Incidence and predictors of new onset left ventricular diastolic dysfunction in asymptomatic patients with rheumatoid arthritis without overt cardiac disease

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Abstract

Rheumatoid arthritis (RA) is associated with higher risk of heart failure. Several studies report that left ventricular (LV) diastolic dysfunction (LVDD), a silent precursor of heart failure, is widely present in RA patients. Very little is known about the factors related to the development of LVDD in this disease. In this study we assessed the incidence and the predictors of new-onset LVDD in RA patients. Two-hundred-ninety-five adults with RA without overt cardiac disease were prospectively analyzed from March 2014 to March 2015 by Doppler echocardiography. Among the 295 subjects evaluated, 217 (73.6%) had normal LV diastolic function and represented the final study population. At 1-year follow-up, 53 of 217 patients (24%) developed LVDD, which was of degree I (mild dysfunction) in all of them. By multivariate logistic regression analysis, lower E/A ratio of transmitral flow (ratio between the peak velocity of early diastolic "E" wave and late diastolic "A" wave of transmitral flow) was independently associated with new-onset LVDD (OR 0.17 [CI 0.09–0.57]), together with older age and higher systolic blood pressure. In a clinical predictive model derived from multivariate analysis, the new-onset LVDD rate event ranged from 0% (patients without any factor) to 75% (patients in whom the three predictors coexisted). A significant portion of patients with RA without overt cardiac disease develop LVDD at 1-year follow-up. This condition can be predicted by a simple clinical model which could improve the clinical management and the prognostic stratification of patients with RA.

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Introduction

Rheumatoid arthritis (RA) is associated with increased cardiovascular morbidity and mortality [1-6]. In particular, patients with RA have an approximately 2-fold higher incidence of congestive heart failure (CHF), compared to the general population [7,8]. Several studies report that left ventricular (LV) diastolic function is impaired in a consistent portion of patients with RA without clinically evident cardiac disease [9-23], thus suggesting that subclinical LV diastolic dysfunction (LVDD) is an early predictor of subsequent overt CHF. LVDD is the result of mechanical and structural abnormalities such as interstitial fibrosis, impaired myocyte relaxation, decreased distensibility [24,25], and it is ordinarily recognized in clinical practice by standard transthoracic Doppler echocardiography. In RA patients, LVDD has been variously described as reduced E/A ratio, prolonged isovolumetric relaxation time, larger left atrial size and/or high systolic pulmonary artery pressure [9-23]. However, very little is available on the incidence and the predictors of new onset LVDD in RA and conflicting data exist on the relationship between RA disease duration and alteration of LV diastolic function [11,12,17-20,26]. Recently, Davis *et al.* evaluated longitudinal changes in cardiac structure and function of 160 patients with RA compared with 1391 non-RA persons used as controls. They demonstrated that subclinical changes in diastolic function occurred early and the

rates of these changes were significantly higher in patients with RA over five years than in the general population [27].

Accordingly, this study was conceived to assess the factors related to new-onset LVDD and its incidence at 1-year follow-up in a large cohort of asymptomatic RA patients without history of cardiac disease and normal LV diastolic function at baseline echocardiographic evaluation.

Materials and Methods

Study population

Study participants were 295 adults with RA diagnosed according to the American College of Rheumatology criteria [28], without history of cardiac disease. They were recruited from March 2014 to March 2015 and represented the whole RA population surveyed by the Division of Rheumatology of the Verona University where they underwent echocardiographic, clinical and laboratory evaluations. All subjects were free of symptoms and clinical signs of cardiac disease at enrollment. Exclusion criteria were a history of myocardial infarction, myocarditis or CHF, coronary heart disease diagnosed by clinical, electrocardiographic evaluation at rest and by the results of exercise/scintigraphy/echo-stress test, alcoholic cardiomyopathy, primary hypertrophic cardiomyopathy, asymptomatic known LV systolic dysfunction, prior myocardial revascularization, significant valve heart disease, atrial fibrillation.

Among the 295 patients with RA, 78 patients (26%) were excluded because LVDD was already present at echocardiographic baseline evaluation. Thus, the remaining 217 subjects with normal LV diastolic function represented the final study population. They were re-evaluated after one year by Doppler echocardiography (Figure 1). All patients gave written informed consent and the study was approved by Ethical Committees in all participating Centers. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as revised in 2000.

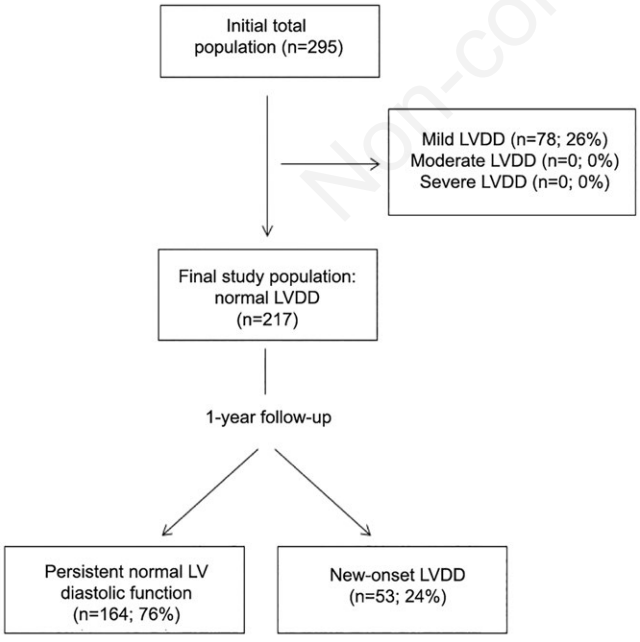

Figure 1. Study design. Flow chart of patient's selection showing the number of subjects included in the study and the classification of left ventricular diastolic dysfunction (LVDD).

Definitions

Hypertension was defined as a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg, and/or pharmacologically treated blood pressure of unknown cause. Obesity was diagnosed if patients had body mass index ≥30 kg/m^2. Dyslipidemia was defined as levels of total serum cholesterol above 190 mg/dl and/or triglycerides above 150 mg/dl, or pharmacologically treated high lipid serum levels. To assess renal function, we considered the glomerular filtration rate (GFR) estimated with the CKD-EPI equation.

Echocardiography

All Doppler-echocardiographic studies were performed using Alpha Esaote machine (Florence, Italy) equipped with a 2.5-3.5 MHz annular-array transducer by experienced cardiologists who followed a standardized protocol. Images were stored on CD or MO disks and forwarded for final interpretation at the Echocardiography Core Laboratory at Villa Bianca Hospital of Trento, Italy. Sonographers (GC, FO) were blinded to clinical data. LV chamber dimensions and wall thicknesses were measured by the American Society of Echocardiography guidelines and LV mass was calculated using a validated formula [29]. LV mass was normalized for height to the 2.7 power and LV hypertrophy was defined as LV mass ≥49.2 g/m$^{2.7}$ for men and ≥46.7 for women [30]. Relative wall thickness was calculated as the 2* end-diastolic ratio posterior wall thickness/LV diameter and indicated concentric LV geometry if ≥0.43 (the 97.5 percentile in a normal population) [31]. LV end-diastolic and end-systolic volumes were measured by the biplane method of disks from 2D apical 4 chamber + 2 chamber views and used to calculate LV ejection fraction (LVEF), defined as reduced if <50%.

Transmitral and pulmonary vein pulsed wave Doppler curves and early diastolic Tissue Doppler velocity of mitral annulus (E', expressed as mean of 4 measurements obtained in septal, lateral, inferior and anterior mitral annular position) were assessed according to the recommendations of the American Society of Echocardiography [32]. Early diastolic velocity of transmitral flow (E) was divided by E' and used to classify LV diastolic function together with other parameters including E/A ratio of transmitral flow (ratio between the peak velocity of early diastolic "E" wave and late diastolic "A" wave of transmitral flow), deceleration time of E and the difference in duration of atrial wave on pulmonary vein flow and atrial wave on transmitral flow) in 4 degrees as proposed by Redfield *et al.* [33] and according to the progression of diastolic dysfunction: degree I=normal; degree II=mild dysfunction (impaired relaxation without evidence of increased LV filling pressures; degree III=moderate dysfunction (impaired relaxation associated with mild to moderate elevation of LV filling pressures); degree IV=severe dysfunction (restrictive physiology with highly increased filling pressures). Pulmonary capillary wedge pressure (PCWP) was non-invasively estimated by the formula validated by Nagueh *et al.* [34]. Maximal left atrial volume was also computed from 2D apical 4-chamber view using the area - length method and was normalized for body surface area. Left atrial systolic force was calculated using the formula validated by Manning and coworkers [35].

Statistical analysis

Data are reported as mean values±1 standard deviation (medians and interquartile ranges for variables deviating from normality) or percentages. Unpaired Student's *t*-test and χ^2 statistics were used for descriptive statistics. Between-group comparisons of categorical and continuous variables were performed by χ^2 test and analysis of variance (ANOVA) with comparison between each group by Scheffé's test for unequal sample, as appropriate. The study population was stratified by the development of new-onset LVDD during follow-up. Variables that were significantly related to the development of this condition in univariate tests ($p<0.01$) were included in the multivariate models. Two multivariate logistic regression analyses were performed to identify the independent predictors of new-onset LVDD detected during follow-up. In the first one, only clinical variables were considered. The variables included in this analysis were: age, systolic blood pressure, history of hypertension, serum protein C reactive levels. In the second one, clinical and echocardiographic variables were taken into account. The following variables were included in this model: age, systolic blood pressure, E/A ratio of transmitral flow, concentric LV geometry, peak E', left atrial ejection force. The independent predictors of new-onset LVDD emerging by multiple logistic regression analysis were subsequently handled as categorical variables using cut-points derived by specific receiver operating characteristic (ROC) curve analyses and combined to find a multivariable model which better predicted new-onset LVDD among RA patients. The ROC curves were compared using the z statistics with the curves resulting by each single variable, without correction for multiple comparisons, to lessen the probability of type 1 error [36]. All analyses were performed using statistical package SPSS 19.0 (SPSS Inc. Chicago, IL, USA) and statistical significance was identified by two-tailed $p<0.05$.

Results

The study population consisted of 217 patients with RA (mean age of 57±13 years, 67% women) whose principal features are shown in Table 1. They had a prevalence of hypertension of 43% and dyslipidemia of 63%, a long history of RA disease (mean 14±10 years), a high number of joints involved (mean 11±9), 6% of them showed extra-articular manifestations of RA, the disease activity was high in 15% of cases. Looking at the echocardiographic variables, 63% of patients had concentric LV geometry, LVEF was normal in all patients as well as PCWP (mean value 10±2 mmHg), confirming the presence of a compensated hemodynamic state in each enrolled subject (Table 2). Echocardiographic examination at 1-year follow-up showed that 164 patients (76%) maintained a normal LV diastolic function, while the remaining 53 (24%) developed LVDD, which was of degree I (mild dysfunction) in all of them.

Baseline features of new-onset LVDD patients

Patients with new-onset LVDD were older, had higher systolic blood pressures, higher prevalence of history of arterial hypertension and higher serum protein C reactive levels than those with persistent normal LV diastolic function (Table 3). Body mass index, prevalence of female gender, renal function, lipid and glycometabolic profile were similar between the two study groups. Similarly, no difference in pharmacological treatment for the control of the cardiovascular risk factors existed between the two groups. Considering the echocardiographic variables, the patients with new-onset LVDD had a higher prevalence of LV concentric geometry, lower E/A ratio of transmitral flow, higher E/E' ratio, larger maximal left atrial volume and higher left atrial systolic

Table 1. Main clinical characteristics of the 217 study patients.

Variables	Study population
Clinical	
Age (yrs)	57±13
Female gender (%)	67
Body Mass index (kg/m^2)	25.0±4.3
Waist circumference (cm)	90±13
Obese (%)	10
Hypertension (%)	43
Systolic blood pressure (mmHg)	131±17
Diastolic blood pressure (mmHg)	81±9
Dyslipidemia (%)	63
Active smoker (%)	39
Diabetes mellitus (%)	8
Heart rate (beats/min)	70±11
Duration of rheumatoid arthritis (yrs)	14±10
Number of joints involved	11±10
Extra-articular manifestations (%)	6
High activity of disease (%)	15
Clinical disease activity index	10±8
Laboratory	
Hemoglobin (gr/dl)	13.9±1.4
GFR (ml/min/1.73m^2)	94±23
GFR < 60 ml/min/1.73m^2 (%)	5
Total cholesterol (mg/dl) (median IQR)	208 (184-239)
Cholesterol LDL (mg/dl) (median IQR)	121 (97.5-139)
Triglycerides (mg/dl) (median IQR)	101 (71-134)
C reactive protein (mg/l) (median IQR)	1.6 (0.6-3.5)
Rheumatoid factor positive (%)	42
Cyclic citrullinated peptide positive (%)	40
Pharmacological treatment	
Betablockers (%)	15
ACEi / ARB (%)	26
Diuretics (%)	13
Calcium antagonists (%)	11
Anti-platelets agents (%)	14
Statins (%)	23
NSAIDs (%)	34
Metotrexate (%)	44
Hydroxychloroquine (%)	11
Immunomodulatory and anti-cytotoxic agents (%)	69
Corticosteroids (%)	42

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin T1 receptor blockers; GFR, glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs. Values are indicated as mean ±SD.

force than the counterparts with persistent normal LV diastolic function (Table 3).

Predictors of new-onset LVDD

To identify the predictors of new-onset LVDD, two multivariate logistic regression analyses were performed (Table 4). In a first model, which encompassed only clinical variables (Table 4, model 1), older age was closely associated with new-onset LVDD together with higher systolic blood pressure and history of hypertension, while no association was found with serum protein C reactive levels. In a second model, both clinical and echocardiographic variables were considered. Lower E/A ratio of transmitral flow emerged as independent condition associated with new-onset LVDD (OR 0.17, CI 0.09-0.57), together with older age and higher systolic blood pressure (Table 4, model 2). No independent association was found between the presence of new-onset LVDD and the other variables considered in the analysis including concentric LV geometry, peak E', left atrial systolic force.

Clinical predictive model for new-onset LVDD

A clinical model for the prediction of new-onset LVDD was derived by the results of the multivariate regression analysis and included age, systolic blood pressure and E/A ratio of transmitral flow. ROC curve analyses showed that the best cut-off value for age was 57 years, 131 mmHg for systolic blood pressure and 0.96 for E/A ratio of transmitral flow. Figure 2 shows the distribution of RA patients who developed LVDD according to the number of the factors considered in the model. The rate of new-onset LVDD events ranged from 0% in patients without any factor to 75% in those in whom the three factors coexisted. Figure 3 shows the accuracy for the prediction of new-onset LVDD when the three variables were considered individually or as elements of the predictive model.

Discussion

This prospective study provides new data regarding the incidence and the predictors of new-onset LVDD in individuals with RA and no history of cardiac disease. A first result of our research is that

Table 2. Echocardiographic characteristics of 217study patients.

Variables	Study population
LV end-diastolic diameter (cm/m^2)	2.6±0.3
LV end-diastolic volume (ml/m^2)	48±10
LV Relative wall thickness	0.45±0.07
Concentric LV geometry (%)	63
LV mass index (g/m$^{2.7}$)	43±11
LV ejection fraction (%)	66±6
Transmitral flow	
Peak E wave velocity (cm/s)	72±15
Peak A wave velocity (cm/s)	70±17
A wave duration (ms)	125±22
E wave deceleration time (ms)	203±51
E wave deceleration rate	3.7±1
E / A ratio	1.08±0.35
Peak E' (cm/s)	11±3
E / E' ratio	6.6±1.8
Pulmonary venous flow	
Peak systolic velocity (cm/s)	60±13
Peak diastolic velocity (cm/s)	45±10
Systolic fraction (%)	57±5
A wave duration (ms)	103±19
Z - A (ms)	22
PCWP (mmHg)	10±2
Maximal left atrial volume (ml/m^2)	19±7
Left atrial ejection force (kdynes/cm^2)	11.1±5.9
PAPs (mmHg)	26±9

LV, left ventricular; Peak E', early diastolic Tissue Doppler velocity of mitral annulus; PCWP, pulmonary capillary wedge pressure; PAPs, pulmonary artery systolic pressure; Z - A, difference between the duration of left atrial reverse wave of pulmonary venous flow and duration of A wave of transmitral flow. Values are indicated as mean ±SD.

Table 3. Clinical and echocardiographic variables significantly different between patients with persistent normal left ventricular diastolic function and those who developed diastolic dysfunction during follow-up.

Variables	Persistent normal diastolic function (n=164 patients)	New-onset diastolic dysfunction (n=53 patients)	p
Age (yrs)	53±11	63±8	<0.001
Systolic blood pressure (mmHg)	130±15	142±17	<0.001
Hypertension (%)	33	71	<0.001
C reactive protein (mg/l) (median IQR)	1.43 (0.76-3.00)	3.15 (0.60-7.00)	<0.001
LV Relative wall thickness	0.45±0.06	0.49±0.07	=0.01
Maximal left atrial volume (ml/m^2)	17±5	20±4	=0.02
Peak A wave velocity of transmitral flow (cm/s)	65.9±13.5	79.9±17.5	<0.001
E / A ratio of transmitral flow	1.11±0.28	0.89±0.13	<0.001
E / E' ratio	6.4±1.4	7.2±2.1	=0.02
Peak E' (cm/s)	11±2	10±2	=0.01
Pulmonary capillary wedge pressure (mmHg)	9.8±1.7	10.8±2.6	=0.02
Left atrial systolic force (kdynes/cm^2)	10.4±5.6	14.7±7.4	<0.001

Values are indicated as mean ±SD.

approximately a quarter of patients with RA developed new-onset LVDD at 1-year follow-up. Several studies have previously analyzed LV diastolic function in these patients [9-23], as well as in those with other systemic inflammatory diseases [37], but no data was available on the incidence of new-onset LVDD in RA disease; thus, this has to be considered a new and original finding. Similarly, the prognosticators of this phenomenon are unknown. This issue has been investigated in detail in our study. In particular, we demonstrated that a lower E/A ratio of transmitral flow was the strongest independent condition related to new-onset LVDD together with older age and higher systolic blood pressure. Patients who developed new-onset LVDD had a mean value of E/A ratio of transmitral flow at baseline evaluation of 0.89. This value was very close to that indicated by Redfied *et al.* (E/A=0.75) [33], as well as that more recently reported by Nagueh *et al*. (E/A=0.80) in the ASE recommendations for the evaluation of LV diastolic function by echocardiography [32] as cut-off for identifying grade I LVDD. Our evidence that a lower E/A ratio of transmitral flow may predict the development of new-onset LVDD seems to indicate the presence of a chronic pathophysiological course of LV diastolic function that slowly progresses during the time and can be followed by echocardiography. Several studies have analyzed the relationship between E/A ratio and RA disease duration and activity [11,12,17-20,26,27], based on the hypothesis that an ongoing subclinical myocardial inflammatory process could impact LV myocardial function. These analyses, however, led to conflicting results. In our experience, no association was found between the development of LVDD and any baseline clinical parameter of RA disease. A second predictor of new-onset LVDD was

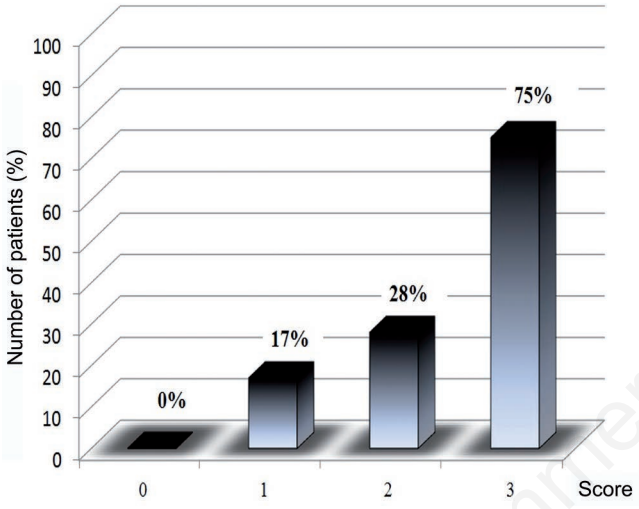

Figure 2. Distribution of rheumatoid arthritis (RA) patients who developed left ventricular diastolic dysfunction (LVDD) according to the number of the factors considered in the model. The rate of new-onset LVDD events ranged from 0% in patients without any factor to 75% in those in whom the three factors coexisted.

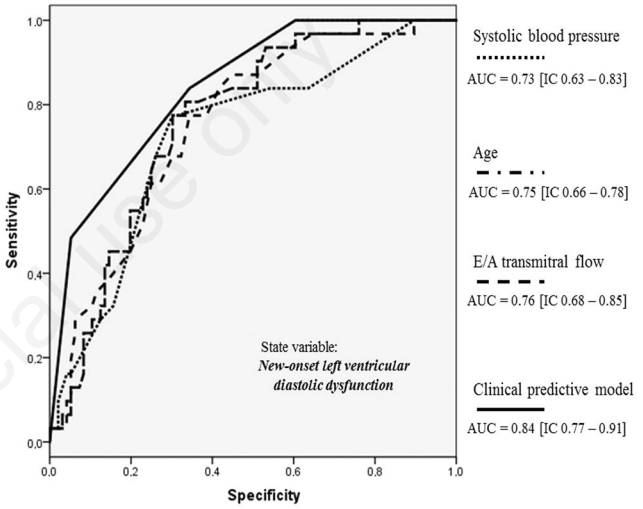

Figure 3. Accuracy for the prediction of new-onset left ventricular diastolic dysfunction (LVDD) when the three variables were considered individually or as elements of the predictive model.

Table 4. Variables independently associated with new-onset diastolic dysfunction recognized at 1-year follow up. Multivariate logistic regression analyses.

Variables	OR	95% Confidence intervals	p
Clinical model (1)			
Systolic blood pressure (mmHg)	1.03	1.00-1.07	=0.02
Age (yrs)	1.06	1.00-1.11	=0.04
Hypertension (%)	2.98	1.06-8.40	=0.04
C reactive protein (mg/l)	1.08	0.99-1.16	=0.05
Clinical + echocardiographic model (2)			
E / A ratio of transmitral flow	0.17	0.09-0.57	=0.004
Age (yrs)	1.07	1.01-1.15	=0.02
Systolic blood pressure (mmHg)	1.04	1.00-1.07	=0.03
Concentric left ventricular geometry (%)	1.81	0.50-6.49	=0.36
Peak E' (cm/s)	1.18	0.87-1.59	=0.29
Left atrial ejection force (kdynes/cm^2)	0.99	0.92-1.08	=0.95

older age. The progressive impairment of LV diastolic function with age is well known [38]. As a matter of fact, normal aging is associated with increased LV stiffness and slowing of myocardial relaxation. In our study, however, the mean age of the patients who developed new onset LVDD was 63 years and ROC curve analysis showed that the best cut-off value identifying the RA patients at higher risk for new onset LVDD was 57 years, corresponding to a middle-aged population. This finding has a clinical relevance and is in line with that reported by Montecucco *et al*. [18] and the more recent study of Davis *et al.* [27] which demonstrated that LVDD was observed at a younger age in the RA patients compared with the controls, suggesting a much earlier deterioration of diastolic function in the former. A third predictor of new-onset LVDD was higher systolic blood pressure. This was an expected finding, that accords with the well-established notion that hypertension leads to LVDD by increasing interstitial fibrosis, disturbance of calcium homeostasis and increased deposition of collagen [39]. Interestingly, in our study, the mean systolic blood pressure of patients who had new onset LVDD was 142 mmHg, a value just a little bit higher than that considered as normal, and the risk for developing this condition significantly increased over 131 mmHg (as emerged by ROC curve analysis), a value within the range of normality of blood pressure. The present data lead to speculate that, in RA patients the optimization of systolic blood pressure control could reduce the risk of developing LVDD. Such hypothesis represents an intriguing challenge that should be tested by randomized trials specifically designed for this purpose. A final consideration regards the clinical predictive model for new-onset LVDD which emerged by the ROC curve analyses. We built this model with the attempt to identify patients at high risk for developing LVDD during time. The accuracy of the model for this purpose is moderate (sensitivity 68%; specificity 65%). However, the present model has almighty negative prediction value. In fact, none of the patients without predictors of new-onset LVDD developed this condition during FU.

Study limitations and strengths

The main limitation of the present investigation is that LVDD was assessed by echocardiography, while no invasive hemodynamic data were available. However, Grant *et al.* [40] recently demonstrated that echocardiographic grading of LV diastolic function is significantly related to invasive hemodynamics, even if their relationship is modest. Furthermore, our findings do not take into consideration the possible effects of some pharmacological or non-pharmacological treatment for RA disease or hypertension on LV diastolic function. These conditions do not allow to precisely assess the pure impact of RA in the development of new-onset LVDD. Finally, no prognostic information was provided.

Strengths of our study consist of its prospective design, a large number of participants of both genders who were consecutively enrolled, the comprehensive nature of the dataset and the systematic approach to the study of left ventricular diastolic function, not only based on the Doppler indexes, but integrating Doppler patterns with other echo-parameters [41].

Clinical implications and conclusions

LVDD is a complex phenomenon that depends on a variety of factors and has been recognized as a primary cause of CHF. In this study we demonstrated that a significant portion of patients with RA without overt cardiac disease and normal LV diastolic function, develops new-onset LVDD at 1-year follow-up. This condition can be predicted by a simple clinical model, which could improve the clinical management and the prognostic stratification of patients with RA.

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