The Prognostic Value of Early Left Ventricular Longitudinal Systolic Dysfunction in Asymptomatic Subjects With Cardiovascular Risk Factors

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ABSTRACT

Background: Early diagnosis of left ventricular (LV) dysfunction represents a major challenge in asymptomatic subjects with cardiovascular (CV) risk factors. Tissue Doppler imaging (TDI) has emerged as an important tool with clinical relevance in several cardiac diseases.

Hypothesis: To evaluate the prognostic ability of TDI in detecting early longitudinal ventricular dysfunction in a large group of asymptomatic subjects with CV risk factors (RsF), normal LV systolic function, and normal diastolic function.

Methods: A total of 554 subjects (mean age 55 ± 13 years, 39% men) formed our study population: controls, 144 healthy subjects; group 1, 163 subjects with 1 CV RsF; group 2, 147 subjects with 2 CV RsF; group 3, 100 subjects with ≥3 CV RsF. All subjects underwent a comprehensive standard echo-Doppler evaluation, including posterior wall TDI study. Follow-up data were available in all the studied samples (mean 28 ± 16 mo).

Results: Upon follow-up, 18 individuals (3.2%) developed a first overt CV event. The presence of a peak systolic velocity <7.5 cm/second showed a significant additional predictive value compared with the presence of CV RsF ($P < 0.001$).

Conclusions: Tissue Doppler imaging is able to identify early longitudinal LV systolic abnormalities in the presence of apparently normal systolic and diastolic function. It demonstrated a significant additional prognostic value compared with the simple presence of coexisting CV RsF. These findings could be clinically relevant in identifying asymptomatic subjects with CV RsF who need early, tailored preventive treatment.

Introduction

To prevent death and morbidity from cardiovascular (CV) disease, there is great interest in identifying high-risk asymptomatic patients who would be candidates for more intensive medical interventions that could reduce CV disease risk.[1–3] Although not everyone with CV risk factors (RsF) will experience a clinical CV event, the greater the degree of subclinical atherosclerosis, the greater the risk for future CV events.[4–8]

Echocardiography is the most commonly used noninvasive tool for the assessment of cardiac anatomy and function, and it plays an important clinical role in prognostic assessment.[9–11] Conventional echocardiographic predictors of poor outcome, such as left ventricular (LV) ejection fraction (EF) and restrictive filling pattern,[9–11] have recently been supplemented by tissue Doppler imaging (TDI) parameters. Tissue Doppler imaging has been proposed as a strong "prognosticator"[12] in several cardiac diseases, and even in

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heart failure patients with a normal LVEF, such as "diastolic heart failure."[12]

So far, no studies have assessed the prognostic ability of TDI parameters in asymptomatic subjects with both normal systolic and diastolic function as assessed by conventional echocardiography.

The study aim was to evaluate the prognostic ability of TDI in a large sample of asymptomatic subjects with CV RsF and LVEF >55%, and normal diastolic function, as assessed by flow Doppler analysis.

Methods

Study Population

This multicenter prospective study designed by the Italian Society of Cardiovascular Echography included consecutive asymptomatic subjects age >18 years admitted to 26 echocardiographic laboratories for transthoracic examination as screening evaluation in presence of ≥1 CV RsF.

All laboratories were selected according to the competence of the operators, level 3, in agreement with the American Society of Echocardiography requirement.[13] The study was approved by the local research ethics committees.

Exclusion criteria were history of heart failure (HF), history of coronary artery disease (CAD), symptoms or clinical and instrumental signs of HF or CAD, chronic obstructive pulmonary disease, valvular heart disease > mild, previous cardiac surgery or percutaneous coronary intervention, history of paroxysmal or persistent atrial fibrillation, LVEF ≤55%, presence of LV regional wall systolic abnormalities, abnormal diastolic function, anemia (hemoglobin <12 mg/dL in women and <13 mg/dL in men), renal failure (serum creatinine >1.3 mg/dL), and endocrinological diseases. The following parameters were assessed to classify diastolic function[14,15]: E wave velocity, A wave velocity, E/A, Δ E/A (changes from basal to Valsalva maneuver), E wave deceleration time (DT), A wave duration (Adur), E/peak early diastolic velocity (E/Em), pulmonary venous flow [(systolic velocity (S), diastolic velocity (D), A reverse wave duration (ARdur)].

Left atrial volume (LAV) was calculated using the biplane area-length formula, $8(A1)(A2) / 3\pi (L)$, where A1 and A2 represent the maximal planimetered LA area acquired from the apical 4- and 2-chamber views, respectively, and L is length. The LAV was measured at ventricular end systole, and LA appendage and pulmonary veins were excluded from the area tracing. All subjects gave written informed consent and provided detailed medical history, in particular on CV RsF, comorbidities, and drug therapies.

For the purposes of this study, these 6 CV RsF were considered: hypertension (systolic blood pressure [BP] ≥140 mm Hg or diastolic BP ≥90 mm Hg), diabetes mellitus (DM; fasting glycemia ≥7.0 mmol/L^{-1}), hypercholesterolemia (>200 mg/dL), a history of premature CV disease (before age 55 years in males and before 65 in females) in first-degree relatives, smoking (≥1 cigarette/d; cessation of smoking <10 years was still considered as smoking), obesity (body mass index [BMI] ≥30 kg/m^2).

According to the presence of CV RsF, patients were divided into 3 groups: group 1 (1 CV RsF), group 2 (2 CV RsF), and group 3 (≥3 RsF).

Using an identical protocol, we also studied healthy subjects with no detectable CV RsF.

Diagnostic Criteria

All patients enrolled in the study underwent physical examination, 12-lead electrocardiogram, and a transthoracic echocardiographic examination.[16] Anthropometric measurements (weight, height) were obtained, and BMI was calculated. The BP was measured twice at the right arm after a 10-minute rest in the supine position using a calibrated sphygmomanometer and averaged. Quantitative analysis was done, for each laboratory, by the same expert operator.

Left ventricular ejection fraction was measured using the modified biplane Simpson's rule as a mean of 3 cardiac cycles. Left ventricular diastolic function was evaluated according to the standard criteria.[14,15] Only subjects with normal diastolic function ($0.75<E/A<1.5$, DT>140 msec, $\Delta E/A<0.5$ during Valsalva maneuver, S ≥ D, ARdur<Adur)[14,15] were included in the study.

Left ventricular mass was calculated and indexed for height$^{2.7}$ (LVMI).[16] Left ventricular hypertrophy was defined as LVMI >49.2 g/$m^{2.7}$ in men and >46.7 g/$m^{2.7}$ in women.[17] In accordance with American Society of Echocardiography/European Society of Cardiology guidelines, a LAV >29 mL/m^2 was used for both sexes to identify abnormal LAV.[18]

TDI Study

Mitral annular velocities were recorded from the apical 4-chamber view with the pulse-wave Doppler sample volume placed in the septal corner of the mitral annulus. We measured peak annular velocity, during ejection (Sm), during early diastolic filling (Em), and during atrial contraction (Am), from 3 cardiac cycles, and the results were averaged.[19] According to previous studies, an Sm value <7.5 cm/second was considered as reduced longitudinal systolic function,[20] and an E/Em ratio ≥13 was considered as impaired diastolic function.[21]

All the echocardiographic assessments were made by physicians blinded to the results of follow-up.

Follow-Up and Outcome Events

Patients were contacted every 6 months by telephone to obtain clinical data and adverse events using a standard questionnaire.[22]

The outcome for the present investigation was the occurrence of a first overt CV event on follow-up, defined as a composite of CAD (recognized or unrecognized myocardial infarction, angina, coronary insufficiency, or CAD death), cerebrovascular disease (stroke or transient ischemic attack), or congestive HF. The diagnostic criteria for CV events have been detailed elsewhere.[23]

Statistical Analysis

Categorical variables are presented as percentages. Continuous variables are presented as mean ± SD or median and interquartile range, when appropriate. The correlation

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of age according to the RsF groups was tested using nonparametric Kruskal-Wallis test.

One-way analysis of variance was used to examine differences of continuous variables (BMI, systolic and diastolic BP, heart rate, and echocardiographic parameters) among RsF groups. Categorical variables were compared using the χ^2 test.

The relation of longitudinal systolic function (reduced when Sm value was <7.5) to the cumulative event-free survival was univariately evaluated by Kaplan-Meier analysis, and groups were compared by the log-rank test.

Hazard ratios were calculated by univariate Cox regression analysis. Factors with a univariate significance were stepwise included in a multivariate Cox regression model in order to adjust factors for their interdependency.

A 2-tailed P value of <0.05 was considered significant. All data were analyzed using SPSS software, version 12.1 (SPSS, Inc., Chicago, IL).

Results

Among 758 subjects evaluated, 96 were excluded for EF <55% and 108 for abnormal diastolic function. A total of 554 subjects (mean age 55 ± 13 years, 39% men) formed our study population. General clinical characteristics of the study population are presented in Table 1.

Age, BMI, and BP were significantly increased in the groups, compared with controls. In our selected population, hypertension was the most frequent CV RsF, and DM was the least frequent RsF.

Angiotensin-converting enzyme inhibitors were the most-used drug (24%), whereas β-blockers were used by 15% of the studied population.

Regarding LV morphology and systolic function (Table 2), as expected, systolic function, assessed by LVEF, was not different among the 4 groups. Left ventricular volumes and LAVI were significantly increased in subjects with ≥2 CV RsF compared with controls. Also, LVMI was significantly increased in subjects with CV RsF compared with controls ($P < 0.0001$).

Although all the studied subjects had a comprehensive normal diastolic function, E/A ratio was found significantly reduced in the 3 groups compared with controls. E wave deceleration time was significantly prolonged in the 3 groups compared with controls (Table 2).

In the TDI study, LV global longitudinal systolic function, assessed by Sm, was significantly reduced in subjects with ≥1 CV RsF compared with controls ($P = 0.016$). Left

Table 1. Clinical Characteristics of the Studied Sample

Characteristic	Group 0 (n = 144)	Group 1 (n = 163)	Group 2 (n = 147)	Group 3 (n = 100)	Total (n = 554)	*P* Value
Age (y)	50 ± 10[a]	55 ± 8[b]	60 ± 6	62 ± 7	55 ± 13	0.000
BMI (kg/m²)	24 ± 3[b]	25 ± 3[b]	27 ± 4[c]	29 ± 5	26 ± 4	0.000
SBP (mm Hg)	120 ± 5[a]	135 ± 7 [b]	140 ± 10[c]	143 ± 10	135 ± 12	0.000
DBP (mm Hg)	80 ± 5	80 ± 10	80 ± 10	85 ± 10[a]	80 ± 10	0.000
Male sex, n (%)	42 (29.2)	71 (43.6)	56 (38.1)	46 (46.0)	215 (38.8)	0.024
DM, n (%)	0[a] (0.0)	7[c] (4.3)	14 (9.5)	26 (26.0)	47 (8.5)	0.000
Hypertension, n (%)	0[a] (0.0)	58[c] (35.6)	97 (66.0)	86 (86.0)	241 (43.5)	0.000
Smoking, n (%)	0[a] (0.0)	38 (23.3)	34 (23.1)	32 (32.0)	104 (18.8)	0.000
Dyslipidemia, n (%)	0[a] (0.0)	17[b] (10.4)	45 (30.6)	67 (67.0)	129 (23.3)	0.000
Obesity, n (%)	0[a] (0.0)	11[b] (6.7)	29 (19.7)	51 (51.0)	91 (16.4)	0.000
Family history of CVD, n (%)	0[a] (0.0)	32[b] (19.6)	75 (51.0)	73 (73.0)	180 (32.5)	0.000
Medical therapy, n (%)						
Diuretics	0[a] (0.0)	16[b] (9.8)	25 (17.0)	26 (26.0)	70 (12.6)	0.000
ACEIs	0[a] (0.0)	32[b] (19.6)	43 (29.3)	50 (50.0)	129 (23.3)	0.000
AII antagonists	0[a] (0.0)	6 (3.7)	14 (9.5)	9 (9.0)	29 (5.2)	0.000
Diidropridin calcium antagonists	0[a] (0.0)	13 (8.0)	22 (15.0)	10 (10.0)	45 (8.1)	0.000
β-Blockers	0[a] (0.0)	17[c] (10.4)	24 (16.3)	23 (23.0)	68 (12.3)	0.000
ASA	0[a] (0.0)	13[c] (8.0)	12 (8.2)	29 (29.0)	61 (11.0)	0.000
Statins	0[a] (0.0)	3[b] (1.8)	14 (9.5)	23 (23.0)	40 (7.2)	0.000

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; AII, angiotensin II; ASA, aspirin; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; SBP, systolic blood pressure. [a]$P < 0.001$ vs all the groups. [b]$P < 0.001$ vs Group 2 and Group 3. [c]$P < 0.05$ vs Group 3.

Table 2. Standard Echocardiographic and TDI Parameters of the Studied Sample

	Group 0	Group 1	Group 2	Group 3	Total	*P* Value
IVS-EDD (mm)	9.54 ± 1.73	9.98 ± 1.89	9.95 ± 2.20	10.69 ± 2.28[a]	9.98 ± 2.04	0.000
PWEDD (mm)	8.84 ± 1.54[b]	9.32 ± 1.62	9.11 ± 1.70	9.61 ± 1.70	9.19 ± 1.66	0.002
LVMI (g/m$^{2.7}$)	40.51 ± 10.54[a]	44.56 ± 14.65	45.65 ± 14.48	48.65 ± 12.28	44.53 ± 13.47	0.000
LVEDV (mL)	92.30 ± 21.45[c]	94.22 ± 34.35	102.73 ± 37.24	113.66 ± 38.59[a]	99.49 ± 35.98	0.000
LVESV (mL)	30.60 ± 12.02[d]	31.94 ± 13.41	34.37 ± 13.76	36.37 ± 16.78	33.04 ± 13.96	0.006
EF (%)	66.88 ± 5.90	66.12 ± 6.01	66.34 ± 6.03	68.08 ± 7.97	66.73 ± 6.41	0.087
E (cm/s)	73.13 ± 16.38	70.99 ± 17.54	70.27 ± 19.84	74.77 ± 17.20	72.04 ± 17.87	0.182
LAVI (mL/m^2)	23.3 ± 14.1[c]	24.2 ± 14.6	26.5 ± 16.6	28.9 ± 16.5	24.3 ± 15.6	0.0001
A (cm/s)	57.10 ± 16.52[a]	73.02 ± 16.58	74.37 ± 20.38	82.33 ± 20.41[a]	73.52 ± 18.98	0.000
E/A	1.35 ± 0.38[a]	1.02 ± 0.35	0.99 ± 0.35	0.96 ± 0.31	1.04 ± 0.36	0.000
E-DT (msec)	207.96 ± 50.57	219.13 ± 58.55	209.52 ± 55.97	214.23 ± 66.85	212.79 ± 57.57	0.320
E/Em	8.69 ± 3.70[e]	14.98 ± 19.87	15.48 ± 19.28	11.21 ± 4.39	13.70 ± 17.63	0.143
Sm (cm/s)	8.82 ± 1.21[a]	6.82 ± 2.45	6.65 ± 2.58	6.32 ± 2.39	6.75 ± 2.50	0.016
Em (cm/s)	8.91 ± 2.10[a]	7.62 ± 3.14	7.28 ± 3.10	7.46 ± 2.75	7.79 ± 3.10	0.000

Abbreviations: A, atrial kick peak velocity; E, early diastolic peak velocity; E-DT, E wave deceleration time; EF, ejection fraction; Em, early diastolic peak velocity wave assessed by TDI on the septal mitral annulus; IVS-EDD, interventricular septum end diastolic diameter; LAVI, left atrial volume indexed for body surface area; LVEDV, left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; LVMI, left ventricular mass indexed for height$^{2.7}$; PWEDD, posterior wall end diastolic diameter; Sm, peak systolic velocity assessed by TDI on the septal mitral annulus; TDI, tissue Doppler imaging. [a]$P < 0.001$ vs all groups. [b]$P < 0.05$ vs Group 1 and Group 3. [c]$P < 0.01$ vs Group 2 and Group 3. [d]$P < 0.001$ vs Group 3. [e]$P < 0.001$ vs Group 1 and Group 2.

ventricular Em was significantly decreased in subjects with CV RsF ($P = 0.000$). The E/Em ratio was comparable between subjects with CV RsF and controls (Table 2).

Prognostic Significance of Subclinical Longitudinal Dysfunction

Follow-up data were available in all 554 studied subjects. Upon follow-up (mean 28 ± 16 mo), 18 individuals (3.2%) had developed a first overt CV event (recognized myocardial infarction, n = 1; CAD requiring revascularization, n = 12; CAD death, n = 2; transient ischemic attack, n = 1; congestive HF, n = 2).

Cardiovascular events happened in subjects with an Sm value <7.5 cm/second (Figure 1). Dichotomization of the patient population according to the Sm value <7.5 cm/second showed a significant additional predictive value compared with the presence of CV RsF as assessed by Kaplan-Meier analysis (Figure 1).

The Sm velocity significantly influenced event-free survival, in addition to established prognostic factors such as DM, dyslipidemia, obesity, and echocardiographic parameters such as LV volumes (Table 3). Age, hypertension, family history of CV, EF, LVMI, E/A, E/Em, and Em were weakly associated with a worse outcome, but did not reach statistical significance.

To determine independent predictors of CV events among these variables, we used a stepwise multivariate model of regression analysis including every factor with a univariate significant influence. Among these, Sm, gender (male), DM, and dyslipidemia remained the only independent predictors of cardiovascular events (Table 4).

Discussion

This study demonstrated, for the first time in a large sample of asymptomatic subjects with ≥1 CV RsF, the additional prognostic ability of early functional abnormalities of global longitudinal systolic function, despite a LVEF >55% and a normal diastolic function.[14,15]

The best echocardiographic predictor of CV events at follow-up was a reduced Sm, showing a significant additional prognostic value compared with the simple presence of coexisting CV RsF. Thus, our results suggest that longitudinal systolic function could be a better marker of early functional cardiac abnormalities than LV diastolic function.

Posterior Wall Tissue Doppler Imaging Study

Our results, in agreement with the recent HF classification[24] that identifies the HF stage A as normal conventional systolic function (LVEF <55%) and presence of CV RsF, clearly documented the usefulness of PW-TDI longitudinal function analysis in the stratification of the above-mentioned subjects, previously not allowed by conventional echocardiographic approach.

Identifying individuals with early markers for this CV disease process raises the possibility for pharmacotherapy to slow the progression and delay or prevent future morbid events.[3,4] Most attempts to identify individuals at risk for CV

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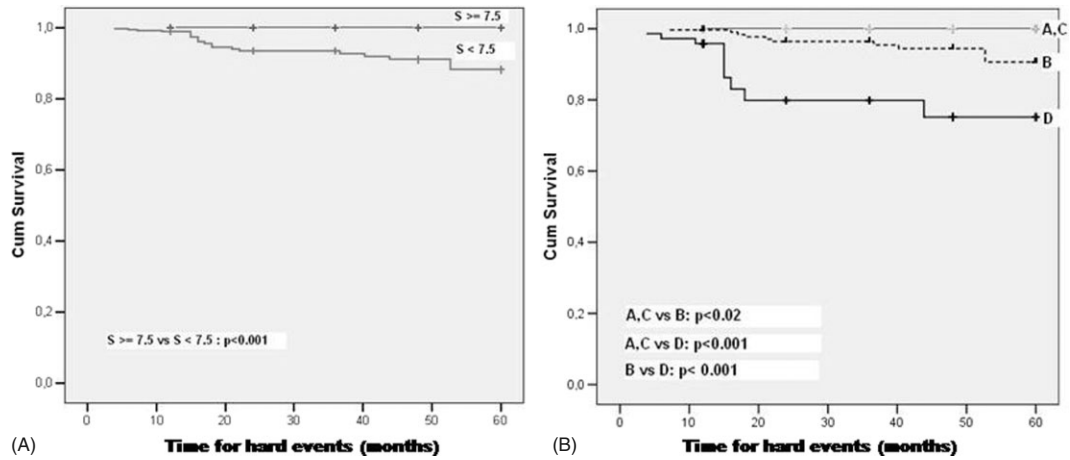

Figure 1. Occurrence of CV events according to (A) TDI peak systolic velocity and (B) the presence of CV RsF and the presence of Sm <7.5 cm/sec. Abbreviations: A, patients with Sm ≥7.5 cm/sec and <3 CV RsF; B, patients with Sm <7.5 cm/sec and <3 CV RsF; C, patients with Sm ≥7.5 cm/sec and ≥3CV RsF; Cum, cumulative; CV, cardiovascular; D, patients with both Sm <7.5 cm/sec and ≥3 CV RsF; RsF, risk factors; S, peak systolic velocity; TDI, tissue Doppler imaging.

Table 3. Univariate Cox Regression Analysis of Prognostic Factors for Cardiovascular Events

	Univariate Hazard Ratio (95% CI)	*P* Value
Age	1.03 (0.99–1.06)	0.182
Male sex	4.09 (1.53–10.9)	0.005
DM	5.32 (1.71–16.5)	0.004
Hypertension	1.23 (0.49–3.13)	0.657
Smoking	1.80 (0.64–5.08)	0.264
Dyslipidemia	4.35 (1.72–11.00)	0.003
Obesity	2.85 (1.07–7.61)	0.037
Family history of CVD	2.08 (0.82–5.28)	0.121
EF	1.02 (0.95–1.11)	0.492
LVEDV	1.01 (1.01–1.03)	0.004
VESV	1.03 (1.00–1.06)	0.026
LVMI	1.01 (0.97–1.04)	0.552
LAVI	1.01 (0.99–1.06)	0.593
E/A	1.07 (0.31–3.74)	0.914
E/Em	1.01 (0.97–1.05)	0.583
Em	2.45 (1.06–5.61)	0.005
Sm	0.70 (0.55–0.88)	0.003

Abbreviations: A, atrial kick peak velocity; CI, confidence interval; DM, diabetes mellitus; E, early diastolic peak velocity; EF, ejection fraction; Em, early diastolic peak velocity wave assessed by TDI on the septal mitral annulus; LAVI, left atrial volume indexed for body surface area; LVEDV, left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; LVMI, left ventricular mass indexed for height 2.7; Sm, peak systolic velocity assessed by TDI on the septal mitral annulus; TDI, tissue Doppler imaging.

Table 4. Stepwise Multivariate Cox Regression Analysis of the Predictive Value of Prognostic Factors for Cardiovascular Events

	Variable	Hazard Ratio (95% CI)	*P* Value
Step 1	Dyslipidemia	4.36 (1.72–11)	0.002
Step 2	DM	4.99 (1.59–15.67)	0.006
	Dyslipidemia	4.20 (1.66–10.64)	0.002
Step 3	Sm	0.69 (0.54–0.88)	0.003
	DM	6.01 (1.87–19.36)	0.003
	Dyslipidemia	3.97 (1.56–10.11)	0.004
Step 4	Sm	0.67 (0.52–0.85)	0.001
	Male sex	4.18 (1.54–11.37)	0.005
	DM	5.08 (1.58–16.30)	0.006
	Dyslipidemia	4.73 (1.83–12.23)	0.001

Abbreviations: CI, confidence interval; DM, diabetes mellitus; Sm, peak systolic velocity assessed by TDI on the septal mitral annulus; TDI, tissue Doppler imaging.

events have involved screening for RsF that are statistically associated with future CV events.[5] Unfortunately, this approach does not provide any insight as to how the RsF are impacting the biologic target organs, particularly the heart. Indeed, these traditional RsF do not seem to be useful in stratifying the severity of disease in individual patients.[6] Nowadays the therapeutic focus has begun to shift toward prevention of disease progression at earlier stages. Noninvasive, inexpensive, no-radiation-exposure diagnostic tests, such as PW-TDI, are now available to assess subclinical CV disease[12] in asymptomatic individuals.

A potential explanation of the prognostic power of the functional systolic parameter Sm in discriminating among the groups with increasing CV RsF, as demonstrated by

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multivariable analysis, could be dependent by the more vulnerability of longitudinal subendocardium to ischemia and to interstitial fibrosis.[25] For this reason, a decrease in longitudinal function might be a sensitive marker for subclinical alterations in LV systolic performance. This has been confirmed by our findings that the presence of a reduced longitudinal systolic function (an Sm value <7.5 cm/sec) has a significant additional prognostic value for the development of CV events compared with simple coexistence of CV RsF. Indeed, subjects with <3 CV RsF but with a Sm <7.5 cm/second showed a worse prognosis compared with patients with ≥3 CV RsF and normal longitudinal systolic function.

Pulsed TDI is a simple and useful method of assessing LV longitudinal function.

In our study, a TDI-derived Sm <7.5 cm/second, recorded on the annular septum, was able to discriminate healthy subjects from subjects with CV RsF, and to predict later CV events. The prognostic ability of Sm in detecting early cardiac abnormalities is not surprising, and several studies already confirmed the clinical value of a decreased Sm velocity.[12] Worthy of note, in our study Sm was reduced in the presence of both normal global systolic and diastolic function as assessed by standard echocardiography. This finding strongly suggests that early abnormalities of cardiac function first involve longitudinal systolic function.

It is noteworthy that in our study at multivariate analysis the most sensitive parameter to detect early abnormalities and later CV events in healthy subjects with CV RsF was a systolic parameter, whereas all the diastolic parameters, conventional and TDI-derived, were not significantly able to discriminate among the 3 groups with different numbers of CV RsF nor to predict CV events.

Probably, this finding could be in part related to our selection criteria. Indeed, the diagnostic workup for excluding diastolic dysfunction by conventional flow Doppler echocardiography[14,15] was more sophisticated than the simple determination of LV systolic dysfunction by means of EF.

However, we hypothesized that this finding, in agreement with the Torrent-Guasp theory, could be related to an early involvement of the subendocardial fibers, responsible for systolic longitudinal shortening.[26] Conversely, subepicardial longitudinal fibers, mainly responsible for the diastolic LV lengthening, are involved later in the disease.[27]

Study Limitations

In this study, we assessed PW-TDI on the septal mitral annulus. A more detailed description of longitudinal function would include the analysis of all the mitral annulus segments. However, the clinical value of PW-TDI on the septal annulus alone already has been demonstrated.[23] In addition, because of the multicenter nature of the study, we decided to use a simplified study protocol assessing only the septal mitral annulus.

The choice of the cutoff values for PW-TDI studied parameters could be considered arbitrary, and in the literature several cutoff values have been proposed,[12] but the superiority of one value against the others has not been demonstrated. Our cutoff values were already used in previous studies[20] and are in the range of the other proposed cutoff values.[12]

Left ventricular hypertrophy was not considered as a RsF for the division into subgroups of our patients because, in agreement with previous studies,[25] it is already a measure of subclinical disease.

In this study, the number of events recorded during the follow-up may be considered low; however, this is not surprising, taking into account our selection criteria and the aim of our study.

In evaluating this study, the effects of pharmacotherapy (especially antihypertensive drugs) on Sm should be taken into account. Sm is not load-independent, and the fact that patients with more CV RsF were more often taking agents that could affect loading could have influenced our results. However, in our study, Sm <7.5 cm/second had an additional prognostic value compared with the number of CV RsF, suggesting that this additional value is not simply a reflection of loading conditions. Moreover, all the studied echocardiographic parameters are load-dependent, but only Sm showed an additional prognostic value.

Conclusion

The results of our study suggest that the presence of CV RsF, in otherwise asymptomatic patients, strongly recommends performing a TDI analysis. The presence of an Sm <7.5 cm/second in subjects with CV RsF, even if LVEF is >55% and diastolic function is normal, suggests starting a more aggressive primary prevention strategy.

Appendix

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