



Subclinical ventricular dysfunction in rheumatoid arthritis

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Abstract

Patients with rheumatoid arthritis (RA) are at higher risk for having underdiagnosed heart failure, however there are no recommendations regarding echocardiographic screening. We aimed to determine the prevalence of subclinical ventricular dysfunction in RA applying current echocardiographic guidelines, its association with patients' characteristics, biomarkers and prognostic parameters and compare the 2016 guidelines to the recommendations from 2009. Prospective study of RA patients without known heart disease, categorized as preserved ventricular function (PVF), systolic dysfunction (SD), isolated diastolic dysfunction (DD) or indeterminate diastolic function (IDF) as per the 2016 echocardiography guidelines—or any ventricular dysfunction (AVD) comprehending the last 3. The median age was 58 years and 78% were females. The majority had PVF (73%), followed by DD (13%), IDF (11%) and SD (4%). Concordance with the 2009 echocardiographic guidelines was low. Compared with PVF, AVD patients were older (65 vs 55 years, $p < 0.001$), had a higher prevalence of hypertension and dyslipidaemia (56% vs 38%, $p = 0.003$ and 60% vs 41%, $p = 0.002$, respectively). In multivariable analysis, age (particularly > 57 years) was the only independent predictor of AVD or DD. AVD was significantly associated with higher NT-proBNP and lower distance in 6-min walk test. There were no significant independent associations between characteristics of RA disease and ventricular function. A total of 17% of RA patients without known cardiovascular disease presented subclinical systolic or diastolic dysfunction, which was associated with older age. The echocardiographic screening may have clinical value in identifying subclinical ventricular dysfunction, especially in older RA patients.

Keywords Rheumatoid arthritis · Echocardiogram · Systolic dysfunction · Diastolic dysfunction · Biomarkers

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, involving autoimmune mechanisms, characterized by a symmetric peripheral polyarthritis; however, extra-articular involvement can occur. RA has been associated with heart

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disease, the pericardium being frequently affected, while coronary artery disease (CAD) and heart failure (HF) (both ischemic and non-ischemic) are also more common than in the general population [1, 2].

Aiming to better predict the cardiovascular (CV) risk in RA patients, the European League Against Rheumatism (EULAR) suggested applying a 1.5 multiplication factor to algorithms conceived for the general population [3] since patients with RA seem to have a two-fold higher incidence of HF and an increased mortality risk [4, 5]. Although HF with reduced ejection fraction is not particularly frequent, diastolic impairment and left ventricular hypertrophy seem to be more common in RA [6, 7]. Underlying HF aetiologies include atherosclerotic CAD, dilated cardiomyopathy, myocarditis and vasculitis. The role of anti-inflammatory therapies or disease-modifying anti-rheumatic drugs (DMARDs) in heart disease remains unclear [8].

Patients with RA present some specificities and the discrimination of their symptoms is often difficult because symptoms may be non-specific or conditioned by articular limitations [9]. HF may be underdiagnosed in RA patients and there are no available recommendations for HF screening specific for patients with RA. Subclinical ventricular dysfunction can be quickly identified by echocardiography, while surrogate biomarkers can be easily studied. Other studies have already suggested the prognostic utility of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and rheumatoid factor (RF), but the value of anti-cyclic citrullinated peptide (anti-CCP) antibodies, erythrocyte sedimentation rate and troponin is still more uncertain [10, 11].

An earlier diagnosis could improve treatment decisions and consequently prognosis. The non-invasive diagnosis of diastolic dysfunction—which can be linked to HF with preserved ejection fraction [12]—is particularly challenging. A change in echocardiographic guidelines in 2016 reformulated the previous algorithm, with the expectation of a better performance in clinical practice [13, 14]. Prior studies have not focused on subclinical disease following the 2016 guidelines, with a rigorous state-of-the-art homogeneous echocardiographic analysis (most used the 2009 guidelines, or only one or two parameters and did not the complete echocardiographic algorithm).

In the present study, we assess a relatively large sample of RA patients, adjust for covariates that were systematically investigated, and complement our analysis with biomarker evaluation. Our main objectives were: (1) to assess the prevalence and characterize the type of cardiac dysfunction in RA patients without known heart disease; (2) compare the characteristics of patients with RA according to their ventricular function classification, aiming to identify the predictors of ventricular dysfunction (and the patients that would benefit the most from the screening); and (3) validate

the value of the identification of subclinical ventricular dysfunction by analysing associations with surrogate prognostic markers. The secondary objectives were to determine the prevalence of a possible precursor stage of HF with preserved ejection fraction (HFpEF), using a combination of echocardiographic findings and biomarkers, and compare diastolic dysfunction definitions using the actual 2016 echocardiographic guidelines [14] and the previous guidelines from 2009 [13].

Methods

Study design and ethics

This is a prospective study that enrolled patients followed in the outpatient clinic of Autoimmune Disorders at Centro Hospitalar Universitário do Porto, previously diagnosed with RA, between June 2016 and June 2018. Follow-up was updated in August 2019. The protocol for this study was a priori registered at ClinicalTrials.gov under the number NCT03960515.

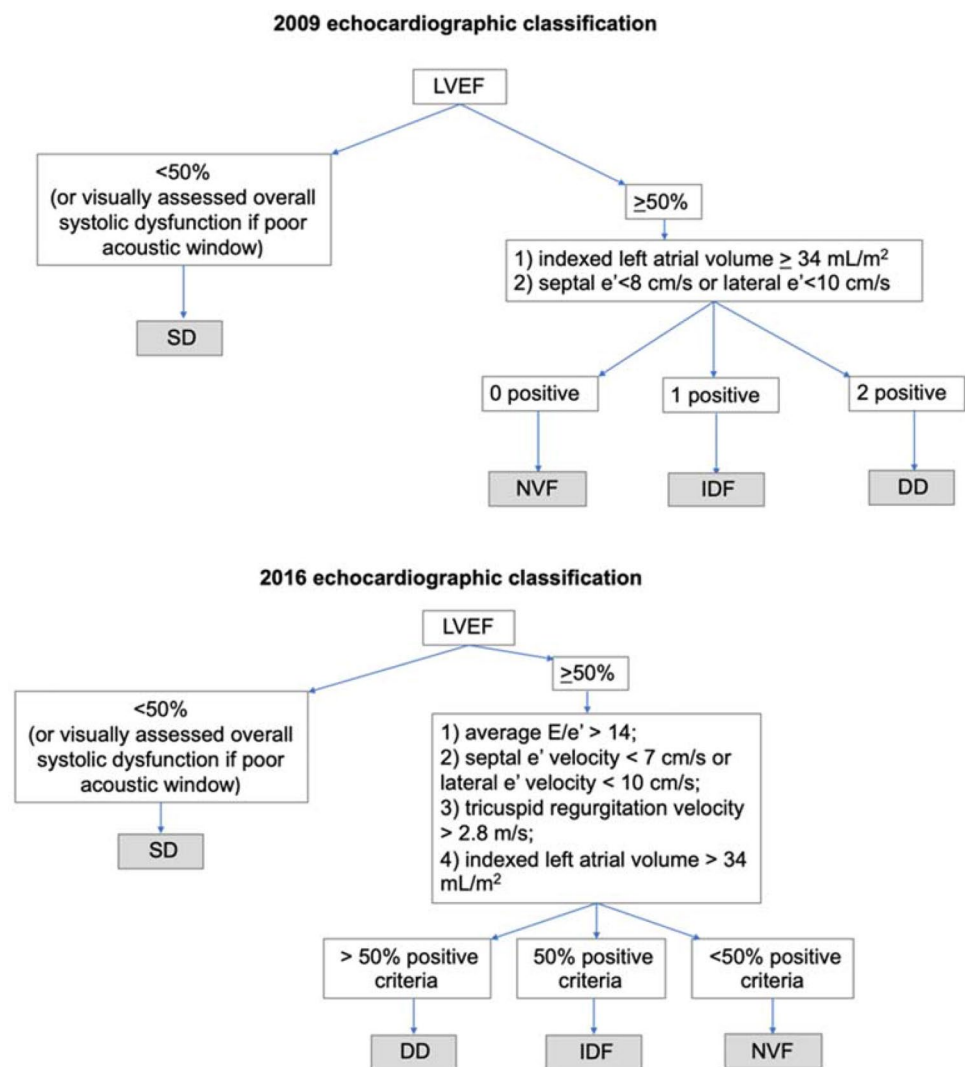
This study was approved by the Hospital's Ethics Committee and was conducted in accordance to the principles of the 1975 Declaration of Helsinki. All participants provided written informed consent before enrollment in the study.

Patient selection

The diagnosis of RA was made according to 2010 ACR/EULAR Classification Criteria [15]. Patients with an active neoplasm or severe comorbidity, an expected survival of less than 6 months, dementia, inability to walk or totally dependent in their daily life activities were excluded. For the present analysis, patients with previously known heart disease (HF, CAD, previous percutaneous or surgical coronary revascularization, previous cardiac surgery, at least moderate valve disease, or atrial fibrillation at the time of the echocardiogram) or those that did not perform an echocardiogram were also excluded.

Patients were divided into four categories of ventricular function, according to transthoracic echocardiogram (TTE) results: preserved ventricular function (PVF); systolic (\pm diastolic) dysfunction (SD); (isolated) diastolic dysfunction (DD); indeterminate diastolic function (IDF). The definition of groups was made according the 2016 European Heart Failure guidelines [12], 2016 guidelines for diastolic evaluation [14] and the 2009 recommendations of the American Society of Echocardiography [13], as depicted in Fig. 1. If half (or more) of the variables needed for each classification were missing, the diastolic classification was registered as missing. In the main analyses, the diastolic function categorization followed the 2016

Fig. 1 Simplified 2009 and 2016 echocardiographic guidelines for ventricular function classification. *DD* diastolic dysfunction, *IDF* indeterminate diastolic function, *NVF* normal ventricular function, *SD* systolic dysfunction. Using 2016 guidelines, if a patient had only 3 parameters available and 2 or 3 were abnormal, he/she was categorized as having DD, if 2 were normal, as having normal diastolic function. If only 2 or less variables were available, diastolic classification was recorded as missing. Using 2009 guidelines, it was mandatory that a patient had at least one e' value and indexed LA volume; if one of those variables was missing, diastolic classification was recorded as missing



guidelines. We grouped patients with IDF, DD or SD, as per the 2016 guidelines, into one category of “any ventricular dysfunction” (AVD), that was compared to PVF.

Using the 2016 HF European guidelines [12], we also analysed a category of potential subclinical heart failure with preserved ejection fraction (“HFpEF risk”), with the following characteristics: LVEF $\geq 50\%$ and NT-proBNP > 125 pg/mL and structural echocardiographic changes (left ventricular hypertrophy or indexed LA volume or diastolic dysfunction as per 2016 echocardiographic guidelines). We use the term “risk” because the presence of signs or symptoms of HF was not necessary.

Our sample of RA patients was compared with a cohort of the general population (from the EPIPorto study [16], $n = 1000$) that has similar demographic characteristics and risk factors (except for the presence of RA), which was also evaluated using the 2016 European/American guidelines.

Data collection and variables

Clinical data

Biometric and clinical data was collected and included age, gender, body mass index (BMI), comorbidities, year of diagnosis of RA, Disease Activity Score 28 (DAS28) assessment—that measures disease activity by counting the number of tender or swollen joints [17], combined with the value of erythrocyte sedimentation rate (ESR)—and medication (all the medication used for RA and cardiovascular medication).

Transthoracic echocardiogram (TTE)

Echocardiographic evaluation was analysed by one cardiologist, that was blinded to the clinical information or the results of any other exams, using Philips® iE33 ultrasound

machine. To certify the external validity of the echocardiographic measurements, a random sample of 25 anonymized exams was evaluated at the Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu at Nancy, France, showing good correlation of the measurements (intra-class correlation coefficient > 0.75 for variables that are used in diastolic evaluation).

The evaluated parameters included the dimensions of the cardiac chambers (left atrial and end-diastolic ventricular volumes calculated using Simpson's rule and indexed to body surface area), left ventricular wall thickness and mass, left ventricular ejection fraction (using modified Simpson's biplane method), valvular disease, pericardial disease and diastolic function as per the 2016 American and European guidelines [14]. The Chamber Quantification European guidelines [18] were followed for all cardiac chambers analyses.

We assessed the relationship between echocardiographic categories and surrogate prognostic markers (biomarkers, physical exercise capacity and cardiovascular events) because the echocardiographic identification of ventricular dysfunction is more relevant if it is associated with prognosis.

Biomarkers

We analysed several biomarkers in the hospital lab that included the NT-proBNP, high-sensitivity troponin T (hsTnT), CRP and erythrocyte sedimentation rate (ESR). We also checked if patients tested positive for anti-CCP antibodies or rheumatoid factor (RF) and their estimated glomerular filtration rate (eGFR).

Physical exercise capacity

Patients performed a 6-min walk test (6MWT) as recommended by the American Thoracic Society [19].

Statistical analyses

Statistical analyses were conducted using the STATA version 13 and SPSS® version 23 software. A two-sided p -value of < 0.05 was used as statistical significance for all statistical tests. Continuous data were described as mean \pm standard deviation for gaussian distribution or median (IQR—interquartile range between the 25th and 75th quartiles) for non-gaussian distributions. The Shapiro–Wilk test was used to test the normality of distribution. Categorical data were presented as absolute frequencies (n) and percentages (%). We analysed the relationship between two categories of ventricular function and patients' characteristics using independent-samples t test or Mann–Whitney U test for continuous variables, and Chi-squared or Fisher exact test

for categorical variables, as appropriate. The four groups of LV function were compared using ANOVA, Kruskal–Wallis tests or multinomial logistic regression.

Linear regression was used to analyse the associations between continuous variables. Multivariable logistic regression, using categories of ventricular function as dependent variable (taking PVF as reference) was performed to estimate independent predictors of ventricular function (covariates with a significant association in the univariable analysis were used in the model), obtaining odds ratio (OR) and the respective 95% confidence intervals (CI). Hosmer–Lemeshow test was used to determine goodness of fit of model and area under the Receiver Operating Characteristic curve (AUC ROC) to determine its discriminative power. Logistic regression was also used to compare the prevalence of diastolic dysfunction in our sample with a cohort from the general population (EPIPorto study [16]).

We computed the Cohen's Kappa coefficient (κ) to test the concordance between 2009 and 2016 classifications of diastolic function.

Results

Baseline characteristics

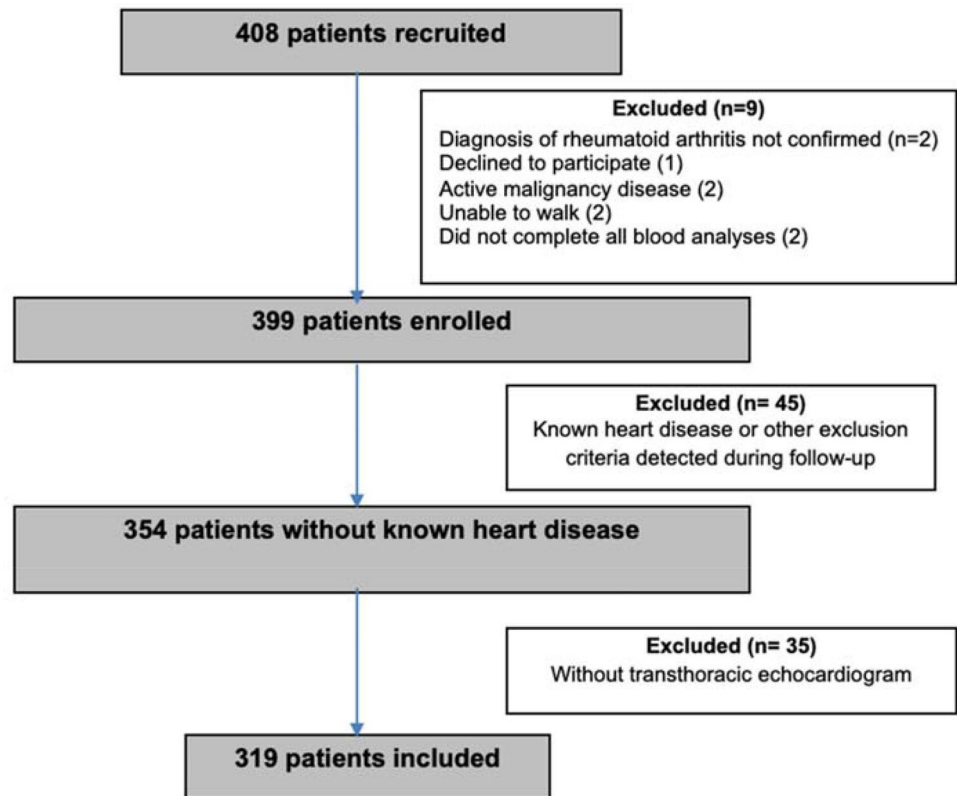
We included a total of 319 RA patients without known heart disease (Fig. 2). The median age was 58 years (IQR 19) and 78% ($n = 249$) were females. Patients' characteristics are presented in Table 1.

Patients with any ventricular dysfunction (AVD)

Eighty-seven patients (27%) had AVD (Table 1). These patients were older, presented more frequently hypertension, dyslipidaemia, used corticosteroids more often, reported a lower dosage of cardiovascular medications (ACEi or ARB and statin), had increased NT-proBNP and lower eGFR concentrations, and showed poorer physical performance in the 6MWT test. In the multivariable analysis (model adjusted for age, hypertension, dyslipidaemia, corticosteroids and eGFR), age was the only independent predictor of AVD (OR 1.079; 95% CI, 1.045 to 1.114). The AUC ROC was 0.71 (95% CI, 0.65 to 0.77) with the best cut-off point (best sum of sensitivity and specificity) of 57 years old (sensitivity of 78% and specificity of 58%).

Comparison between categories of ventricular function (using 2016 echocardiographic guidelines)

Systolic dysfunction was found in 4% ($n = 13$), being mild (LVEF between 40 and 50%) in 11 patients and moderate (LVEF between 40 and 30%) in 2 patients.

Fig. 2 Study flowchart, summarizing participants' selection

Patients with $LVEF \geq 50\%$, were classified according to the 2016 guidelines. An example of a patient with diastolic dysfunction is presented in Fig. 3.

Isolated DD was documented in 40 patients (13%) and 34 patients (11%) had IDF. Tricuspid regurgitation (TR) velocity could be adequately determined in only 151 patients (47%).

Age, hypertension and dyslipidaemia were expressed significantly different amongst categories of ventricular function (Table 2). The RA variables, which included the RA duration, anti-CCP/RF positivity, DAS28-ESR, ESR and RA medication were not associated with TTE results, however corticosteroids were more frequently used in patients with DD and CRP was higher in SD, as compared to reference category (preserved ventricular function). In the multivariable analysis (adjusted for age, hypertension, dyslipidaemia, corticosteroids and CRP), age was the only independent factor associated with categories of ventricular function, with an OR for DD (PVF as reference) of 1.097 (95% CI 1.055 to 1.141; $p < 0.001$).

Comparing DD category to PVF, there were significant differences in age (66.5 (IQR 12) vs 54.5 (IQR 19); OR 5.826; 95% CI 3.704 to 7.048; $p < 0.001$), dyslipidaemia (65% vs 41%; OR 1.645; 95% CI 1.158 to 2.336; $p = 0.005$), corticosteroid use (58% vs 39%; OR 1.457; 95% CI 1.036 to 2.048; $p = 0.031$), eGFR (86.5 (IQR 22.2) vs 95.0 (IQR 28.0); OR 2.214; 95% CI 0.639 to 12.566; $p = 0.041$) and

family history of ischaemic heart disease (2.5% vs 17.3%; OR 0.351; 95% CI 0.128 to 0.960; $p = 0.041$). In multivariable analysis, age, eGFR and family history were independently related with DD.

The prevalence of DD was significantly higher in patients with RA as compared to the general population from the EPIPorto cohort (13% vs 1.4%; $p < 0.001$).

“HFpEF risk”: combined strategy of echocardiographic evaluation and NT-proBNP

Excluding those with systolic dysfunction or without NT-proBNP analysis ($n = 298$ of 319), we identified 40 patients (13%) at “HFpEF risk” ($LVEF \geq 50\%$ and $NT\text{-}proBNP > 125$ pg/mL and structural echocardiographic changes [12]). After analysis of all covariates in Table 1, age (OR 1.078; $p < 0.001$), CKD (OR 0.178; $p = 0.013$), eGFR (OR 0.977; $p = 0.005$) and RA duration (OR 1.031; $p = 0.037$) were associated with “HFpEF risk”. On multivariable analysis, age was the only independent predictor of “HFpEF risk”.

The “HFpEF risk” was significantly associated with ventricular function categories, with 82% of those without “HFpEF risk” showing preserved ventricular function (vs 35% with risk). However, patients with “HFpEF risk” were equally distributed among preserved ventricular function

Table 1 Patients' characteristics according to the presence of any signs of ventricular dysfunction

	Total (n = 319)	Preserved ventricular function (n = 232)	Any ventricular dysfunction (n = 87)	p value
Age (years)	58 (19)	55 (19)	65 (12)	< 0.001
Sex (male), n(%)	70 (22%)	51 (22%)	19 (27%)	0.978
Diabetes mellitus, n(%)	37 (12%)	28 (12%)	9 (24%)	0.669
Hypertension, n(%)	136 (43%)	87 (38%)	49 (56%)	0.003
Systolic blood pressure (mmHg)	130 (23)	128 (24)	135 (22)	< 0.001
Diastolic blood pressure (mmHg)	76 ± 10	75 ± 11	78 ± 8	0.050
Heart rate (bpm)	78 (18)	78 (19)	75 (77)	0.477
Smoking ^a , n(%)	111 (35%)	83 (36%)	28 (32%)	0.549
Dyslipidaemia, n(%)	146 (46%)	94 (41%)	52 (60%)	0.002
BMI (kg/m ²)	26 (6)	26 (6)	27 (6)	0.272
Obesity (BMI ≥ 30), n(%)	63 (20%)	47 (20%)	16 (18%)	0.709
Chronic kidney failure, n(%)	10 (3)	6 (3%)	4 (5%)	0.365
COPD, n (%)	16 (5%)	14 (6%)	2 (2%)	0.190
Family history of ischemic CVD, n(%)	48 (15%)	39 (17%)	9 (10%)	0.154
Cardiovascular medication, n (%)				
ACEi or ARB	111 (35%)	69 (30%)	42 (48%)	0.002
Beta blocker	19 (6%)	11 (5%)	8 (9%)	0.141
Thiazide	49 (15%)	30 (13%)	19 (22%)	0.052
Loop diuretic	5 (2%)	5 (2%)	0	–
MRA	1 (0.3%)	0	0	–
CCB	30 (9%)	19 (8%)	11 (13%)	0.228
Statin	114 (36%)	71 (31%)	43 (49%)	0.002
RA duration (years)	8 (13)	7 (13)	9 (12)	0.325
DAS28-ESR	2.6 (1.5)	2.5 (1.6)	2.8 (1.3)	0.482
RA medication ^b , n(%)				
NSAIDS	85 (27%)	58 (25%)	27 (31%)	0.279
Corticosteroids	136 (43%)	91 (39%)	45 (52%)	0.045
Methotrexate	197 (62%)	146 (63%)	51 (59%)	0.554
Biologics	61 (19%)	50 (22%)	11 (13%)	0.075
Other drugs	129 (40%)	93 (41%)	34 (39%)	0.762
Biomarkers				
NT-proBNP, pg/mL	75 (94)	68 (84)	103 (141)	0.008
hs-troponin T, ng/mL	0.004 (0.005)	0.003 (0.004)	0.005 (0.004)	0.236
ESR, mm	20 (25)	20 (22)	21 (28)	0.260
CRP, mg/dL	3.0 (6.4)	3.0 (6.4)	3.3 (6.9)	0.361
eGFR, mL/min/1.73m ²	93 (27)	95 (28)	90 (26)	0.010
Anti-CCP or RF, n(%)	249 (78%)	185 (80%)	64 (74%)	0.236
Distance in 6MWT, m	390 (105)	390 (90)	360 (86)	0.001

Significant associations (p values < 0.05) are in bold

Ventricular function was classified as per 2016 guidelines. Patients in any category of ventricular dysfunction (systolic, diastolic or indeterminate) were categorized as “any ventricular dysfunction” and all the others as “preserved ventricular function”. Continuous variables are represented as mean ± standard deviation or as median (75–25 interquartile range), according to their gaussian or non-gaussian distribution, respectively. Values of blood pressure and heart rate were obtained when patients were enrolled

ACEi angiotensin-converting enzyme inhibitor, *Anti-CCP+* positive for anti-cyclic citrullinated peptide antibodies, *ARB* angiotensin receptor blocker, *BMI* body mass index, *CCB* calcium channel blocker, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *DAS28* Disease Activity Score 28, *eGFR* estimated glomerular filtration rate, *ESR* erythrocyte sedimentation rate, *MRA* mineralocorticoid receptor antagonist, *RA* rheumatoid arthritis, *RF+* positive for rheumatoid factor, *6MWT* 6-min walk test (distance in meters), *CVD* cardiovascular disease

^aCurrent or previous smoking habits were considered

^bMore than one medication per patient was allowed

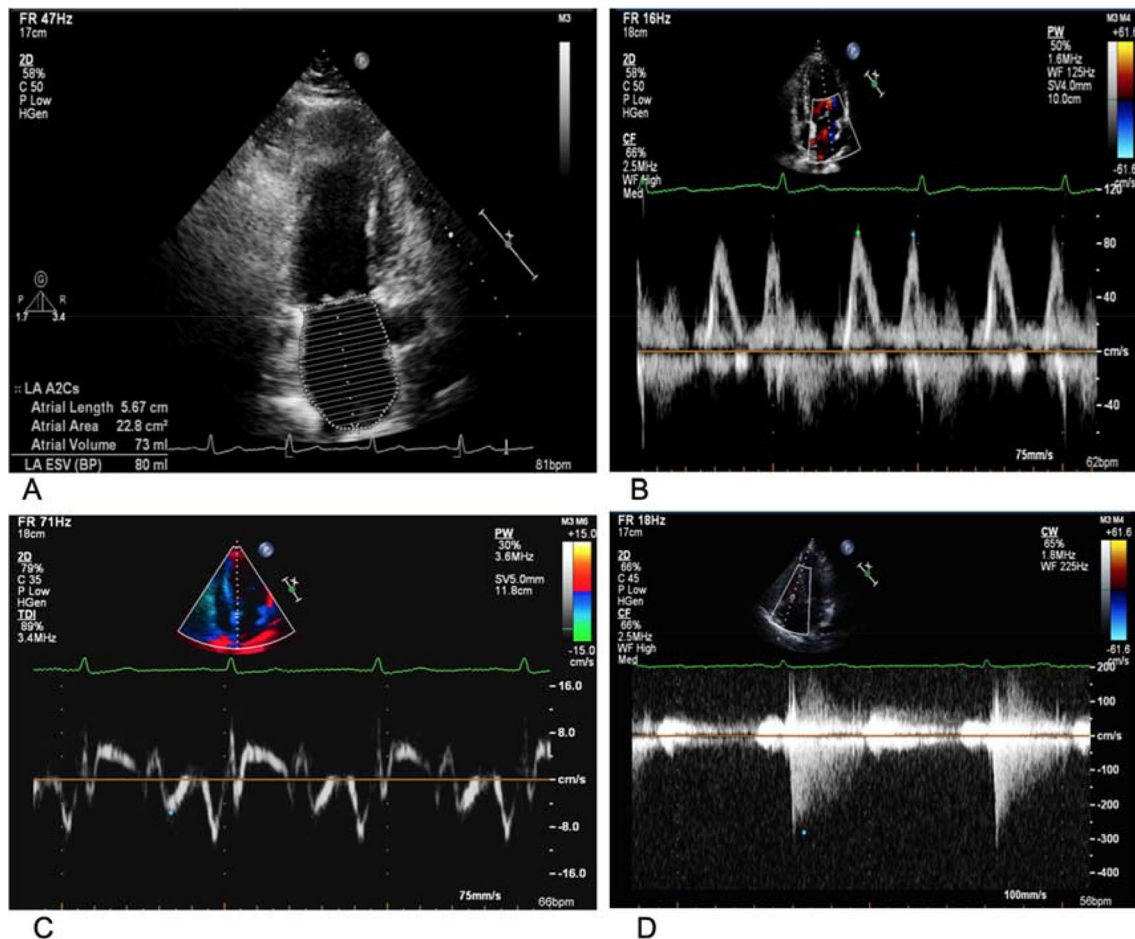


Fig. 3 Example of a patient with diastolic dysfunction, as per the 2016 echocardiographic classification. **a** Apical 2-chamber view used for estimation of left atrial volume (which is complemented by an identical measurement in 4-chamber view). **b** Mitral inflow pattern in 4-chamber view, with measurement of E and A wave maximal velocities (marked in green E wave velocity=88 cm/s; marked in blue A wave velocity=87 cm/s; E/A ratio=1). **c** Tissue Doppler recording, used to measure septal mitral annular e' velocity (marked

in blue). **d** Estimation of maximal tricuspid regurgitation systolic jet velocity using CW Doppler (suboptimal envelope in this case). This patient had preserved ejection fraction and all the parameters for having diastolic dysfunction: a left atrial volume of 44 mL/m², septal e' of 5.5 cm/s, lateral e' of 6.3 cm/s; septal E/e' of 16, lateral E/e' of 14 (and average E/e' of 15) and tricuspid regurgitation velocity of approximately 2.83 m/s

(14/40), indeterminate diastolic function (13/40) and diastolic dysfunction (13/40).

Comparison with 2009 guidelines for diastolic dysfunction classification

A total of 311 patients (97%) had enough data to compare the 2009 and 2016 classifications. When we applied a simplified model of the 2009 recommendations [13] to classify diastolic dysfunction, more patients would fulfil criteria for DD (23% versus 13% using the 2016

criteria)—Fig. 4 and Supplementary Table 1. The percentage of IDF would also be much higher (47% vs 11%). The concordance between both classifications was low (Cohen's Kappa = 0.25).

The specific echocardiographic parameters that can represent structural or functional changes related to HF were on average within normal limits (Supplementary Table 2). Most of these echocardiographic parameters were associated with several cofactors, namely age, hypertension and diabetes, and correlated with NT-proBNP and 6MWT.

Table 2 Patients' characteristics according to categories of ventricular function

	Total (n = 319)	Preserved ven- tricular function (n = 232)	Indeterminate dias- tolic function (n = 34)	Isolated diastolic dysfunction (n = 40)	Systolic (\pm dias- tolic) dysfunction (n = 13)	p value
Age (years)	58 (19)	55 (19)	63 (12) p < 0.001	67 (12) p < 0.001	59 (16) p = 0.263	< 0.001
Sex (male), n(%)	70 (22%)	51 (22%)	5 (15%) p = 0.328	8 (20%) p = 0.764	6 (46%) p = 0.056	0.140
Diabetes mellitus, n (%)	37 (12%)	28 (12%)	3 (9%) p = 0.597	4 (10%) p = 0.724	2 (15%) p = 0.713	0.900
Hypertension, n (%)	136 (43%)	87 (38%)	23 (68%) p = 0.001	20 (50%) p = 0.115	6 (46%) p = 0.496	0.005
Systolic blood pressure (mmHg)	130 (23)	128 (24)	136 (21) p = 0.010	134 (23) p = 0.003	136 (23) p = 0.219	0.004
Diastolic blood pressure (mmHg)	76 \pm 10	75 \pm 11	76 \pm 7 p = 0.595	78 \pm 8 p = 0.096	81 \pm 11 p = 0.045	0.067
Heart rate (bpm)	78 (18)	78 (19)	75 (11) p = 0.394	76 (17) p = 0.270	79 (30) p = 0.156	0.340
Smoking ^a , n (%)	111 (35%)	83 (36%)	12 (35%) p = 0.991	9 (22%) p = 0.115	7 (54%) p = 0.188	0.190
Dyslipidaemia, n (%)	146 (46%)	94 (41%)	19 (56%) p = 0.099	26 (65%) p = 0.005	7 (54%) p = 0.354	0.018
BMI (kg/m ²)	26 (6)	26 (6)	26 (5) p = 0.622	28 (6) p = 0.120	26 (5) p = 0.874	0.289
Obesity (BMI \geq 30), n(%)	63 (20%)	47 (20%)	4 (12%) p = 0.310	10 (25%) p = 0.385	2 (15%) p = 0.745	0.530
Chronic kidney failure, n(%)	10 (3)	6 (3%)	1 (3%) p = 0.923	2 (5%) p = 0.431	1 (8%) p = 0.319	0.680
COPD, n(%)	16 (5%)	14 (6%)	0	2 (5%) p = 0.770	0	0.380
Family history of ischemic cardio-vascular disease, n(%)	48 (15%)	39 (17%)	6 (18%) p = 0.955	1 (3%) p = 0.041	2 (15%) p = 0.862	0.120
Cardiovascular medication, n (%)						
ACEi or ARB	111 (35%)	69 (30%)	21 (62%) p < 0.001	16 (40%) p = 0.195	5 (39%) p = 0.503	0.003
Beta blocker	19 (6%)	11 (5%)	4 (12%) p = 0.120	4 (10%) p = 0.204	0	0.220
Thiazide	49 (15%)	30 (13%)	11 (32%) p = 0.003	6 (15%) p = 0.590	2 (15%) p = 0.713	0.020
Loop diuretic	5 (2%)	5 (2%)	0	0	0	0.580
MRA	1 (0.3%)	0	0	0	0	–
CCB	30 (9%)	19 (8%)	5 (15%) p = 0.204	6 (15%) p = 0.159	0	0.210
Statin	114 (36%)	71 (31%)	15 (44%) p = 0.118	21 (52%) p = 0.008	7 (54%) p = 0.089	0.015
RA duration, years	8 (13)	7 (13)	9 (14) p = 0.210	11 (12) p = 0.591	6 (17) p = 0.936	0.361
DAS28-ESR	2.6 (1.5)	2.5 (1.6)	2.6 (1.1) p = 0.829	3.0 (1.2) p = 0.482	2.9 (1.4) p = 0.805	0.590
RA medication ^b , n(%)						
NSAIDS	85 (27%)	58 (25%)	11 (32%) p = 0.319	10 (25%) p = 0.928	6 (46%) p = 0.090	0.290
Corticosteroids	136 (43%)	91 (39%)	14 (41%) p = 0.803	23 (58%) p = 0.031	8 (62%) p = 0.117	0.078
Methotrexate	197 (62%)	146 (63%)	17 (50%) p = 0.141	28 (70%) p = 0.414	6 (50%) p = 0.359	0.260

Table 2 (continued)

	Total (n = 319)	Preserved ven- tricular function (n = 232)	Indeterminate dias- tolic function (n = 34)	Isolated diastolic dysfunction (n = 40)	Systolic (± dias- tolic) dysfunction (n = 13)	p value
Biologics	61 (19%)	50 (22%)	5 (15%) p=0.411	5 (12%) p=0.228	1 (8%) p=0.276	0.380
Other drugs	129 (40%)	93 (41%)	16 (47%) p=0.516	13 (32%) p=0.305	5 (38%) p=0.848	0.630
Biomarkers						
NT-proBNP (pg/mL)	75 (94)	68 (84)	120 (139) p = 0.011	90 (140) p=0.280	107 (550) p = 0.007	0.002
hs-troponin T (ng/mL)	0.004 (0.005)	0.003 (0.004)	0.005 (0.004) p=0.702	0.005 (0.006) p=0.355	0.006 (0.002) p=0.183	< 0.001
ESR, mm	20 (25)	20 (22)	21 (21) p=0.777	27 (28) p=0.100	16 (41) p=0.355	0.377
CRP (mg/dL)	3.0 (6.4)	3.0 (6.4)	3.2 (4.2) p=0.550	2.8 (6.8) p=0.505	11.0 (34.1) p = 0.029	0.098
eGFR (mL/min/1.73m ²)	93 (27)	95 (28)	90 (30) p=0.059	87 (22) p=0.051	95 (76) p=0.304	0.078
Anti-CCP or RF, n(%)	249 (78%)	185 (80%)	26 (77%) p=0.671	28 (70%) p=0.177	10 (77%) p=0.813	0.590
Distance in 6MWT (m)	390 (105)	390 (90)	360 (75) p = 0.006	360 (90) p = 0.007	360 (98) p=0.153	< 0.001

Significant associations (p values < 0.05) are in bold

Ventricular function was classified as per 2016 guidelines. Continuous variables are represented as mean ± standard deviation or as median (75–25 interquartile range), according to their gaussian or non-gaussian distribution, respectively. The p value in the right-hand side column represents the comparison between the four categories of ventricular function; the p value presented under each category refers to the comparison with the reference category (preserved ventricular function). Values of blood pressure and heart rate were obtained when patients were enrolled

ACEi angiotensin-converting enzyme inhibitor, *Anti-CCP+* positive for anti-cyclic citrullinated peptide antibodies, *ARB* angiotensin receptor blocker, *BMI* body mass index, *CCB* calcium channel blocker, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *DAS28* Disease Activity Score 28, *eGFR* estimated glomerular filtration rate, *ESR* erythrocyte sedimentation rate, *MRA* mineralocorticoid receptor antagonist, *RA* rheumatoid arthritis, *RF+* positive for rheumatoid factor, *6MWT* 6-min walk test (distance in meters)

^aCurrent or previous smoking habits were considered

^bMore than one medication per patient was allowed

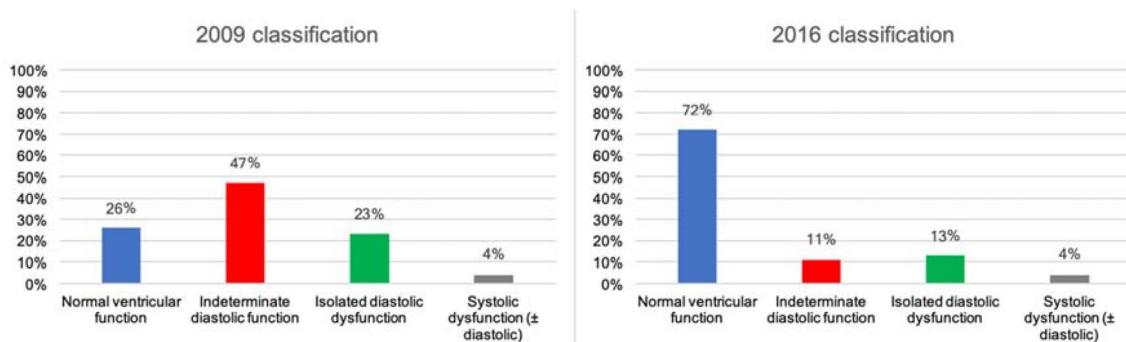


Fig. 4 Patients' distribution according to echocardiographic ventricular function categories, according to 2016 and 2009 criteria of diastolic function

Cardiovascular surrogate markers

NT-proBNP

The NT-proBNP levels were associated with “any ventricular dysfunction” and with the categorization of ventricular function using either 2009 or 2016 guidelines (but were not significantly different between DD and PVF). NT-proBNP levels were also significantly associated with most echocardiographic parameters (shown in Supplementary Table 3). Overall, 87 of the 311 patients (28%) presented an NT-proBNP \geq 125 pg/mL (cut-off generally set for chronic HF), corresponding to 34% of DD and 46% of SD patients.

hsTnT

The hsTnT levels were associated with categories of ventricular function (using 2009 or 2016 classification), but were not significantly associated with having “any ventricular dysfunction” or “HFpEF risk”. The log(hsTnT) was associated with having DD versus PVF. Overall, 25 of 311 patients (8%) had a hsTnT above normal (> 0.014 pg/mL), but only 2 patients had a value above the cut-off value considered at our laboratory for acute coronary syndrome (> 0.054 pg/mL).

6MWT

All the major echocardiographic parameters were significantly associated with 6MWT performance. The total distance walked in 6MWT was also significantly associated with ventricular function as per the 2016 or 2009 classifications (and specifically with DD versus PVF), with “any ventricular dysfunction” and “HFpEF risk”.

Cardiovascular events

During a mean follow-up time of 2.8 ± 0.6 years (54 to 1095 days), only 9 cardiovascular events (cardiovascular death, heart failure or other cardiovascular driven hospitalization) were recorded, without association with ventricular function or with “HFpEF risk”.

Discussion

The main finding of our study is that RA patients without known cardiac disease showed a 4% prevalence of subclinical systolic function and 13% of diastolic dysfunction. An increasing age was the most important independent predictor of ventricular function.

Most previous studies used the 2009 guidelines [13], but their application is complex and different authors applied distinct algorithms; in most cases the presence of one DD

parameter was sufficient [20–22]. Our findings also support the belief that the 2009 guidelines have a poor agreement with newer 2016 classification [16, 23–25]. Using the 2009 guidelines instead of the 2016 recommendations, the proportion of DD would have risen from 13 to 23%, while IDF would be found in 47% of patients instead of 11%. Invasive studies suggested that the 2016 guidelines are more specific [26] and that both guidelines cannot be used interchangeably. Even when using the same 2016 guidelines, the application of those recommendations and the number of parameters taken into consideration differs amongst studies, which can result in a significant discrepancy of the reported prevalence of DD [27]. Using the latest 2016 guidelines, the diastolic function can be considered normal or abnormal if $> 50\%$ of the available variables (and not necessarily 3 out of 4) are normal or abnormal, respectively. Therefore, we considered that 3 parameters were enough to classify diastolic function, but patients with less than 3 parameters had to be excluded.

In our study, that reflects real world circumstances, the TR velocity could not be properly assessed in more than half of the patients, which played an important role in the determination of ventricular function. In such cases, other parameters can be used—such as pulmonary vein flow, S' velocity, E/A with Valsalva, atrial longitudinal strain, global left ventricular longitudinal strain and stress echocardiography—but when applied to a large-scale screening program it is unrealistic to use a non-standardized classification. Therefore, only participants with 4 measurable parameters could be labelled with IDF (none of the patients with only 3 available parameters could be classified with IDF since it is impossible to have 50% of abnormal parameters when only 3 are considered). Patients with 3 abnormal parameters out of 3 available parameters were classified with DD and patients with only 2 abnormal parameters out of 3 were also classified with DD, since they had $> 50\%$ positive criteria (albeit in patients without significant tricuspid regurgitation it is unlikely that the pulmonary pressures are increased). If we had considered that 3 *abnormal* parameters were mandatory to classify DD, then the number of DD would be much lower and IDF much higher. Unfortunately, most authors using 2016 guidelines do not specify how they classified participants with missing parameters. We could also have applied a different algorithm for patients with some ventricular hypertrophy that was proposed for myocardial disease in 2016 guidelines [14], but this was not done in other studies, namely in the main study we used for comparison [16]. The normal echocardiographic parameters in the elderly are different from a younger population and both the 2009 and 2016 classifications do not contemplate the age factor.

Acknowledging all these precautions needed when comparing studies, we compared our results to the EPIPorto cohort [16], that used the same classification for DD and was conducted in the general population of the same city, sharing

similar biometric and sociodemographic features and that excluded patients with systolic dysfunction [16]. The study comprised a sample of 1,000 individuals and presented a 1.4% prevalence of DD, which is substantially smaller than in our cohort with RA patients (13%). Similarly, the STANLISLAS cohort [23] included a sample of 1,485 participants and also found a smaller overall prevalence of DD (1.3%)—even when comparing to their cohort with over 60 years of age, the prevalence of DD was only 3.1%. In opposition to other studies, we focused on subclinical ventricular dysfunction in patients RA—older studies [6, 28] have reported a DD prevalence of 30–50% in RA patients versus 25–30% in the general population, but these studies have considered patients who already had cardiovascular events and used different definitions of DD.

The terms DD and HFpEF are often used as interchangeable terms, but in fact their overlap is limited. We found that 13% of the patients had HFpEF features according to the 2016 HF European criteria [12], but interestingly the correspondence with ventricular dysfunction categories was weak. The echocardiographic parameters most frequently used to assess diastolic function or structural changes that are related to HFpEF were associated with traditional cardiovascular risk factors and showed a generally good correlation with prognostic surrogate markers, such as 6MWT, NT-proBNP and even hsTnT.

Given the short follow-up and small number of cardiovascular events, and albeit the association between ventricular function and surrogate prognostic markers such as 6MWT, NT-proBNP and hsTnT, our sample was probably underpowered to detect an association between echocardiographic classification and events. Most patients with ventricular dysfunction presented NT-proBNP and hsTnT levels that were within the normal range, and it is therefore difficult to use these biomarkers in clinical practice to detect subclinical ventricular impairment. The NT-proBNP and hsTnT levels were also changed in IDF and not specifically in DD or SD.

Overall, we did not find significant associations between characteristics of RA disease and echocardiographic parameters. Nonetheless, inflammatory markers, particularly ESR, showed a significant association with most echocardiographic findings (and also with other outcomes), suggesting that the inflammatory pathways may play a role in the development of cardiovascular diseases in patients with RA.

Compared to the general population, the prevalence of DD was significantly higher in our cohort of RA patients, particularly in older patients, who can benefit the most from echocardiographic screening. An early diagnosis would allow for a close follow-up and can improve effectiveness of treatment strategies to decrease the risk of HF. Even though RA and other autoimmune diseases have been identified as increasing the HF risk, there are no recommendations to date on how to follow-up and diagnose these patients.

Limitations

We acknowledge that our study has some limitations in addition to those inherent to the definition of DD that are previously discussed. Despite being a prospective study, the follow-up duration was short. Due to its observational nature, we cannot infer causality, but only associations. Considering the relatively low prevalence of systolic and diastolic dysfunction, our sample size was probably underpowered to detect other independent predictors of SD and DD.

We did not explore different grades of diastolic dysfunction, given the reduced group size. We used the most common operational definition for systolic impairment, but it is possible that patients with LVEF > 50% may also have some systolic dysfunction. We did not evaluate other echocardiographic parameters, such as global longitudinal strain, that can detect early systolic ventricular dysfunction—however, this would make screening much more cumbersome and there are no recommendations on how to manage changes in ventricular mechanics in the absence of systolic or diastolic dysfunction.

When analyzing NT-proBNP levels and particularly for the classification of “HFpEF risk”, one should be aware that age-stratified cut-offs may be more appropriate. Moreover, this biomarker is affected by renal function and weight. Our goal was to assess current guidelines, but we believe that future guidelines may take stratified thresholds into consideration.

In future studies, our intention is to continue the follow-up of these patients, particularly those with indeterminate diastolic function, to ascertain what is their evolution and prognosis. We believe that our ongoing search of the optimal echocardiographic identification of diastolic dysfunction must be guided by clinical outcomes.

Conclusion

Patients with RA without any known cardiac disease showed a 4% prevalence of subclinical systolic function and 13% of diastolic dysfunction. The prevalence of diastolic dysfunction was higher than a comparable general population. Older age (particularly > 57 years) stood out as the most important independent predictor of ventricular dysfunction in patients with RA. A screening strategy using TTE may therefore be useful in older RA patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto (number 2016-023; 020-DEFI/020-CES).

Informed consent All participants gave written informed consent.

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