


Disease Activity and Anticitrullinated Peptide Antibody Positivity Predict the Worsening of Ventricular Function in Rheumatoid Arthritis

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Objective. This prospective study was designed to analyze the incidence and the factors associated with impairment in left ventricular systolic function (LVSF) overtime in patients with rheumatoid arthritis (RA) without overt cardiac disease. In particular, we verified the hypothesis that a relationship between worsening of LVSF and markers of RA disease activity exists.

Methods. One hundred forty outpatients with RA without overt heart disease underwent clinical, laboratory, and echocardiographic evaluation at baseline and after 35 (interquartile range [IQR] 23–47) months of follow-up. A clinical Disease Activity Index (DAI) score greater than 10 indicated the presence of moderate-high RA disease activity; data on anticitrullinated peptide antibody (ACPA) positivity were recorded at baseline. Stress-corrected midwall fractional shortening (sc-MFS) was used as a measure of LVSF and was considered impaired if less than 86.5%.

Results. At 36 (IQR 23–47) months follow-up, impaired sc-MFS was detected in 60 of 140 (43%) patients, compared with 80 patients with normal sc-MFS. Disease duration and activity, ACPA positivity, inflammatory markers, cardiovascular and antirheumatic therapies, and sc-MFS were similar between the two groups at baseline. A multiple logistic regression analysis showed ACPA positivity, moderate-high disease activity (DAI greater than 10), and disease duration as independent predictors of impaired sc-MFS at follow-up. Finally, a simple clinical score to predict worsening of LVSF at midterm was built (area under the curve of 0.80, with a sensibility and specificity of 78% and 82%, respectively).

Conclusion. Disease duration, ACPA positivity, and moderate-high disease activity are independent prognosticators of LVSF impairment in RA. Adverse changes in heart function could be prevented by good control of inflammation and modulation of autoimmunity.

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive systemic inflammatory disease associated with excess cardiovascular (CV) mortality and morbidity (1–3). Patients with RA develop increased arterial stiffness and left ventricular (LV) geometric and functional abnormalities overtime, resulting from the effect of immunological anomalies hastening vascular atherosclerosis and myocardial ultrastructural damage (4,5). We recently demonstrated that changes in LV geometry and function in patients with RA are closely related to the impairment of LV midwall mechanics (6,7), whose functions are detectable by standard echocardiography through the evaluation of stress-corrected midwall fractional shortening (sc-MFS). In

particular, we showed that sc-MFS is impaired in an early phase of RA disease in more than half of patients (6,7) when conventionally used echocardiographic indexes of LV systolic performance, such as left ventricular ejection fraction (LVEF), are still normal and patients have no symptoms of heart disease (8,9). Such discrepancy between different measures of left ventricular systolic function (LVSF) (ie, sc-MFS and LVEF) is due to the binary effect of contraction on both the longitudinal (shortening) and circumferential (thickening) axes of the myocardial fibers: the shortening of single myocardial fibers is amplified at the level of the endocardium, and there is a positive linear correlation between this amplification and wall thickness. At the endocardial level, greater wall thickness expands the effect of myocardial fibers with reduced

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SIGNIFICANCE & INNOVATIONS

- Changes in left ventricular systolic function (LVSF) leading to left ventricular systolic dysfunction (LVSD) detected after a mid-term period are strongly correlated with markers of moderate-high disease activity.
- Our results also suggest that impaired LVSD at the end of follow-up may be a consequence of rheumatoid arthritis disease more than an effect of multiple comorbidities.
- The worsening of LVSF can be predicted by a simple clinical/laboratory assessment by which patients at high risk for impaired LVSF could be selected and screened for echocardiography.
- Our findings may be interesting by the pathophysiological point of view and clinically stimulating in patients who do not systematically undergo baseline echocardiographic examination.

shortening, preserving LVEF and cardiac output even in the presence of abnormal midwall mechanics through a contractile gradient proceeding from the epicardium to the endocardium (named cross-fiber shortening phenomenon) (8,9).

The incongruity between chamber and wall mechanics, realized in all clinical conditions that lead to changes in LV geometry toward a concentric fashion, is at the basis of the more-accurate estimation of CV risk in patients with these characteristics by measures of LV wall mechanics than by measures of LV chamber function. Concordantly, sc-MFS has been proved as an accurate long-term prognosticator of adverse CV events in many pathologic conditions related, at least in part, to systemic inflammatory status such as arterial hypertension (10), type 2 diabetes mellitus (11), and chronic heart failure (HF) with preserved LVEF (12). In these patients, sc-MFS tends to impair overtime, mainly depending on the progression of LV hypertrophy and concentric remodeling. The physiognomies and meanings of these changes have never been investigated in people with RA. Thus, this prospective study was designed to analyze the incidence and the factors associated with changes overtime in sc-MFS between baseline evaluation (sc-MFS-BL) and the end follow-up (sc-MFS-follow-up) in patients with RA without overt cardiac disease, with the aim to verify the hypothesis that a relationship between impaired sc-MFS-follow-up and markers of RA disease activity exists.

METHODS

Study population. The design of the study was prospective. Study participants included 140 noninstitutionalized subjects over 18 years of age diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA (13). Participants were consecutively recruited between March 2014 and

December 2014 at the Division of Rheumatology, Department of Medicine, University of Verona and Azienda Ospedaliera Universitaria Integrata of Verona (Italy), where patients underwent echocardiographic, clinical, and laboratory evaluations at enrollment. An echocardiographic evaluation was repeated in all patients between January 2017 and May 2018.

All subjects were free of symptoms/signs of cardiac disease at enrollment and did not have a history of heart disease. All patients gave written informed consent, signing a specific institutional consent form. The study was approved by ethical committees of Verona University and conforms to the ethical guidelines of the Declaration of Helsinki as revised in 2000.

Definitions. The changes in sc-MFS were defined for each patient, taking into consideration the values of sc-MFS-BL and sc-MFS-follow-up. Details on the patient's classification according to the sc-MFS changes during the time are reported in the Statistical analysis section. The degree of activity of RA disease was evaluated by using the Clinical Disease Activity Index (CDAI) score (14), an index closely related to cardiovascular risk scores. Moderate-high disease activity was defined as a CDAI score greater than 10 (15), whereas all other conditions were classified as low activity. Hypertension was defined as a systolic blood pressure level greater than or equal to 140 mm Hg, a diastolic blood pressure level greater than or equal to 90 mm Hg, and/or pharmacologically treated blood pressure of unknown etiology. Obesity was recognized as a body mass index greater than or equal to 30 kg/m². Dyslipidemia was defined as levels of total serum cholesterol greater than 190 mg/dl, triglyceride levels greater than 150 mg/dl, or pharmacologically treated high serum lipid levels.

Echocardiography. All Doppler-echocardiographic studies were performed by using an Alpha Esaote Biomedica machine (Florence, Italy), following a standardized protocol. LV chamber dimensions and wall thicknesses were measured by using the American Society of Echocardiography (ASE) guidelines, and LV mass was calculated by using a validated formula (16). LV mass was normalized for height to the 2.7 power, and LV hypertrophy was defined as LV mass greater than or equal to 49.2 g/m^{2.7} for men and greater than or equal to 46.7 g/m^{2.7} for women (17). Relative wall thickness was calculated as 2 × the end-diastolic ratio of posterior wall thickness/LV diameter and indicated concentric LV geometry if it was greater than or equal to 0.43 (the 97.5 percentile in a normal population) (18). LV end-diastolic and end-systolic volumes and stroke volume were measured by using the biplane method of disks from a two-dimensional apical four- and two-chamber view and used to calculate LVEF (defined as reduced if less than 50%) and cardiac index.

LVSF was assessed by measuring the systolic shortening of the LV minor axis at the midwall level. Midwall fractional shortening (MFS) was calculated considering the epicardial migration of the midwall during systole caused by the architectural organization

of myocardial fibers, as previously described (8,9,19). Because myocardial afterload is a determinant of LVSF, the value of MFS predicted for the observed level of circumferential end-systolic stress (CESS) was calculated to assess afterload-independent

LVSF (8,9,19). The ratio between observed MFS and the value predicted from CESS, expressed as a percentage and named sc-MFS, provides an accurate measure of myocardial contractility. To calculate sc-MFS, five parameters easily detected by the stand-

Table 1. Main baseline clinical characteristics of the study patients (140 subjects with RA) and comparison between the subgroup of 60 patients with impaired sc-MFS and 80 patients with normal sc-MFS at the final evaluation

Variables	Impaired sc-MFS (60 patients)	Normal sc-MFS (80 patients)	P	Whole Study Population (140 patients)
Clinical				
Age, y, mean ± SD	61 ± 12	58 ± 10	0.12	60 ± 12
Female sex, %	82	84	0.75	83
Body mass index, kg/m ² , mean ± SD	25.7 ± 4.4	25.1 ± 4.6	0.51	25.3 ± 4.2
Obesity, %	10	13	0.65	12
Hypertension, %	58	41	0.06	48
Dyslipidemia, %	67	66	0.97	66
Diabetes, %	3	9	0.22	7
Systolic blood pressure, mm Hg, mean ± SD	136 ± 21	131 ± 15	0.10	133 ± 13
Diastolic blood pressure, mm Hg, mean ± SD	84 ± 9	83 ± 10	0.63	81 ± 10
Heart rate, beats/min, mean ± SD	71 ± 9	70 ± 11	0.86	70 ± 9
Duration of RA, y, mean ± SD	18 ± 11	14 ± 10	0.04	16 ± 10
Laboratory				
Glycemia, mg/dl, mean ± SD	96 ± 31	87 ± 24	0.22	90 ± 24
Hemoglobin, g/dl, mean ± SD	13.7 ± 1.3	13.6 ± 1.3	0.80	13.6 ± 1.3
GFR, ml/min/1.73m ² , mean ± SD	92 ± 20	93 ± 19	0.75	93 ± 19
GFR < 60 ml/min/1.73m ² , %	5	3	0.46	4
Total cholesterol, mg/dl, median (IQR)	216 (186-244)	216 (179-248)	0.98	216 (181-246)
LDL cholesterol, mg/dl, median (IQR)	128 (101-146)	122 (99-143)	0.75	124 (102-146)
LDL cholesterol > 100 mg/dl, %	77	76	0.93	76
Triglycerides, mg/dl, median (IQR)	112 (90-139)	110 (86-134)	0.87	110 (80-140)
Macroalbuminuria (>300 mg/g), %	2	3	0.70	3
Erythrocyte sedimentation rate, mm/h, median (IQR)	23 (13-37)	20 (10-32)	0.25	21 (11-33)
C-reactive protein, mg/l, median (IQR)	4.5 (2.2-6.6)	3.9 (1.9-7.0)	0.72	4.1 (2.1-6.7)
Rheumatoid factor-positive, %	71	45	0.005	55
Anticyclic citrullinated peptide-positive, %	81	48	<0.001	61
CDAI, mean ± SD	11.5 ± 6.1	9.6 ± 5.9	0.27	10.3 ± 5.9
Moderate-high disease activity (CDAI > 10), %	26	11	0.03	17
Pharmacological treatment				
Beta-blockers, %	25	16	0.16	19
ACEis/ARBs, %	41	27	0.06	32
Diuretics, %	15	18	0.62	17
Calcium antagonists, %	4	8	0.34	6
Antiplatelet agents, %	17	10	0.30	13
Statins, %	24	28	0.56	26
NSAIDs, %	31	27	0.57	28
Methotrexate, %	48	48	0.99	48
Hydroxychloroquine, %	20	8	0.06	12
Corticosteroids, %	57	58	0.94	58
Biologic DMARDs, %	68	53	0.08	59
Anti-TNF-α	63	73	0.85	63
Anti-IL-6a	13	9	0.18	12
CTLA 4lg	18	12	0.25	17
anti-CD20a	6	6	0.91	6
Biologic DMARDs (number of different agents from RA diagnosis to end of follow-up), mean ± SD	2.4 ± 1.6	2.2 ± 1.5	0.65	2.3 ± 1.5
Biologic DMARDs (number of different agents used during the follow-up), mean ± SD	1.3 ± 0.7	1.4 ± 0.6	0.69	1.6 ± 0.7
Biologic DMARDs (number of naive patients who started any agent during the follow-up), n (%)	6 (10)	23 (29)	0.03	29 (21)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin T1 receptor blocker; CDAI, Clinical Disease Activity Index; CTLA, cytotoxic T-lymphocyte antigen; DMARD, disease-modifying antirheumatic drug; GFR, glomerular filtration rate; IL-6, interleukin 6; IQR, interquartile range; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; sc-MFS, stress-corrected midwall fractional shortening; TNF-α, tumor necrosis factor α.

aPercentage among patients who were receiving biologic DMARDs.

ard M-mode technique plus systolic blood pressure (measured at the end of the examination) were used. An sc-MFS less than 86.5% (10th-percentile distribution of sc-MFS in the reference healthy population analyzed in our center) was considered indicative of left ventricular systolic dysfunction (LVSD), as previously reported (6,7).

Transmitral and pulmonary vein pulsed-wave Doppler curves and early diastolic tissue Doppler velocity of mitral annulus (E') were assessed according to the recommendations of the ASE (20). Early diastolic velocity of transmitral flow (E) was divided by E' and used to classify LV diastolic function together with other diastolic parameters in accordance with the four-point ordinal scale proposed by Redfield et al (21): normal, mild dysfunction, moderate dysfunction, and severe dysfunction. Maximal left atrial volume was also computed from a two-dimensional apical four-chamber view by using the area – length method and was normalized for body surface area.

Statistical analysis. Continuous data are reported as mean values \pm 1 SD or median (interquartile ranges [IQRs]) for variables deviating from normality or percentages for categorical data. 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 using the χ^2 test and analysis of variance, with comparisons between each group by using the Scheffè test for unequal samples as appropriate. The study population was initially stratified according to sc-MFS–BL. The cutoff value for impaired sc-MFS–BL was a priori identified as less than 86.5%, as previously reported (6,7). Thus, we considered sc-MFS–follow-up to distinguish patients with persistent or de novo impairment of sc-MFS–follow-up (less than 86.5%) from those with normal sc-MFS–follow-up. Variables that were significantly related to the primary end point (impaired sc-MFS–follow-up) in the univariate test ($P < 0.05$) were included in the multivariate logistic regression model. Sensitivity, specificity, and predictive accuracy of disease-activity markers for impaired sc-MFS–follow-up (which emerged from the multivariate analysis) were derived from receiver operating characteristic (ROC) analyses, and ROC curves were showed. Finally, the independent predictors of sc-MFS–follow-up that emerged from the multiple logistic regression analysis were combined to build a clinical score that better predicted the primary study end point. The ROC curves resulting from the score were compared by using the z statistics, with the curves resulting from each single element of the score (22). All analyses were performed by using statistical package SPSS version 19.0 (IBM SPSS Statistics; IBM Corporation), and statistical significance was identified by two-tailed $P < 0.05$.

Reproducibility of sc-MFS. Echocardiographic reproducibility of sc-MFS was tested by using the baseline recordings of 40 patients who were part of the study cohort and randomly selected. The mean difference between two measurements was $\pm 4.85\%$. The SD of this difference was $\pm 5\%$. Bland-Altman plot

showed that the intraobserved variability was statistically tolerable (data not shown). In none of these 40 subjects did the deviation of values of sc-MFS–BL, measured twice at two different times in the same patient, exceed 2 SDs of the mean sc-MFS–BL value between the two measures. Interobserver variability for sc-MFS–BL was tested by comparing these measures with those acquired by a second sonographer: the mean difference between two measurements was 3.85%. The SD of this difference was $\pm 5\%$.

RESULTS

Study population. The main clinical characteristics of the 140 study patients are shown in Table 1. They had a mean age of 60 ± 12 years, with a large prevalence of women; the duration of RA disease was 16 ± 10 years; nearly half of the included patients had a diagnosis of arterial hypertension and two-thirds had a diagnosis of dyslipidemia. Disease activity was moderate-high in 24 of 140 (17%) subjects at baseline evaluation. Positivity for rheumatoid factor and anticitrullinated peptide antibody (ACPA) was found in 55% and 61% of patients, respectively. At enrollment, more than half of patients were taking biologic disease-modifying antirheumatic drugs (DMARDs), whereas concomitant methotrexate was given in nearly half of them. Considering the echocardiographic features, concentric LV geometry was recognized in two-thirds of patients and LV hypertrophy in one-third of them. Looking at LVSF, LVEF was abnormal in 1%, whereas sc-MFS–BL was impaired in 61% of patients. LV diastolic dysfunction was found in nearly one-fourth of patients (mild degree in all cases) (Table 2).

Changes in sc-MFS during follow-up. Figure 1 shows the changes in sc-MFS from baseline to final evaluation, performed after a median period of 36 (between 23 and 47) months. Forty-one of the 86 patients with impaired sc-MFS–BL had persistent impaired sc-MFS–follow-up, and 19 patients who had normal sc-MFS–BL showed de novo impaired sc-MFS–follow-up. These patients formed the group of 60 patients with impaired sc-MFS–follow-up whose baseline variables were compared with those of the 80 patients with normal sc-MFS–follow-up. The extent of changes in sc-MFS in the subgroups of patients with normal sc-MFS–follow-up and impaired sc-MFS–follow-up is shown in Figure 2. The two groups had similar sc-MFS–BL, which was significantly different at the end. Sc-MFS had a 6% ($P = 0.02$) absolute decrease and a 12% ($P < 0.001$) absolute increase from baseline to the final evaluation in the group of patients with impaired and normal sc-MFS–follow-up, respectively.

Group with impaired versus normal sc-MFS–follow-up. At baseline, the two groups had similar clinical characteristics, but duration of RA was longer in patients who had impaired sc-MFS–follow-up compared with those who had not. Prevalence of patients with rheumatoid factor and/or ACPA positivity was significantly higher in the former than in the latter,

Table 2. Echocardiographic characteristics assessed at the baseline evaluation

Variables	Impaired sc-MFS (60 patients)	Normal sc-MFS (80 patients)	<i>P</i>	Whole Study Population (140 patients)
LVEDD, ml/m ² , mean ± SD	2.6 ± 0.3	2.7 ± 0.3	0.12	2.7 ± 0.3
LVEDV, ml/m ² , mean ± SD	46 ± 9	47 ± 10	0.75	47 ± 10
LV relative wall thickness, mean ± SD	0.47 ± 0.07	0.45 ± 0.07	0.15	0.46 ± 0.07
Concentric LV geometry, %	75	55	0.01	68
LV mass index, g/m ^{2.7} , mean ± SD	44 ± 10	44 ± 10	0.78	44 ± 10
LV hypertrophy, %	33	37	0.61	36
LV stroke volume, ml, mean ± SD	53 ± 13	55 ± 15	0.40	54 ± 15
Cardiac index, l/min/ m ² , mean ± SD	2.1 ± 0.5	2.2 ± 0.6	0.23	2.2 ± 0.6
LVEF, %, mean ± SD	66 ± 5	68 ± 6	0.06	67 ± 6
Low LVEF (<50%), %	2	1	0.78	1
LV CESS, dynes/cm ² , mean ± SD	110 ± 28	103 ± 26	0.10	105 ± 28
LV midwall shortening, %, mean ± SD	15.5 ± 2.9	16.4 ± 2.6	0.06	16.2 ± 2.5
LV sc-MFS, %, mean ± SD	82 ± 15	86 ± 16	0.08	85 ± 15
Impaired LV sc-MFS, %	68	56	0.22	61
E wave of transmitral flow, cm/s, mean ± SD	64 ± 15	69 ± 16	0.06	67 ± 15
A wave of transmitral flow, cm/s, mean ± SD	75 ± 16	74 ± 18	0.16	74 ± 17
E/A ratio, mean ± SD	0.85 ± 0.30	0.93 ± 0.38	0.04	0.94 ± 0.33
Deceleration-time E wave, ms, mean ± SD	222 ± 54	209 ± 53	0.04	215 ± 50
Peak E' (tissue Doppler), cm/s, mean ± SD	10.0 ± 2.4	11.0 ± 2.3	0.06	10.6 ± 2.4
E/E' ratio, mean ± SD	6.5 ± 1.5	6.5 ± 1.5	0.98	6.5 ± 1.5
LV diastolic dysfunction, %	37	21	0.04	28
Grade I	37	21	...	28
Grade II	0	0	...	0
Grade III	0	0	...	0
Maximal left atrial volume, ml/ m ² , mean ± SD	19 ± 5	18 ± 7	0.34	18 ± 5

Abbreviations: CESS, circumferential end-systolic stress; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; peak E', early diastolic tissue Doppler velocity of mitral annulus; sc-MFS, stress-corrected midwall fractional shortening.

as well as that of patients with moderate-high disease activity. The pharmacological treatment was similar in the two groups (Table 1). Considering the baseline echocardiographic variables, excluding the prevalence of concentric LV geometry and diastolic dysfunction, which were slightly higher in patients with than without impaired sc-MFS–follow-up, the two study groups could not be distinguished for any echocardiographic parameter.

Variables measured at the end follow-up in the two study groups. At the final evaluation, systemic blood pressure was similar in the two groups as well as renal function and lipid profile. Similarly, all markers of the disease activity did not differ between the patients who had impaired sc-MFS–follow-up and those who did not. As expected, the former showed a higher LV relative wall thickness and higher prevalence of concentric LV geometry (parameters closely related to sc-MFS) than the latter, whereas the prevalence of LV diastolic dysfunction was similar between the study groups (Table 3).

Management of biologic DMARDs during the study in the two study groups. At baseline evaluation, 83 patients (59%) were receiving a biologic DMARD. During the follow-up, a biologic DMARD was started in 29 patients (21%). All baseline clinical, laboratory, and echocardiographic parameters of these 29 patients

did not differ from the counterparts who did not change biologic DMARD. At baseline, 68% of patients who had impaired sc-MFS–follow-up and 53% of patients who did not ($P = 0.08$) were receiving a biologic DMARD. During the follow-up, a biologic DMARD was started in 6 patients (10%) who had impaired sc-MFS–follow-up and 23 patients (29%) who did not ($P = 0.03$). The patients belonging to the former group started or changed a similar number of biologic DMARDs during the follow-up as the latter group (1.3 ± 0.7 vs 1.4 ± 0.6 , respectively; $P = 0.69$). In total, the mean number of biologic DMARD/patient received by the first diagnosis of RA to the end follow-up was similar in the groups with and without impaired sc-MFS–follow-up (2.4 ± 1.6 vs 2.2 ± 1.5 , respectively; $P = 0.65$).

Predictors of impaired sc-MFS–follow-up. The variables considered as covariates in the multivariate model derived by the univariate analysis were duration of RA disease, ACPA positivity, high disease activity, starting a biologic DMARD during the follow-up, the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, the use of hydroxychloroquine, concentric LV geometry, and LV diastolic dysfunction (defined as dichotomic variable = yes vs no). Age and female gender were initially forced into the model and then removed once the adjustment was considered irrelevant on the results. Multivariate logistic regression analysis showed that ACPA positivity (odds ratio [OR], 6.24; confidence interval [CI], 2.61–

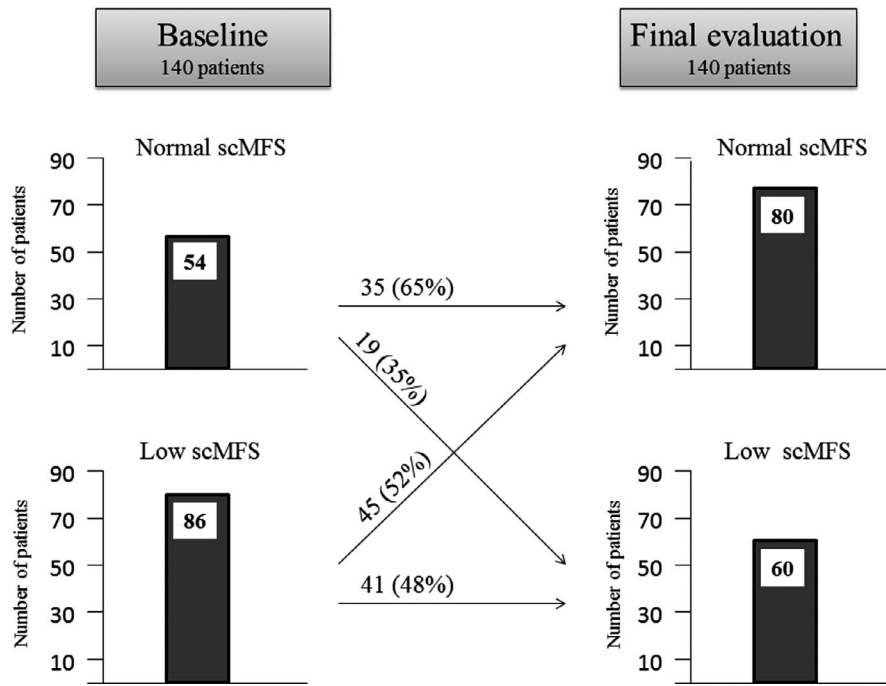


Figure 1. Distribution of patients according to changes in left ventricular function. Distribution of 140 patients with rheumatoid arthritis at the baseline echocardiographic evaluation and at the end of follow-up according to the values of stress-corrected midwall fractional shortening (scMFS). Values lower or higher than 86.5% identified patients with impaired or normal scMFS, respectively.

15.80; $P < 0.001$), duration of RA disease (OR, 1.05; CI, 1.01-1.09; $P = 0.01$), and moderate-high disease activity (OR, 3.09; CI, 1.11-8.58; $P = 0.03$) were the three variables independently associated with impaired sc-MFS-follow-up. Starting a biologic DMARD did not reach statistical significance (OR, 1.49; CI, 0.55-4.06; $P = 0.44$), whereas ACPA positivity and, more decisively, the duration of RA disease were considered in the model.

Relationship between markers of the disease activity and impaired sc-MFS-follow-up. Figure 3 shows the sensitivity, specificity, and predictive accuracy (derived by ROC analyses) of ACPA positivity, moderate-high disease activity, and duration of RA disease for impaired sc-MFS-follow-up. The relationship between these three parameters (considered individually) and LVSD was highly significant, particularly if ACPA positivity was considered.

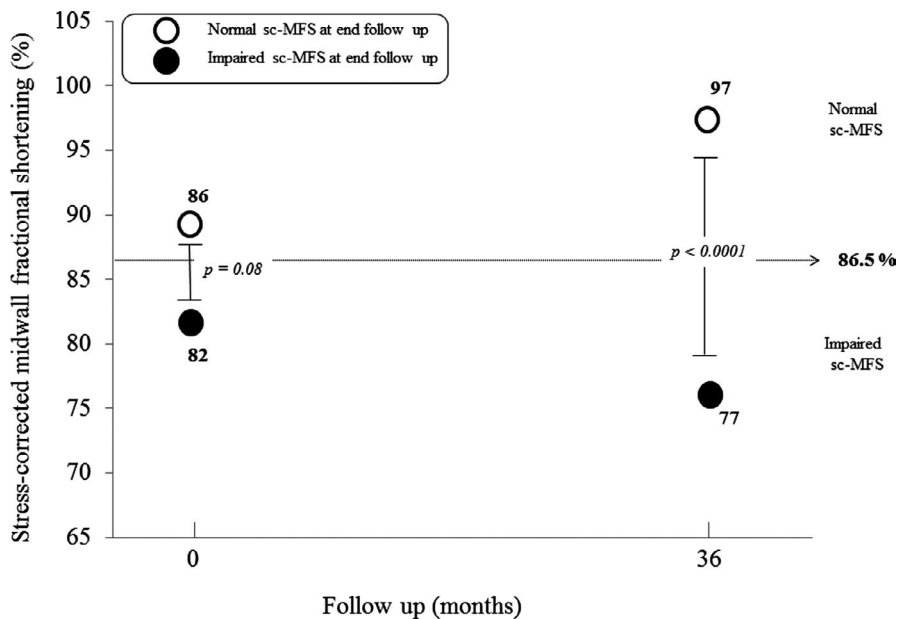


Figure 2. Changes in left ventricular systolic function in the study groups over time. Changes in stress-corrected midwall shortening (sc-MFS) during the time in the subgroups of patients with normal sc-MFS (dotted line) and impaired sc-MFS (solid line) at the end of follow-up.

Table 3. Comparison between the two study groups of the main clinical and echocardiographic characteristics assessed at the final evaluation after a median period of 36 months of follow-up

Variables	Impaired sc-MFS (60 patients)	Normal sc-MFS (80 patients)	<i>P</i>
Systolic blood pressure, mm Hg, mean ± SD	131 ± 13	132 ± 16	0.70
Diastolic blood pressure, mm Hg, mean ± SD	81 ± 5	81 ± 8	0.89
Duration of rheumatoid arthritis, y, mean ± SD	21 ± 12	17 ± 11	0.04
GFR, ml/min/1.73m ² , mean ± SD	100 ± 24	92 ± 20	0.60
Total cholesterol, mg/dl, median (IQR)	202 (180-234)	200 (170-238)	0.93
LDL cholesterol, mg/dl, median (IQR)	117 (100-138)	121 (98-140)	0.73
Triglycerides, mg/dl, median (IQR)	98 (82-131)	90 (81-130)	0.64
Erythrocyte sedimentation rate, mm/h, median (IQR)	17 (11-34)	19 (10-28)	0.71
C-reactive protein, mg/l, median (IQR)	3.8 (2.0-6.4)	5.3 (2.1-7.9)	0.46
CDAI, mean ± SD	10.1 ± 5.1	12.0 ± 6.9	0.18
Moderate-high disease activity (CDAI > 10), %	26	35	0.35
LV end-diastolic volume, ml/m ² , mean ± SD	47 ± 9	47 ± 10	0.89
LV relative wall thickness, mean ± SD	0.46 ± 0.07	0.39 ± 0.04	0.003
Concentric LV geometry, %	72	55	0.02
LV mass index, g/m ^{2.7} , mean ± SD	42 ± 10	41 ± 8	0.74
LV hypertrophy, %	38	32	0.47
LV stroke volume, ml, mean ± SD	52 ± 12	53 ± 14	0.75
Cardiac index, l/min/m ² , mean ± SD	2.2 ± 0.5	2.3 ± 0.7	0.45
LVEF, %, mean ± SD	67 ± 5	67 ± 4	0.69
E/A ratio, mean ± SD	0.79 ± 0.23	0.93 ± 0.24	0.001
LV diastolic dysfunction, %	33	23	0.51
Maximal left atrial volume, ml/ m ² , mean ± SD	20 ± 5	20 ± 5	0.75
Pharmacological treatment, %			
Beta-blockers	24	22	0.88
ACEis/ARBs	42	34	0.30
Diuretics	10	16	0.48
Calcium antagonists	3	5	0.74
Antiplatelet agents	25	20	0.58
Statins	30	29	0.83
NSAIDs	16	16	0.98
Methotrexate	40	48	0.63
Hydroxychloroquine	8	5	0.73
Biologic agents	74	73	0.95
Corticosteroids	36	28	0.44

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin T1 receptor blocker; CDAI, Clinical Disease Activity Index; GFR, glomerular filtration rate; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drug.

Associated indicators of impaired sc-MFS-follow-up. A performance indicator was built in consideration of the three variables that emerged by multiple logistic regression analysis as independent predictors of sc-MFS-follow-up. ROC curve analysis showed that the best cutoff values for duration of RA disease was 13 years. According to the ORs that emerged by multivariate analysis, seven points were given to each patient with ACPA positivity, three points were added if high disease activity was present, and one point was accredited if duration of RA disease was longer than 13 years. Thus, the performance indicator ranged from 0 to 11 points, in case none or all three conditions were satisfied, respectively. Figure 3 shows that the performance indicator had an area under the curve of 0.80 with a sensibility and specificity for the prediction of impaired sc-MFS-follow-up of 78% and 82%, respectively. The ROC curve resulting from the performance indicator was compared by using the z statistics with the curves of the three prognosticators considered alone and the gap in accuracy for the prediction on

impaired sc-MFS-follow-up was statistically significant ($P = 0.04$ vs ACPA positivity, $P = 0.007$ vs duration of RA disease, and $P = 0.003$ vs moderate-high disease activity). A final analysis was performed to assess the observed event rate (impaired sc-MFS-follow-up) occurring in the study patients divided in four classes based on quartiles of the performance indicator. The prevalence of impaired sc-MFS-follow-up of patients belonging to the lowest quartile (including patients with zero points) was 4% (1 of 25 patients), the low-median quartile (1-6 points) was 32% (12 of 37 patients), the high-median quartile (7-8 points) was 53% (31 of 58 patients), and to the highest quartile of the performance indicator (9-11 points) was 80%.

DISCUSSION

The results of the current study provide evidence that in patients with RA without history of cardiac disease, the impairment of LVSF overtime is strongly correlated with a higher dis-

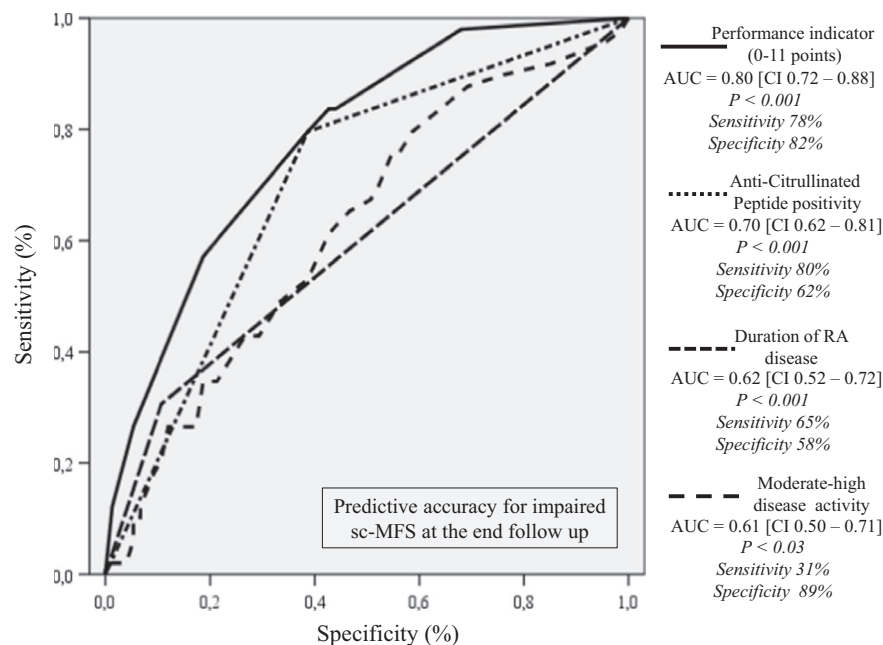


Figure 3. Performance indicator of the left ventricular systolic dysfunction prediction at the end of follow-up: receiver operating characteristic analysis. Sensitivity, specificity, and predictive accuracy of the three variables associated with impaired stress-corrected midwall fractional shortening (sc-MFS) at the end of follow-up. The receiver operating characteristic curve (derived by receiver operating characteristic analysis), the area under the curve (AUC), and confidence intervals (CI) are shown. The receiver operating characteristic curve built on the basis of the performance indicator for impaired sc-MFS at the end of follow-up, derived by the association of the three predictors, is also shown. RA, rheumatoid arthritis.

ease activity, ACPA positivity, and a longer duration of RA. In our study, we individuated and characterized the subgroup of patients with occult LVSD at the end follow-up, comparing them with the remaining 80 patients with normal LVSF. As shown in the Figure 2, the values of sc-MFS largely diverged between the two groups over time, suggesting a possible tendency toward a further worsening or improvement in LVSF in patients with or without impaired sc-MFS-follow-up, respectively, over a longer time period.

How might this strikingly different evolution after 3 years of observation be explained? The duration of RA evidently plays a role in these distinct behaviors. A longer RA duration at enrollment was significantly associated with impaired sc-MFS-follow-up in our study population. It is well known that longer RA duration is correlated with acceleration of atherosclerosis and coronary artery calcification (23,24), which can progressively lead to subclinical myocardial ischemia, fibrosis, inappropriate mass growth, and LVSD (25). This process and the detrimental effect of long duration of RA disease is also evident in RA populations with few traditional risk factors of adverse CV events (26), which suggests inflammation, added to hemodynamic and/or neurohormonal factors, as a central cause of LVSD. Even more relevant, patients with RA and a longer disease duration appear to be less responsive to immunosuppressive medications (27,28). In the present study, the total number of biologic DMARDs/patient given from the first diagnosis of RA disease did not emerge as a prognosticator of sc-MFS impairment over time. This is mainly due to the large overlap between this variable and the duration of RA disease, whose

relevant role on LVSF was visibly documented by multivariate logistic regression analysis. Interestingly, in our experience, the incidence of patients who started a biologic DMARD during the period of observation was threefold higher in patients without than those with impaired sc-MFS-follow-up, suggesting a potential (positive) influence of these agents on myocardial mechanics mediated by their anti-inflammatory and/or immunomodulatory effect.

The present experience clearly shows that a higher disease activity is associated with a worsening of LVSF overtime, independently of LV geometry or mass, LVEF, or any pharmacological intervention. Interestingly, our results testify that at both baseline and final evaluation, patients who had impaired sc-MFS-follow-up showed similar prevalence of the traditional CV risk factors as those who did not have impaired sc-MFS-follow-up, which suggests that impaired sc-MFS-follow-up is a consequence of RA disease more than multicorbidities. Our study also demonstrates that high disease activity heralds and sustains LVSD, which may persist once remission takes place or inflammation status attenuates. Indeed, none of the markers of the disease activity measured at the end follow-up were different between our patients with or without impaired sc-MFS-follow-up. The link between RA disease activity and cardiac abnormalities has been well established over recent years (6,7,27,29,30). Midtbø et al evaluated 119 patients with RA and found that patients with active disease (Simplified Disease Activity Index score > 3.3) compared with those in remission had lower LVSF (31). In 39 patients with RA with no known CV disease, Ntusi et al, by means of cardiac MR, detected diffuse

and focal areas of myocardial fibrosis as well as inflammation, both of which positively correlated with the Disease Activity Score 28-C-reactive protein score (32). Unexpectedly, in this study, myocardial fibrosis was not associated with the presence of rheumatoid factor or ACPA. This finding is in contrast with a number of studies demonstrating the high specificity (90%-98%) of the ACPA in RA and its correlation with erosive arthritis and poorer outcome (33,34). The prognostic role of ACPA referred to adverse CV events could be due to the possible harmful effect of these antibodies on LV geometry and function. This speculation is founded upon data published by Geraldino-Pardilla et al (35), which shows that higher levels of antibodies targeting citrullinated fibrinogen and vimentin peptides or protein were associated with a higher LV mass, potentially implicating autoimmune targeting of citrullinated proteins in myocardial remodeling in RA patients. Furthermore, Løgstrup et al (36) recently demonstrated that patients with persistently elevated ACPA, compared to those with nonpersistently elevated ACPA, had significantly less improvement in LVSF after 2 years of optimized therapy for RA. Our findings are in accord with these results. The mechanism of how ACPA impacts LVSF is not completely acknowledged. From what we can gather right now based on the data in the literature, ACPAs mediate increased proinflammatory cytokine production by stimulating macrophages in vitro and are associated with increased systemic inflammation and disease activity in patients with RA (37).

Finally, we propose a simple performance indicator based on the association of the variables predicting occult LVSD at midterm in our RA patients. The indicator has a good performance and could be clinically useful, particularly for selecting candidates for CV clinical assessment that includes echocardiography. However, it should be tested in a validation cohort of RA patients and then used as a predictive risk score.

Although the strong negative impact of asymptomatic LVSD on clinical outcomes over the long term is well known, this study does not allow for any prognostic inference of sc-MFS impairment over time in patients with RA. Furthermore, even though our statistical models were extensive, unmeasured confounders (ie, vascular function or ventricular-arterial coupling) could potentially explain the observed associations. Strengths of our study include its prospective nature and design, a large number of participants, the prospective and complete nature of the data set, the ability to adjust for several CV risk factors, and the reliable and appropriate method for the assessment of LVSD in RA patients.

The impairment of sc-MFS is a powerful pointer of the transition phase between asymptomatic LVSD and overt heart failure (38). This phenomenon is frequent in patients suffering from RA, depends on RA per se beyond the traditional CV risk factors, and can be detected in the early asymptomatic phase of disease. Changes in LVSF leading to LVSD detected after a midterm period are strongly correlated with markers of disease activity and can be predicted by a simple clinical/biochemical evaluation. Our findings may lead to select those patients at higher risk who do

not systematically undergo CV assessment and/or echocardiographic examination due to their asymptomatic condition and, often, normal blood pressure values. These patients should be more aggressively treated for better control of CV risk factors, inflammation, and modulation of autoimmunity.

AVAILABILITY OF DATA AND SUPPORTING MATERIALS SECTION

Data are available at any time; please contact the corresponding author for data requests.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Cioffi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Cioffi, Giollo, Rossini, Viapiana.

Acquisition of data. Cioffi, Giollo, Orsolini, Idolazzi, Dalbeni, Ognibeni, Fracassi, Gatti, Fassio, Viapiana.

Analysis and interpretation of data. Cioffi, Giollo, Orsolini, Gatti, Rossini, Viapiana.

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