Pisa, [8]Clinical and Experimental Medicine, Messina, Italy

Abstract

Introduction: Doppler echocardiography with early diastolic transmitral velocity (E)/early mitral annular diastolic velocity (E') ratio has been proposed as the best predictor for evaluating left ventricle (LV) filling pressure. A dimensionless index E/(E' × S') ratio (S' = systolic mitral annulus velocity) resulted in readily, reproducible, and reliable predictor of LV filling pressure. We assessed the prognostic impact of E/(E' × S') in patients with asymptomatic heart failure (HF). **Materials and Methods:** We calculated E/(E' × S') in 337 patients (179 male, 53%; age 54.7 ± 13.7 years) using the average of septal and lateral mitral annular velocities. We considered a composite endpoint as follows: all-cause death, acute myocardial infarction, stroke, and HF exacerbation. **Results:** Baseline ejection fraction resulted 60.2 ± 11.8%; E/(E' × S') was 1.45 ± 0.8, with S' 7.4 ± 2.4 cm/s and E/E' 9.5 ± 5.4. After a 22-month median follow-up, there were 42 events: 5 deaths (12%), 3 acute myocardial infarctions (7%), 1 stroke (2%), and 33 HF hospitalizations (79%). In patients reaching the composite endpoint, E/(E' × S') resulted 2.07 ± 1.1 versus 1.3 ± 0.7 in event-free population ($P < 0.001$). In a Cox-regression analysis, adjusted for confounding clinical factors and conventional echo parameters, E/(E' × S') ($P < 0.001$), age ($P < 0.001$), and male gender ($P = 0.03$) resulted independent predictors of the composite endpoint. **Conclusions:** E/(E' × S') was an independent predictor for the future cardiac events in asymptomatic HF.

Keywords: Echocardiography, heart failure, prognosis, tissue Doppler Imaging

Introduction

The prevalence of heart failure (HF) in the general population ranges between 0.4% and 2% and increases with age.[1] The American College of Cardiology/American Heart Association guidelines for HF identifies 4 stages of HF: stage A, at high risk for HF but without structural heart diseases or symptoms of HF; Stage B, structural heart disease but without signs or symptoms of HF; Stage C, structural heart disease with prior or current symptoms of HF; and Stage D, refractory HF requiring specialized interventions.[2] Patients in Stage A and B are ideal targets for HF prevention.[3] Traditional risk factors for cardiovascular diseases (Stage A) are able to lead to maladaptive cardiac remodeling (Stage B) and over time to symptomatic left ventricular (LV) dysfunction. Early detection of subclinical LV dysfunction (systolic or diastolic) is pivotal because this progression can be positively influenced by early treatment.

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The assessment of LV filling pressures is a reliable tool for risk stratification in patient with HF.[2] Given the limitations inherent to invasive measurements (cardiac catheterization), Doppler echocardiography, in particular, tissue Doppler imaging (TDI), has become the principal tool for estimation of LV pressure.[4] Early diastolic transmitral velocity (E)/early mitral annular diastolic velocity (E') ratio (E/E') has been proposed as the most accurate echocardiographic predictor for evaluation of LV filling pressures in different clinical contexts.[5] However, there are many limitations to the E/E' ratio estimation, in addition to its semi-quantitative definition

Address for correspondence: Dr. Nicola Riccardo Pugliese, Dipartimento Di Patologia Medica, Chirurgica, Molecolare E Dell'area Critica, Università Di Pisa, Via Paradisa, 2 - Ospedale Cisanello, 56100 Pisa PI, Italy.
E-mail: n.r.pugliese88@gmail.com

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of filling pressures (including, among others, annular site of measurements, a "wide" gray zone between 8 and 15, the role in healthy individuals, moderate-to-severe mitral valve disease, and presence of regional wall motion abnormalities). Nonetheless, TDI allows a contemporary longitudinal systolic function assessment (s' wave), which is affected variably and at different stages in HF.[6] A dimensionless index combining both systolic and diastolic information, that is, $E/(E' \times S')_{average}$, was proposed as a reliable predictor of LV end-diastolic pressure in sinus rhythm patients, regardless of LV ejection fraction (EF), particularly in those with $E/E'_{average}$ between 8 and 15.[7] Our purpose has been to assess the prognostic impact of $E/(E' \times S')_{average}$ in a cohort of patients asymptomatic for HF (Stage A and B).

Materials and Methods

We retrospectively analyzed a multicenter study designed by the Italian Society of Cardiovascular Echography (SIEC), the Disfunzione Asintomatica del Ventricolo Sinistro (DAVES) study, which enrolled 6679 asymptomatic HF individuals (Stage A and B) aged more than 18 years who were admitted to 19 echocardiographic laboratories for transthoracic examination as a screening evaluation in the presence of one or more cardiovascular risk factors.[8] All laboratories were selected according to the operator's competence, level 3, in agreement with the American Society of Echocardiography (ASE) requirements. The study was approved by the local research ethics committees, in accordance to the Declaration of Helsinki. The study included participants without a clinical history of HF, according to inclusion criteria, with normal electrocardiography (ECG) tracings, and with normal clinical examination results in the presence of one or more cardiovascular risk factors. The definition of a normal ECG scan was according to Marriott's practical ECG normality criteria. All selected participants underwent a comprehensive two-dimensional echocardiographic study to evaluate LV functional and structural findings. Exclusion criteria were symptoms or clinical and instrumental signs of acute coronary syndrome or myocarditis, valvular heart disease (except mild forms not hemodynamically relevant), history of atrial fibrillation/flutter, anemia (hemoglobin <12 mg/dL in women and <13 mg/dL in men), renal failure (serum creatinine >1.3 mg/dL), and endocrine disorders (hypo- and hyperthyroidism, hyperaldosteronism). Pericardial disease, pulmonary hypertension, aortic diseases, and primary cardiomyopathy were excluded based on echocardiography. All participants provided written informed consent and detailed medical history, particularly on cardiovascular risk factors, comorbidities, and drug therapies. For study purposes, 6 cardiovascular risk factors were considered as follows: hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure >90 mm Hg, or in drug treatment), diabetes mellitus (fasting glycemia >7.0 mmol/L^{-1} or in drug treatment), hypercholesterolemia (>200 mg/dL or in drug treatment), family history of cardiovascular disease (including coronary artery disease, cardiomyopathy, and other hereditary forms of cardiomyopathy), smoking (≥1 cigarette/day, cessation of smoking <10 years previously was still considered as smoking), and obesity (body mass index [BMI] ≥30 kg/m^2). All patients enrolled in the study underwent a physical examination, 12-lead electrocardiogram, and comprehensive transthoracic echocardiographic examination, according to the standard protocol based on the ASE recommendations.[9] Anthropometric measurements (weight, height) were obtained, and BMI was calculated (i.e., body weight in kilograms divided by height in meters squared). Blood pressure was measured twice at the right arm after a 10-min rest in the supine position using a calibrated sphygmomanometer and then averaged. Echocardiograms were acceptable when at least 80% of the endocardium was visible. Quantitative analysis was done, for each laboratory, by the same expert operator. Measurements of LV end-diastolic volume (EDV), end-systolic volume, and EF were performed using the modified biplane Simpson's rule as a mean of three cardiac cycles. EF <50% was used as a cutoff for abnormal LVEF (LV systolic dysfunction). The following diastolic parameters were assessed from the Doppler mitral flow and tissue velocities tracings: E-wave velocity, A-wave velocity, E/A, delta E/A (changes from basal to Valsalva maneuver), E-wave deceleration time, A-wave duration, and E/E' average. Pulmonary venous flow (systolic velocity, diastolic velocity, and reverse wave duration) and echo-derived estimated systolic pulmonary artery pressure (sPAP) were evaluated. Finally, diastolic function was classified according to recent joint ASE/European Association of Cardiovascular Imaging recommendations on diastolic functional evaluation.[5] The grading scheme for diastolic dysfunction was mild or Grade I (impaired relaxation pattern), moderate or Grade II (pseudonormalized filling), and severe (restrictive pattern), or Grade III. Diastolic dysfunction was a dichotomous definition (yes/no for any of the previous 3 grades). A random sample of 5% was reanalyzed and reinterpreted in a single core laboratory facility by 2 independent observers (NRP: Nicola Riccardo Pugliese; IF: Iacopo Fabiani). The mean and standard deviation of variability between the two readings and by the same observer for the echocardiographic parameters were as follows: the intraobserver variability for EF was 63% ± 7% versus 65% ± 6% (mean ± standard deviation; $P = 0.07$), and the interobserver values were 63% ± 3% versus 66% ± 4% ($P = 0.08$). If the interobserver and intraobserver variability were considered in the identification of LV systolic or diastolic dysfunction, interobserver variability was 8.7% and intraobserver variability was 8.2% for systolic dysfunction, and interobserver variability was 8.5% and intraobserver variability was 7.7% for diastolic dysfunction. The methodology for $E/(E' \times S')$ ratio evaluation has been described previously.[7] The TDI 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 80–140 frames per second. A 4–5-mm sample volume was positioned sequentially at the lateral and septal corners of the mitral annulus. Two major negative velocities were recorded

with the movement of the annulus toward the base of the heart during diastole, as follows: one during the early phase of diastolic myocardial velocity (E') and another during the late phase of diastolic myocardial velocity (a'). A major positive systolic velocity was recorded with the movement of the annulus toward the cardiac apex during systole. The peak myocardial systolic velocity (S') was defined as the maximum velocity during systole, excluding the isovolumetric contraction. All velocities were recorded for five consecutive cardiac cycles during end-expiratory apnea, and the results were averaged. All tissue Doppler signals were recorded at horizontal time sweep set at 100 mm/s. E/E' and E/(E' × S') were calculated using the average of septal and lateral mitral annular velocities. All 19 echocardiographic laboratories involved in the study agreed to follow-up the recruited patients. Follow-up of patients was performed using clinical controls (cardiologic visit), the hospital database, and phone contact to obtain information on clinical data and adverse events. The present study considered the following composite endpoint: all-cause death, acute myocardial infarction, stroke, and HF exacerbation. For the diagnosis of myocardial infarction and stroke standard laboratory, ECG or examination criteria were used. HF exacerbation was defined as dyspnea, accompanied by pulmonary edema or congestion on chest X-ray requiring hospitalization.

Continuous variables are presented as mean ± standard deviation if normally distributed or median and interquartile range (IQR, 1st–3rd quartile) if not normally distributed. Continuous variables from 2 sets of data were compared using Student's *t*-test or Mann–Whitney U-test when non-Gaussian. Categorical variables are presented as percentages and were compared using the Chi-square test. Clinical and echo-derived parameters were included in a Cox proportional hazard model using univariate and stepwise multivariate procedures to evaluate the association to the composite endpoint (only the first event was taken into account). Significance of 0.05 was required for a variable to be included in the multivariate model, while 0.10 was the cutoff value for exclusion. According to a stepwise selection process, variables were entered into, or removed from, the regression equation on the basis of a computed significance probability value. Hazard ratios with corresponding 95% confidence intervals (CIs) were estimated. The parameters included in the Cox model were established *a priori* to assess how conventional risk factors (both clinical and echo-derived parameters) were able to identify patients at risk for events. The predictive accuracy of proposed parameter for composite endpoint was assessed from receiver operating characteristics curve, including area under the curve (AUC) and 95% CIs. Statistical significance was set at $P < 0.05$. All data were analyzed using SPSS software (version 13.0; SPSS, Inc., Chicago, IL, USA).

Results

From the DAVES database, we retrospectively selected 337 patients where $E/(E' \times S')_{average}$ was derivable, excluding patients in whom TDI measures were not available or accurate and patients lost to follow-up. Table 1 summarizes clinical characteristics of study population, together with risk factors and comorbidities. A clinical history of stable ischemic heart disease (SIHD), defined as a history of angina or previous coronary revascularization, was found in 29 patients (8.6% of the population). Echo-derived parameters were summarized in Table 2. Only 41 patients (12.2%) presented a systolic dysfunction (EF <50%) classified as mildly abnormal LV function (EF >40%), while 116 (34.4%) showed diastolic dysfunction (1st degree or more). $E/(E' \times S')_{average}$ was 1.4 ± 0.8, with S' 7.4 ± 2.4 cm/s and $E/E'_{average}$ 9.4 ± 3.4. Significant correlations were observed between $E/(E' \times S')_{average}$ and both clinical and echocardiographic parameters [Table 3]. After a 22-month median follow-up (IQR, 30–47 months), there were 42 events: 2 cardiac death (5%), 3 noncardiac deaths (7%), 3

Table 1: Clinical characteristics of study population, risk factors, and comorbidities (data are presented as *n* (%) or mean±standard deviation)

Variable	
Male	179 (53.1)
Female	158 (46.9)
Age (years)	54.7±13.7
Weight (kg)	72.6±14.1
Height (cm)	166.5±8.7
BMI (kg/m^2)	26.2±45.6
Body surface area (m^2)	1.8±0.2
Systolic arterial pressure	135.2±18.5
Diastolic arterial pressure	80.9±9.9
Smokers	96 (28.5)
Family history of cerebrovascular disease	159 (47.2)
Diabetes mellitus	39 (11.6)
Hypertension	218 (64.78)
Dyslipidemia	120 (35.6)
Obesity	96 (28.5)
Previous stroke/TIA	1 (0.3)
History of angina	24 (7.1)
Previous coronary revascularization	10 (3)
COPD	7 (2.0)
Peripheral artery disease	8 (2.4)
Therapy	
Diuretics	27 (8)
ACE inhibitors	109 (32.3)
Digoxin	3 (0.9)
ARBs	22 (6.5)
Dihydropyridine calcium-channels blockers	36 (10.7)
Verapamil/diltiazem	8 (2.4)
Beta-blockers	61 (18.1)
Alpha-blockers	10 (3)
Nitroderivates	15 (4.5)
Aspirin/clopidogrel	47 (13.9)
Anticoagulants	5 (1.5)
Antiarrhythmics	4 (1.2)
Statins	40 (11.9)

BMI=Body mass index, TIA=Transient ischemic attack, ARBs=Angiotensin receptor blocker, COPD=Chronic obstructive pulmonary disease

Table 2: Echocardiographic parameters (data are presented as *n* (%) or mean±standard deviation)

Variable	*n* (%)/mean±standard deviation
LV end-diastolic diameter (mm)	50.1±6.0
LV EDV (ml)	100.5±37.7
LV EDV indexed (ml/m^2)	54.8±18.9
Interventricular septum (mm)	10.6±2.1
Posterior wall (mm)	9.7±1.8
RWT	0.4±0.1
Atrial end-systolic area (cm^2)	17.2±5.4
E-wave velocity (cm/s)	66±23.2
A-wave velocity (cm/s)	70±20.4
E/E'$_{average}$	9.5±5.4
S' TDI (cm/s)	7.4±2.4
E/(E' × S')$_{average}$	1.4±0.5
LV EF (%)	60.2±11.8
LV mass index (g/m^2)	95.1±27.7
Estimated sPAP	29.3±7.9
Systolic dysfunction (EF <50%)	41 (12.2)
Diastolic dysfunction*	116 (34.4)
Systolic and/or diastolic dysfunction	128 (37.9)

LV=Left ventricle, RWT=Relative wall thickness, TDI=Tissue Doppler imaging, sPAP=Systolic pulmonary artery pressure, EF=Ejection fraction, EDV=End-diastolic volume

Table 3: Correlation coefficients between E/(E' × S')$_{average}$ and clinical/echocardiographic parameters

	Pearson's correlation coefficient *r*	*P*
LV EDV index	0.6	<0.001
LV EF	0.46	0.003
Age	0.32	0.002
Left atrial volume index	0.4	<0.001
LV mass index	0.39	<0.001
BMI	0.38	<0.001

BMI=Body mass index, EDV=End-diastolic volume, EF=Ejection fraction, LV=Left ventricle

acute myocardial infarctions (7%), 1 stroke (2%) and 33 HF hospitalizations (79%). In patients with events, E/(E' × S')$_{average}$ resulted 1.77 ± 0.11 (vs. 1.36 ± 0.28 in patients with no events, $P < 0.001$); [Figure 1]. To test the association with events, we performed univariate Cox-regression analysis of clinical and echo-derived parameters, including weight, BMI, systolic and diastolic arterial pressure, smoke, family history of cerebrovascular disease, diabetes mellitus, hypertension, dyslipidemia, obesity, classes of drugs, systolic and diastolic dysfunction, LVEDV index, atrial end-systolic area, estimated sPAP, E, E', and S'. Afterward, univariate significant predictors (age, gender, SIHD, E/(E' × S')$_{average}$, and E/E') were entered into a multivariate analysis to observe the occurrence of the composite endpoint. E/(E' × S')$_{average}$ ($P < 0.001$, HR = 2.13, CI 95% 1.41–3.22), male gender ($P = 0.03$, HR = 1.25, CI 95% 1.07–1.89), and age ($P < 0.001$, HR = 1.08, CI 95% 1.02–1.13) resulted independent predictors [Table 4]. The optimal cutoff for E/(E' × S')$_{average}$ in predicting the composite endpoint was 1.68 (AUC 0.81, CI 95% 0.73–0.90; $P < 0.01$; sensitivity 78%; specificity 91%).

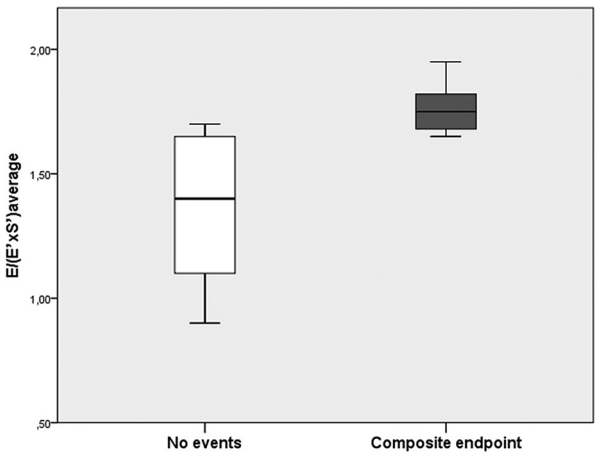

Figure 1: Box plots of E/(E' × S')$_{average}$ distribution in patients with no events ($n = 15$) and patients reaching composite endpoint ($n = 15$) after a 22-month median follow-up: (0.6 ± 0.83% vs. 4.5 ± 2.0%, $P < 0.001$). The box plot displays 25th, 50th (median), and 75th percentiles in the box

Discussion

Identification and treatment of asymptomatic HF individuals, with prevention of its progression, has been the objective of the SIEC, who planned a multicenter perspective study on asymptomatic LVEF to analyze its prevalence and the role of echocardiography in the diagnostic and prognostic strategy. In the present study, we analyzed in asymptomatic patients (Stage A and B) for HF, the prognostic impact of a novel TDI-derived index, combining conventional Doppler echocardiography of the transmitral flow (E velocity) with 2 TDI parameters (E' and S'). Systolic dysfunction is, together with diastolic impairment, one of the primary drivers for HF development. Previous studies already confirmed the prognostic impact of systolic and diastolic dysfunction in HF population.[10] Moreover, as previously demonstrated by our group, even in participants with apparently normal systolic/diastolic function at echocardiography, single or multiple risk factors play a significant prognostic role.[11] One of the reasons could be the impact of these risk factors on the interplay between systolic and diastolic function. That's why the assessment of an index capable of a comprehensive LV function evaluation could help in evaluating the complex pathophysiological mechanism that leads to overt HF. In fact, a clear separation of relaxation from contraction is difficult, and a better approach would be to consider them together as part of a continuous cycle.[12,13] The energy generated during systole is stored in myocardial collagen fibers, and following relaxation, the ventricle uncoils, creating LV suction. There seems to be a relation of proportionality between decline in contractile function and reduction in recoil, with parallel changes in the extracellular matrix. Some authors consider that systolic function is, in fact, one of the most important determinants of diastolic function.[14] LV diastolic dysfunction is usually the result of impaired LV relaxation with or without reduced restoring forces (and early diastolic suction), and

Table 4: Cox proportional hazard model: independent predictive factors for composite endpoint

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
E/E'	4.3	2.33-4.7	0.01	3.13	0.52-5.12	0.09
E/(E' × S')	3.5	1.69-2.9	<0.001	2.13	1.41-3.22	<0.001
Age	1.9	1.1-1.43	<0.001	1.08	1.02-1.13	<0.001
Male gender	1.6	1.4-1.87	<0.001	1.25	1.07-1.89	0.03
SIHD	1.5	1.71-3.36	0.02	1.9	0.64-4.22	0.32

CI=Confidence interval, HR=Hazard ratio, SIHD=Stable ischemic heart disease

increased LV chamber stiffness, which increases cardiac filling pressures. E/E' has been proposed as the best single-Doppler predictor for evaluating LV filling pressure. However, there are some limitations of the E/E' to estimate LV filling pressure, in particular, it is reliable for predicting elevated LV diastolic pressures only in patients with E/E'>14 and in participants with preserved EF, without regional wall motion abnormalities.[5] The analysis of LV long-axis function in TDI (S', a potential early indicator of systolic impairment) demonstrated valuable additive information for the noninvasive assessment of LV filling pressure. Notably, $E/(E' \times S')_{average}$ demonstrated to be a reliable predictor of LV end-diastolic pressure in sinus rhythm patients, and it was superior to E/E', E', S', or E, regardless of LV EF, particularly in those with E/E' between 8 and 15 (the so-called gray area in diastolic dysfunction grading) and in those with regional dysfunction.[7] In addition, this parameter resulted useful also in predicting new-onset atrial fibrillation in patients with HF, in sinus rhythm, regardless of EF, and it was the strongest predictor of new-onset AF compared to several other echocardiographic parameters (conventional and TDI parameters), clinical variables, and plasmatic N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels.[15] Recently, the prognostic value of $E/(E' \times S')_{average}$ was demonstrated in patients with HF with preserved and reduced EF: the dimensionless index was the only independent predictor of future cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and HF exacerbation) in both HF populations.[16] According to the theory of the continuous cycle, the present study demonstrates that $E/(E' \times S')_{average}$ has a significant prognostic impact also in a population of asymptomatic HF patients. In particular, $E/(E' \times S')_{average}$ is the strongest predictor variable in comparison to standard LV systolic and diastolic evaluation, even considering E/E', suggesting that this composite index actually provides supplementary information. Noteworthy, the prognostic impact of the index was independent and additive respective to age, gender, and SIHD. Moreover, we propose a $E/(E' \times S')_{average}$ cutoff of 1.68 for predicting adverse events in clinical practice (sensitivity 78%, specificity 87%). Our cutoff point is consistent with the value described by Dragulescu *et al*. for the assessment of LV end-diastolic pressure,[7] underlining the importance of an accurate estimation of LV filling pressure in terms of prognosis. Finally, the strength of this parameter is its ease of use, thanks to its availability in most of the modern echo machines, making it readily applicable for the bedside assessment of patients.

A study limitation was the use of composite outcomes. The use of standard echocardiographic assessment instead of more sophisticated methods (e.g., strain imaging) could be considered both a limitation and a strength of the study. The limitation is that strain imaging has proved to be more sensitive for detecting subclinical abnormalities of both systolic and diastolic function. Nevertheless, the strength is that the present study was focused on the utility of currently established and widely available echocardiographic techniques. The low prevalence of adverse events described in the present study, because of the study population size and length of follow-up, could be considered another limitation. However, this is not totally surprising if we consider patient inclusion criteria (asymptomatic HF). Another limit of the study is represented by the exclusion of a significant share of the initially enrolled population in the DAVES, due to the inadequacy of TDI measurements. Finally, we did not evaluate natriuretic peptide (B-type natriuretic peptide and NT-pro-BNP) levels. In fact, recent works demonstrated that increased concentrations of both these biochemical markers could accurately detect asymptomatic LV systolic and diastolic dysfunction.[17,18] This promising novel parameter should be tested in larger clinical trials to better delineate his potential role in clinical practice.

Conclusions

$E/(E' \times S')_{average}$ has a prognostic impact in patients asymptomatic for HF, incremental to standard clinical and echo parameters, resulting a useful and promising diagnostic tool for clinical management.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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