Tissue Doppler Imaging as a Long-Term Prognostic Index in Left Ventricular Systolic Dysfunction

Roberto Magalhães Saraiva, Rita de Cássia Castelli da Rocha, Adriana Ferraz Martins, Dario Marins Duarte, Renata da Silva Peixoto, Simone Henriques de Castro, Carla Tavares Gallicchio, Andréa Lúcia de Araújo, Sérgio Emanuel Kaiser
Total Care, Rio de Janeiro, RJ – Brazil

Summary

Background: Tissue Doppler parameters correlate with left ventricular (LV) filling pressure and can be useful as prognostic indexes for patients with heart failure.

Objective: Determine whether tissue Doppler parameters can predict events during long term follow-up of outpatients with LV systolic dysfunction.

Methods: Retrospective study with 73 patients (aged 60.9±12.1 years) who underwent Doppler echocardiogram between March 2001 and May 2004. The primary endpoint studied was death or hospitalization due to heart failure worsening.

Results: The mean follow-up period was 1,367±665 days. After logistic stepwise multivariate analysis, including echocardiographic parameters, the ratio of maximal early diastolic filling wave velocity to maximal early diastolic myocardial velocity (E/E` ratio; p=0.0007), and LV ejection fraction (EF; p=0.01) remained significant predictors of the primary outcome. The optimal cutoffs for primary endpoint prediction for E/E' ratio (AUC 0.77; p=0.0001) and EF (AUC 0.68, p=0.006) were respectively 12.7 and 30%. Accordingly, patients with E/E' ratio > 12.7 (hazard ratio=3.8, p =0.001) or EF <30% (hazard ratio=2.3, p=0.03) had a poorer outcome by survival curve analysis. It is noteworthy that 47% of the patients with EF above the optimal cutoff point, but with high E/E' ratio, presented events during follow-up.

Conclusion: E/E' ratio is an important independent long-term prognostic index of death or hospitalization due to worsening heart failure in outpatients with LV systolic dysfunction. Therefore, we recommend the measurement of this variable in the routine evaluation of such patients. (Arq Bras Cardiol 2008;91(2):77-83)

Key words: Prognosis; echocardiography, Doppler; cardiac output, low; ventricular dysfunction, left.

Introduction

Despite the great advancements in the management of heart failure (HF), responsible for a significant improvement in patient survival during the last 50 years[1], the morbimortality of this syndrome remains elevated[1,2]. However, patients with HF can be grouped in subgroups with distinct prognoses, defined by clinical and laboratory parameters. In addition to the left ventricle (LV) ejection fraction (EF)[3,4], other echocardiographic variables derived from the mitral flow interrogation by pulse Doppler were capable of predicting cardiac events in patients with HF[4-6]. However, the velocities of the mitral flow are influenced by several factors, such as age, heart rate and preload[7]. On the other hand, new echocardiographic indices obtained at the tissue Doppler have shown to be less preload-dependent[8-10]. In parallel, in patients with systolic HF, an index derived from the analysis of the mitral flow and the myocardial velocity of the mitral annulus in early diastole has a good correlation with the final diastolic pressure of the LV. This index is the E/E' ratio, which is the ratio between the maximum LV filling velocity and the myocardial velocity of the mitral annulus measured in early diastole[11-13].

The maximum velocity of the mitral annulus during the atrial contraction (A')[14] also has a good correlation with the final diastolic pressure of the LV. That allows the identification of patients with elevated final diastolic pressure of the LV[11-13].

Recently, some studies demonstrated that the tissue Doppler parameters were capable of adding prognostic information in inpatients[15] or outpatients with HF[14,16,17]. However, the comprehensiveness of the results was limited by the short follow-up period[17,18], or by the disequilibrium that resulted from the excessive number of patients included in the study that were New York Heart Association" (NYHA) Functional Class III or IV[14,18-20].

Therefore, the present study aimed at determining whether the tissue Doppler parameters could also predict long-term events in a situation closer to the routine outpatient clinical practice, where most of the patients refer mild to moderate

Mailing address: Roberto Magalhães Saraiva •
Total Care - Rua Voluntários da Pátria, 445 sala 210 - 22270-000 - Botafogo - Rio de Janeiro, RJ - Brazil
E-mail: rsaraiva@cardiol.br
Manuscript received December 13, 2007; revised manuscript received February 04, 2008; accepted February 19, 2008.

symptoms. Additionally, we tried to determine whether the tissue Doppler obtained at the first examination after the patient's referral to the outpatient clinic is capable of predicting the prognosis of these patients, in contrast with previous studies[14,17,18] that used data obtained from echocardiographic assessments carried out at least 2 months after the patient was clinically stabilized.

Methods

Patients

The studied population consisted of 81 consecutive patients from our Heart Failure Control Program, who underwent their first Doppler echocardiogram at our echocardiogram laboratory between March 2001 and May 2004.

Eligibility criteria included age between 18 and 75 years, EF < 50% and a history of HF according to Framingham's criteria[21]. Patients with heart rate > 100 bpm, severe valvular stenosis, severe pulmonary disease, congenital cardiopathy, malignant neoplasia, permanent pacemaker, atrial fibrillation and patients with inadequate windows for the Doppler echocardiogram were excluded from the study.

The NYHA functional class was evaluated at each visit through a specific activity scale questionnaire[22], but for survival analysis, we considered only the assessment obtained at the first visit. The primary event determined retrospectively consisted of death or hospital admission due to HF worsening. The follow-up information was obtained from electronic medical files or by telephone contact with the patients or their family members.

The study protocol was approved by the Ethics Committee in Research of our institution, following the ethical recommendations from the Declaration of Helsinki of 1975.

Echocardiography

The patients were assessed while lying on left lateral decubitus using standard echocardiographic sections. The studies were carried out using the commercially available echocardiography equipment (Sonos 4500, Hewlett-Packard, Andover, MA), equipped with a 2.5 MHz transducer. The cardiac dimensions were measured according to the recommendations of the American Society of Echocardiography[23]. At least five consecutive beats were obtained from the parasternal view, to obtain the internal diameters of the LV in the short axis of the LV.

The M-mode was used to measure the cardiac dimensions: left atrium diameter (LA) and final diastolic (LVd) and systolic (LVs) diameters of the LV. The EF of the LV was determined using the modified Simpson's method, with images obtained from the 4- and 2-chamber apical views. The mitral flow was obtained by positioning the pulsed Doppler cursor on the tip of the mitral leaflets at the 4-chamber apical view. This flow was used to determine the maximum LV filling velocity at early diastole (E) and during the atrial (A) contraction, the corresponding E/A ratio and the E wave deceleration time (DT).

The tissue Doppler of the mitral annulus was obtained from the 4-chamber apical view in the septal position. The maximum myocardium velocities were measured at early (E') and late (A') diastole and the ratio E'/A' was calculated. The maximum myocardial velocity during systole (S') was also determined. All echocardiographic measurements were recorded to allow posterior analysis.

Statistical Analysis

Statistical calculations were carried out using the GraphPad Prism 3.02 (San Diego, CA) and MedCalc 9.2.0.2 (Mariakerke, Belgium) programs. Continuous variables were expressed as means ± standard deviations. Patients with or without events were compared using the non-paired Student's *t* test or Chi-square test, as appropriate.

Each variable was tested by univariate logistic regression analysis for the final combined outcome of death or hospital admission due to HF worsening. All the variables with a significant association through the univariate analysis were included in the stepwise multivariate logistic regression analysis, with the objective of identifying predictors that were independent from the final study outcome.

Cumulative survival curves were constructed using the Kaplan–Meier method in combination with log rank test. Patients who were lost to follow-up were censored from statistical analysis. ROC (receiver operating characteristic) curves were generated to determine the optimal cutoffs, with the corresponding sensitivities and specificities, to preview the primary final study outcome. The null hypothesis was rejected when p value was < 0.05. A previous study by our group showed high interobserver and intraobserver agreement for the E' and A' measurements[24].

Results

Of an initial population of 81 patients, five were excluded, four of whom presented atrial fibrillation and one had a permanent pacemaker. Other three patients were lost to follow-up soon after the echocardiogram was performed and were excluded from the analysis. Seventy-three patients (54 men) aged 60.9±12.1 years, represented the studied population and were followed for a mean of 1,367±665 days. Twenty-four patients presented the primary event (death, n=12: 9 due to cardiac causes, 2 due to cerebrovascular accident and 1 due to renal failure; hospitalization due to HF worsening, n=12). Of the 11 patients that were censored due to loss of follow-up, the mean follow-up period until the last contact was 1,089±647 days. The mean interval between the echocardiogram and the first event was 785±544 days.

Clinical Data

The clinical characteristics of the patients are listed in Table 1. Most of the patients presented mild to moderate HF (NYHA Class I: 23.3%; Class II: 54.8%; Class III: 19.2%; Class IV: 2.7%). The comparison between patients that presented or not the combined primary event did not show any significant differences regarding age, sex, HF etiology, hospital admission during the last 6 months before the echocardiogram, presence of hypertension and frequency of medication use, except for furosemide. Patients that presented the combined primary event had a worse NYHA

functional class, used furosemide more often and had a higher prevalence of diabetes mellitus (Table 1).

Echocardiographic Characteristics

Patients that presented events had a larger LA diameter and lower EF when compared to patients free of events (Table 2). They also presented worse diastolic function, evaluated by the pulsed Doppler (higher E wave velocity and E/A ratio and lower DT) as well as by the tissue Doppler (higher E/E' ratio; Table 2). S' velocity was also lower in patients with events.

Table 1 - Clinical characteristics of the studied patients

	Total (n=73)	Patients with events (n=24)	Patients without events (n=49)	p
Clinical Parameters				
Age (yrs)	60.9 ± 12.1	62.0 ± 11.8	60.3 ± 12.3	0.58
Male/Female (%)	74/26	66.7/33.3	77.6/22.4	0.32
Functional Class	2.7 ± 0.7	2.3 ± 0.6	1.9 ± 0.7	0.01
ICM/DCM (%)	68.5/31.5	70.8/29.2	67.3/32.7	0.76
Previous Myocardial Infarction (%)	58.9	41.2	67.3	0.03
DM (%)	39.7	58.3	30.6	0.02
Hypertension (%)	53.4	45.8	57.1	0.46
Hospital admission in the last 6 mo (%)	37.0	41.7	34.7	0.56
Medications (%)				
ACEI or ARB	94.5	95.8	93.9	0.73
β-blocker	65.7	54.2	71.4	0.14
Spironolactone	43.8	54.2	38.8	0.21
Digoxin	46.6	58.3	40.8	0.16
Furosemide	64.4	91.7	51.0	0.0007

ARB - angiotensin-receptor blocker; DCM - dilated cardiomyopathy; ICM - ischemic dilated cardiomyopathy; DM diabetes mellitus; ACEI - angiotensin-converting enzyme inhibitor; P value for comparison between patients with or without events.

Table 2 - Echocardiographic characteristics of the studied patients

	Total (n=73)	Patients with events (n=24)	Patients without events (n=49)	p
LVd (cm)	6.62 ± 0.84	6.74 ± 0.93	6.56 ± 0.79	0.40
LVs (cm)	5.34 ± 0.87	5.59 ± 0.93	5.22 ± 0.81	0.09
LA (cm)	4.33 ± 0.65	4.67 ± 0.67	4.17 ± 0.58	0.002
EF (%)	34.6 ± 8.0	31.1 ± 8.8	36.4 ± 7.1	0.008
E wave (cm/s)	82.8 ± 30.2	100.8 ± 32.4	74.0 ± 24.9	0.0002
A wave (cm/s)	68.9 ± 27.1	63.7 ± 5.1	71.4 ± 4.0	0.26
E/A Ratio	1.53 ± 1.05	1.89 ± 0.93	1.36 ± 1.07	0.04
DT (msec)	194.6 ± 71.4	161.4 ± 56.8	211.3 ± 72.6	0.004
Tissue Doppler				
S` (cm/s)	6.3 ± 1.7	5.7 ± 1.6	6.5 ± 1.4	0.02
E` (cm/s)	7.8 ± 2.2	7.3 ± 2.4	7.9 ± 2.3	0.32
A` (cm/s)	9.1 ± 2.4	8.3 ± 2.4	9.4 ± 2.6	0.08
E/E`	11.3 ± 4.7	14.3 ± 4.6	9.8 ± 4.0	<0.0001
E`/ A`	0.9 ± 0.4	1.0 ± 0.5	0.9 ± 0.4	0.55

A - peak LV filling velocity at the atrial contraction; A' - peak myocardial velocity during late diastole; LA - left atrium diameter; E - peak LV filling velocity during early diastole; E' - peak myocardial velocity during early diastole; EF - ejection fraction; S' - maximum myocardial velocity during systole; TD - time of deceleration of the E wave; LVd - final LV diastolic diameter; LVs - LV final systolic diameter; P value for comparisons between patients with or without events.

Association between Clinical and Echocardiographic Parameters and Prognosis

Regarding the clinical characteristics, the univariate analysis showed a significant association between the occurrence of events and functional class, presence of diabetes mellitus or previous myocardial infarction and furosemide use (Table 3). Echocardiographic parameters that also showed to be significantly associated with the occurrence of events at the univariate analysis were LA, EF, E wave velocity, E/A ratio and DT (Table 3). The E/E' ratio and A` velocity were the tissue Doppler parameters that were significantly associated to the occurrence of events at the univariate analysis (Table 3).

Table 3 - Predictors of the primary outcome at the Univariate Analysis

	Chi-square	P
Clinical Parameters		
Functional Class	6.17	0.01
Previous Myocardium Infarction	5.13	0.02
DM	4.36	0.04
Medications		
Furosemide	10.2	0.001
Echocardiography characteristics		
AE	10.4	0.003
FE	7.07	0.008
E Wave	13.5	0.0002
E/A Ratio	4.00	0.04
TD	5	0.002
Tissue Doppler		
A`	4.73	0.03
E/E`	15.8	0.0001

Abbreviations as in Tables 1 and 2.

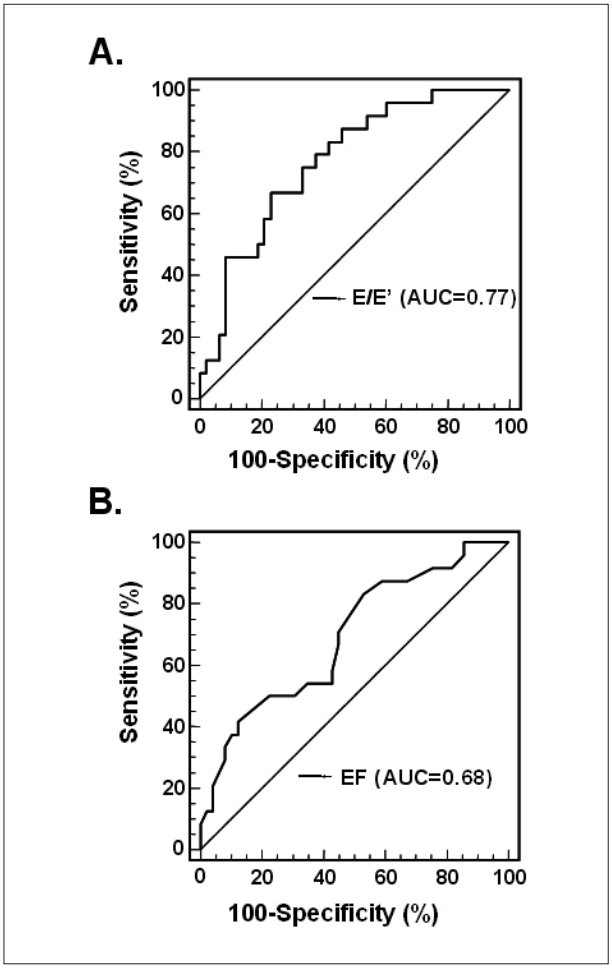

Fig 1 - A - ROC (receiver operating characteristic) curves generated for the ratio between the peak LV filling velocity and peak myocardial velocity during early diastole; E/E' ratio and B - for the LV ejection fraction; EF - in order to determine the optimal cutoff to preview the combined primary event of the study; The areas under the curve; AUC - are described between parentheses.

The stepwise multivariate logistic regression analysis, including all the variables with univariate association and adjusted for sex and age, selected as independent predictors of the combined primary event, only furosemide use (p=0.01, OR=8.1 [95%CI=1.6 to 40.4]), EF (p=0.04, OR=0.91 [95%CI=0.83 to 0.99]) and E/E` ratio ($p$=0.001, OR=1.37 [I95%CI=1.13 to 1.65]). When the same analysis was carried out including only the variables of the Doppler echocardiogram, the EF ($p$=0.01, OR=0.90 [95%CI=0.82 to 0.97]), and the E/E` ratio (p=0.0007, OR=1.31 [95%CI=1.12 to 1.52]) remained as independent predictors of the combined primary event.

ROC curves were generated to identify the optimal cutoffs for the tissue Doppler parameters and EF. The following values arose as the optimal cutoffs to identify the patients that presented the combined primary event (Figure 1a): S'<5.4 cm/s (area under the curve [AUC]=0.67, p=0.008, sensitivity 54.2%, specificity 81.2%), E'<6.8 cm/s (AUC=0.63, p=0.06, sensitivity 58.3%, specificity 68.7%), A'<9.7 cm/s (AUC=0.66, p=0.01, sensitivity 83.3%, specificity 56.2%), and E/E' ratio>12.7 (AUC=0.77, p=0.0001, sensitivity 66.7%, specificity 77.1%). The optimal cutoff for the identification of the patients that presented the combined primary event through the EF was 30% (AUC=0.68, p=0.006, sensitivity 50.0%, specificity 77.1%; Figure 1b).

The areas under the ROC curves for EF and E/E' ratio did not significantly differ (Figure 1). However, when the patients with EF> 30% (50 patients) are divided in two groups, according to the E/E' ratio, we found 19 (38%) who had values ≥ 12.7 and 31 (62%) with a E/E' ratio < 12.7. The first group concentrated 75% (9/12) of the events of patients with EF > 30%, resulting in an incidence of events of 47%, whereas in the second group, only 3 events were recorded, which corresponds to an incidence of events of 9.7%.

According to the Kaplan-Meier analysis of survival, the prognosis was worse in patients with E/E' ratio>12.7 (odds ratio=3.8, 95%CI: 1.8 to 9.6, p=0.001; Figure 2a) or EF<30%

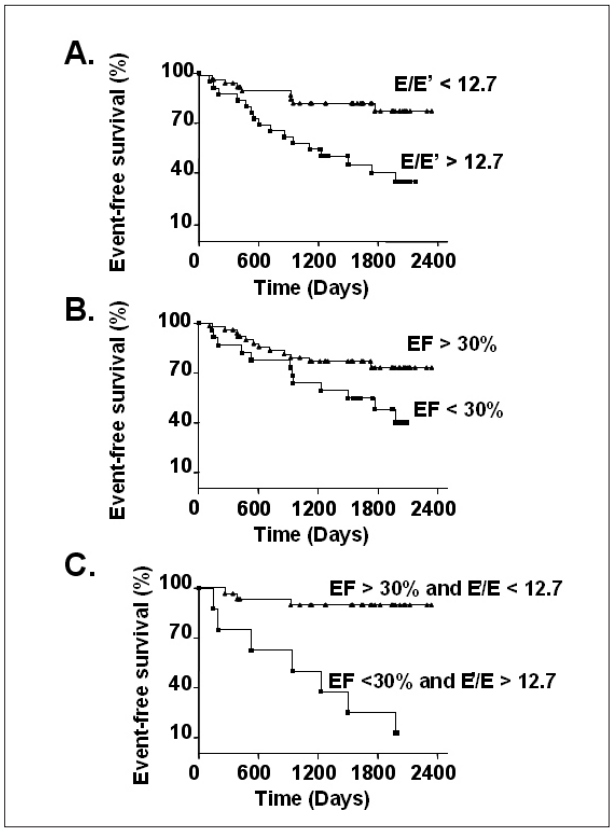

Fig 2 - Kaplan-Meier Curves of event-free survival in outpatients with heart failure classified according to (A) the ratio between the peak LV filling velocity and peak myocardial velocity (E/E' ratio) during early diastole, (B) LV ejection fraction (EF) or (C) the association of both parameters.

(odds ratio =2.3, 95%CI: 1.07 to 6.1, p=0.03; Figure 2B). The comparison between patients with and those without these two abnormalities, simultaneously present: E/E' ratio >12.7 and EF<30%, resulted in a clearer identification of patients with worse prognosis (OR=10.8, 95%CI: 7.2 to 188.0, p<0.0001; Figure 2C). The presence of these two factors resulted in an OR=19.8 (p=0.0005) with high specificity (97.9%), but low sensitivity (29.2%) for the occurrence of events. On the other hand, the presence of at least one of these factors resulted in an OR=9.3 (p=0.0003) with lower specificity (57.1%), but higher sensitivity (87.5%) for the occurrence of events.

Discussion

The main finding of the present study was the indication that the parameters derived from the tissue Doppler obtained as early as after the first outpatient clinic visit can predict events (total mortality or hospitalization due to HF worsening) in patients with LV systolic dysfunction.

The E/E' ratio and the EF were the only echocardiographic variables capable of adding a prognostic value when clinical variables were included in the multivariate analysis. Our analysis is different from those in previous studies, in which the echocardiogram information was obtained at least two months after the start of the standard therapy[14,17,18]. As far as we can see, the high morbimortality associated to HF results in the necessity to obtain prognosis information as soon as possible and, therefore, we chose to use the data obtained at the echocardiogram requested after the patients' first visit to the outpatient clinic program of HF control.

The prognostic value of parameters that measure systolic function in HF has long been known. The decrease in EF[25] as well as the increased final systolic diameter or volume of the LV[25,26] are classically associated to a worse prognosis. In our series, the EF was also an independent predictor of events in the outpatient clinic population with LV systolic dysfunction. Additionally, variable degrees of systolic and diastolic dysfunction can coexist and diastolic function parameters, such as decreased DT or restrictive pattern were also recognized as strong predictors of prognosis[17,27]. In the present study, the decreased DT was also associated with the occurrence of events at the univariate analysis.

The E/E' ratio correlates well with the final diastolic pressure of the LV[11-13] and to the plasma concentration of the brain natriuretic peptide[28]. These findings stimulated the researchers to carry out studies to test and identify the prognostic value of this parameter in the LV systolic dysfunction[15-17,19,20,29]. Additionally, the E/E' ratio has shown to be the strongest predictor of future cardiac events when compared to several other echocardiographic parameters[17,29]. Our study confirmed the prognostic value of the E/E' ratio for the combined outcome of total mortality or hospitalization due to the HF worsening. It is worth mentioning that the cardiac mortality was responsible for most of the cases of death reported in our study. The optimal cutoff for the E/E' ratio described by us (12.7) is similar to that described in another study (12.5)[15] and close to another, reported by a third group (15)[13] that also studied the value of this ratio as a predictor of cardiac events. The classical study[11], describing the capacity to identify elevated final diastolic pressures of the LV through the septal E/E' ratio, found a value of 15 as an optimal cutoff, which is higher than the one described by us to identify prognosis. It is important to mention, however, the difference between the focus of the present study, concentrated on prognosis assessment and the higher implication of the other study, focused on the identification of the elevated diastolic pressure of the LV, possibly contributing to the diversity of results[11].

The superiority of the E/E' ratio over parameters that are derived exclusively from the analysis of the mitral flow can be attributed to the dependence of the mitral flow to several factors, such as the volemic status, left atrial pressure, age and myocardial relaxation[30]. In fact, the DT could predict the prognosis at the univariate analysis, as corroborated by literature data[14,17,19,27], but it was a weaker event predictor when compared to the E/E' ratio in multivariate analysis models, both in our study and in others[14,17].

In our study, differently from what is observed in the literature[17-19,29], the E' velocity was not a predictor of events at the univariate analysis. However, in all, except one, its independent prognostic value was not confirmed after a multivariate analysis[18]. This can be attributed to the small, but significant difference in the mean value of E' between patients with and without events, of only 1 to 2 cm/s in these studies[17-20]. In contrast, the E/E' ratio showed to be the most

accurate marker of diastolic dysfunction in HF and allowed the selection of patients with HF and advanced diastolic dysfunction associated to the highest incidence of events.

The prognostic importance of the A' velocity in patients with HF was demonstrated by a recent publication, where this parameter was selected among other echocardiographic variables, including the E/E' ratio, as the most powerful independent predictor[14]. In fact, previous studies have shown that the A' velocity was significantly lower in patients with events[17-19], and in our study, the A' velocity was a predictor of events at the univariate analysis. However, in our and other studies[17-20], this parameter was not an independent predictor of events.

Although the E/E' ratio and the EF have been recognized as independent prognostic indices in the population with HF of our study, the sensitivities for the identified optimal cutoffs were low, for the E/E' ratio as well as for the EF. Additionally, the specificities were not high, either. One of the possible reasons for these findings is the long period of follow-up, during which other undetected factors might have influenced patient evolution. For instance, coronary disease was highly prevalent in the present series and one cannot rule out the occurrence of ischemic events contributing to the death of the patients. However, the combination of both indices resulted in high specificity for the occurrence of events, when both were altered beyond the cutoff in the same patient and a good sensitivity when one or the other was altered. Another aspect to be pointed out is that ¼ of the patients presented EF above the cutoff, but with an elevated E/E' ratio. These patients had a high incidence of events. This elevated E/E' ratio allowed the identification of a subgroup of patients who presented a high occurrence of events among those that would not be identified based solely on the EF value.

The chronic use of furosemide was also an independent prognostic predictor in our study. This can be attributed to the fact that the more symptomatic patients, and thus, more severe ones, had the loop diuretic included more often in their prescriptions.

Limitations

We did not evaluate the LA volume through the 2-D echocardiography, but only the LA diameter through the M-mode. The inclusion of the LA in the analysis could have resulted in another independent predictor, as the LA volume is closely associated with elevated serum levels of the brain natriuretic peptide[31] and was recognized as an event predictor in HF, as described in the literature[27,29,32]. Other parameters with prognostic meaning in HF, such as tolerance to exercise or the heart rate variability were not analyzed in the present study, either.

Other limitations include the retrospective nature of the study and the selected population that was referred to our service. These results should not be extended to the patients excluded from this study due to characteristics such as atrial fibrillation or severe valvular stenosis. A recent study extended the prognostic value of the E/E' ratio to patients with HF and secondary severe mitral regurgitation[33]. Our population sample consisted of patients with relatively lower risk, as suggested by the low mortality and therefore, the inclusion of more severe patients could lead to different results. It seems, however, that our results are more applicable to the population that is usually treated during routine clinical practice.

Conclusions

Our findings indicate that the E/E' ratio is an important independent long-term prognostic index of death or hospitalization due to HF worsening in patients treated at the outpatient clinic for HF secondary to LV systolic dysfunction. In our series, the E/E' ratio and EF were the only echocardiographic variables that added a prognostic value in a multivariate analysis model that included clinical variables as well as echocardiographic ones. Additionally, our analysis showed a new aspect, as it extracted information from the first echocardiogram performed after the initial examination of the patient at the outpatient clinic, thus allowing the immediate attainment of important prognostic information.

It is worth mentioning that the present study identified a subgroup of patients who, although presented EF higher than our optimal cutoff, had an elevated E/E' ratio and high frequency of events. Consequently, it is recommended that the systematic measurement of this variable, through an easily applicable instrument such as the Doppler echocardiogram, should be included in the routine assessment of outpatients with LV systolic dysfunction and mild or moderate symptoms of HF.

Acknowledgements

The authors wish to thank the technical assistance provided by the members of Total Care. The authors also thank the support received from other physicians from our institution, especially from Dr. Dino Roberto Gomes.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

References

1. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002; 347: 1397-402.

2. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 1993; 22: 6A-13A.

3. Wong M, Staszewsky L, Latini R, Barlera S, Glazer R, Aknay N, et al. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: Valsartan heart failure trial (Val-HeFT) echocardiographic data. J Am Coll Cardiol. 2004; 43: 2022-7.

4. Lapu-Bula R, Robert A, De Kock M, D'Hondt AM, Detry JM, Melin JA, et al. Risk stratification in patients with dilated cardiomyopathy: contribution of Doppler-derived left ventricular filling. Am J Cardiol. 1998; 82: 779-85.

5. Hansen A, Haass M, Zugck C, Krueger C, Unnebrink K, Zimmermann R, et al. Prognostic value of Doppler echocardiographic mitral inflow patterns: implications for risk stratification in patients with chronic congestive heart failure. J Am Coll Cardiol. 2001; 37: 1049-55.

6. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol. 1994; 24: 132-9.

7. Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. J Am Coll Cardiol. 1987; 10: 800-8.

8. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol. 1997; 30: 474-80.

9. Danzmann LC, de Freitas VC, Araujo LF, Torres MA. Assessment of left ventricular diastolic function in hypertensive patients under different hemodynamic conditions: comparative study between transmitral and tissue Doppler echocardiography. Arq Bras Cardiol. 2006; 87: 121-7.

10. Barberato SH, Pecoits FR. Influence of preload reduction on Tei index and other Doppler echocardiographic parameters of left ventricular function. Arq Bras Cardiol. 2006; 86: 425-31.

11. Nagueh SF, Kopelen HA, Zoghbi WA. Feasibility and accuracy of Doppler echocardiographic estimation of pulmonary artery occlusive pressure in the intensive care unit. Am J Cardiol. 1995; 75: 1256-62.

12. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997; 30: 1527-33.

13. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation. 2000; 102: 1788-94.

14. Yamamoto T, Oki T, Yamada H, Tanaka H, Ishimoto T, Wakatsuki T, et al. Prognostic value of the atrial systolic mitral annular motion velocity in patients with left ventricular systolic dysfunction. J Am Soc Echocardiogr. 2003; 16: 333-9.

15. Dokainish H, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. J Am Coll Cardiol. 2005; 45: 1223-6.

16. Bruch C, Rothenburger M, Gotzmann M, Sindermann J, Scheld HH, Breithardt G, et al. Risk stratification in chronic heart failure: independent and incremental prognostic value of echocardiography and brain natriuretic peptide and its N-terminal fragment. J Am Soc Echocardiogr. 2006; 19: 522-8.

17. Acil T, Wichter T, Stypmann J, Janssen F, Paul M, Grude M, et al. Prognostic value of tissue Doppler imaging in patients with chronic congestive heart failure. Int J Cardiol. 2005; 103: 175-81.

18. Bruch C, Gotzmann M, Stypmann J, Wenzelburger F, Rothenburger M, Grude M, et al. Electrocardiography and Doppler echocardiography for risk stratification in patients with chronic heart failure: incremental prognostic value of QRS duration and a restrictive mitral filling pattern. J Am Coll Cardiol. 2005; 45: 1072-5.

19. Troughton RW, Prior DL, Frampton CM, Nash PJ, Pereira JJ, Martin M, et al. Usefulness of tissue doppler and color M-mode indexes of left ventricular diastolic function in predicting outcomes in systolic left ventricular heart failure (from the ADEPT study). Am J Cardiol. 2005; 96: 257-62.

20. Hamdan A, Shapira Y, Bengal T, Mansur M, Vaturi M, Sulkes J, et al. Tissue Doppler imaging in patients with advanced heart failure: relation to functional class and prognosis. J Heart Lung Transplant. 2006; 25: 214-8.

21. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993; 88: 107-15.

22. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. Circulation. 1981; 64: 1227-34.

23. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989; 2: 358-67.

24. Saraiva RM, Duarte DM, Duarte MP, Martins AF, Poltronieri AV, Ferreira ME, et al. Tissue Doppler imaging identifies asymptomatic normotensive diabetics with diastolic dysfunction and reduced exercise tolerance. Echocardiography. 2005; 22: 561-70.

25. Parameshwar J, Keegan J, Sparrow J, Sutton GC, Poole-Wilson PA. Predictors of prognosis in severe chronic heart failure. Am Heart J. 1992; 123: 421-6.

26. Brophy JM, Deslauriers G, Rouleau JL. Long-term prognosis of patients presenting to the emergency room with decompensated congestive heart failure. Can J Cardiol. 1994; 10: 543-7.

27. Giannuzzi P, Temporelli PL, Bosimini E, Silva P, Imparato A, Corra U, et al. Independent and incremental prognostic value of Doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. J Am Coll Cardiol. 1996; 28: 383-90.

28. Troughton RW, Prior DL, Pereira JJ, Martin M, Fogarty A, Morehead A, et al. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. J Am Coll Cardiol. 2004; 43: 416-22.

29. Liang HY, Cauduro SA, Pellikka PA, Bailey KR, Grossardt BR, Yang EH, et al. Comparison of usefulness of echocardiographic Doppler variables to left ventricular end-diastolic pressure in predicting future heart failure events. Am J Cardiol. 2006; 97: 866-71.

30. Mandinov L, Eberli FR, Seiler C, Hess OM. Diastolic heart failure. Cardiovasc Res. 2000; 45: 813-25.

31. Lim TK, Ashrafian H, Dwivedi G, Collinson PO, Senior R. Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular ejection fraction: Implication for diagnosis of diastolic heart failure. Eur J Heart Fail. 2006; 8: 38-45.

32. Dini FL, Cortigiani L, Baldini U, Boni A, Nuti R, Barsotti L, et al. Prognostic value of left atrial enlargement in patients with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy. Am J Cardiol. 2002; 89: 518-23.

33. Bruch C, Klem I, Breithardt G, Wichter T, Gradaus R. Diagnostic usefulness and prognostic implications of the mitral e/e' ratio in patients with heart failure and severe secondary mitral regurgitation. Am J Cardiol. 2007; 100: 860-5.