Combined Circumferential and Longitudinal Left Ventricular Systolic Dysfunction in Patients with Rheumatoid Arthritis without Overt Cardiac Disease

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Background: Patients with rheumatoid arthritis have an increased risk for cardiovascular disease. Because of accelerated atherosclerosis and changes in left ventricular (LV) geometry, circumferential and longitudinal (C&L) LV systolic dysfunction (LVSD) may be impaired in these patients despite preserved LV ejection fraction. The aim of this study was to determine the prevalence of and factors associated with combined C&L LVSD in patients with rheumatoid arthritis.

Methods: One hundred ninety-eight outpatients with rheumatoid arthritis without overt cardiac disease were prospectively analyzed from January through June 2014 and compared with 198 matched control subjects. C&L systolic function was evaluated by stress-corrected midwall shortening (sc-MS) and tissue Doppler mitral annular peak systolic velocity (S′). Combined C&L LVSD was defined if sc-MS was <86.5% and S′ was <9.0 cm/sec (the 10th percentiles of sc-MS and S′ derived in 132 healthy subjects).

Results: Combined C&L LVSD was detected in 56 patients (28%) and was associated with LV mass (odds ratio, 1.03; 95% CI, 1.01–1.06; P = .04) and concentric LV geometry (odds ratio, 2.76; 95% CI, 1.07–7.15; P = .03). By multiple logistic regression analysis, rheumatoid arthritis emerged as an independent predictor of combined C&L LVSD (odds ratio, 2.57; 95% CI, 1.06–6.25). The relationship between sc-MS and S′ was statistically significant in the subgroup of 142 patients without combined C&L LVSD ($r = 0.40$, $F < 0.001$), having the best fitting by a linear function (sc-MS = 58.1 + 3.34 × peak S′; $r^2 = 0.19$, $P < .0001$), absent in patients with combined C&L LVSD.

Conclusions: Combined C&L LVSD is detectable in about one fourth of patients with asymptomatic rheumatoid arthritis and is associated with LV concentric remodeling and hypertrophy. Rheumatoid arthritis predicts this worrisome condition, which may explain the increased risk for cardiovascular events in these patients. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Rheumatoid arthritis, Left ventricular systolic dysfunction, Midwall shortening, Longitudinal function, Primary prevention, Cardiovascular risk

In patients with rheumatoid arthritis, changes in left ventricular (LV) geometry toward a concentric fashion (concentric remodeling or hypertrophy) have been widely found in an early stage of the disease.[1-5] These typologies of LV geometric patterns are closely and consistently associated with depressed LV midwall mechanics and circumferential LV myocardial systolic dysfunction in several groups of patients, such as those with arterial hypertension, type 2 diabetes mellitus, heart failure (HF) with preserved LV ejection fraction (LVEF), aortic stenosis, chronic kidney disease, and obstructive sleep apnea.[6-10] Similarly, reduced LV longitudinal function has been detected in patients with rheumatoid arthritis, depending mostly on the level of disease activity.[11,12] Considered individually, circumferential and longitudinal (C&L) LV systolic dysfunction (LVSD) must be presumed to be reliable indicators of the transitional state between asymptomatic subtle LVSD and clinically manifest congestive HF. Furthermore, these conditions are potent prognosticators of adverse cardiovascular (CV) outcomes, as definitively demonstrated in patients with hypertension,[6] type 2 diabetes mellitus,[7] and aortic stenosis[13] and in the subset of patients with chronic HF in whom LVEF is preserved.[8]

Analogous to patients with HF and preserved LVEF,[14] type 2 diabetes mellitus,[15] or arterial hypertension,[16] C&L LVSD might coexist in some patients with rheumatoid arthritis. The prevalence and predictors of this condition are unknown in patients with rheumatoid arthritis, and its early detection might be important for the clinical

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Abbreviations

C&L = Circumferential and longitudinal

CESS = Circumferential end-systolic stress

CV = Cardiovascular

HF = Heart failure

IVST = Interventricular septal thickness

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVID = Left ventricular internal dimension

LVSD = Left ventricular systolic dysfunction

OR = Odds ratio

PWT = Posterior wall thickness

SBP = Systolic blood pressure

sc-MS = Stress-corrected midwall shortening

2D = Two-dimensional

management of these subjects, who have a significantly higher mortality rate than the general population (approximately 1.6-fold higher), mainly because of CV disease, and comparable with that found in patients with type 2 diabetes mellitus.[17]

Accordingly, we designed this prospective study to assess (1) the prevalence of combined C&L LVSD in patients with asymptomatic rheumatoid arthritis without histories and clinical signs of cardiac disease, (2) the clinical and echocardiographic variables associated with combined C&L LVSD, (3) whether rheumatoid arthritis per se is a prognosticator of this condition, and (4) how the indexes of C&L function are related to one another in these patients.

METHODS

Study Population

The design of the study was prospective. Patients >18 years of age with diagnoses of rheumatoid arthritis ascertained by clinical and laboratory examination underwent echocardiographic, clinical, and laboratory evaluations. All subjects were free of symptoms and clinical signs attributable to some cardiac disease. Exclusion criteria were a history of myocardial infarction, myocarditis, or HF; coronary heart disease diagnosed by clinical or electrocardiographic evaluation at rest and by exercise, scintigraphy, or stress echocardiography; alcoholic cardiomyopathy; primary hypertrophic cardiomyopathy; asymptomatic known LVSD; prior myocardial revascularization; significant valve heart disease; and atrial fibrillation. All patients with rheumatoid arthritis who were evaluated from January 1, 2014, to June 30, 2014, at our Italian referral centers in Verona, Trieste, and Trento and who met the inclusion and exclusion criteria for the study were recruited. During this period, 228 patients were visited and were taken into consideration as participants in the study. Among these patients, 30 were excluded (histories of myocardial infarction in 10, histories of HF in four, moderate or severe aortic stenosis in six, and atrial fibrillation in 10), leaving a final number of 198 subjects who represented the population analyzed in this study.

Participant rheumatologists were provided with a form designed to capture all essential CV risk factor information, laboratory values, data on the clinical expression of rheumatoid arthritis, and current medical therapy (including medications for CV risk factor control), reported at the time of the visit. Rheumatoid arthritis state of activity was classified as high according to the need to administer a disease-modifying antirheumatic drug and in accordance with the measured Clinical Disease Activity Index (CDAI). All information was subsequently input into statistical software for the analyses.

Control Groups

For the purposes of this study, we selected two distinct groups suitable as control subjects. One hundred thirty-two healthy subjects with normal systemic blood pressure, serum glycemic levels, lipid profiles, and echocardiographic findings who were not receiving any medical treatment constituted the first group, defined as "healthy control subjects," with the sole aim of identifying the range of normal values of stress-corrected midwall shortening (sc-MS) and tissue Doppler mitral annular peak systolic velocity (S′) for defining the condition of combined C&L LVSD (for details, see the "Echocardiography" section). These 132 subjects were statistically comparable with the 198 patients with rheumatoid arthritis enrolled in the study for age, gender, and body mass index according to the following procedure: Gower's generalized distance from each of the healthy individuals was computed and ranked in ascending order. The distance was calculated using these variables ordered as follows: age, gender, and body mass index. We gave priority of matching to each variable (in this case, age first, then gender, then body mass index), and all variables were considered together in the statistical procedure. When we ran the analysis, we had a new disposition of the patients in the database: the healthy control subjects were merged with the patients with rheumatoid arthritis in ascending order. According to our input, the first healthy control subjects on the list had the highest probability of having similar age (the variable with the highest priority) as the patients with rheumatoid arthritis and some difference in body mass index (the variable with the lowest priority). The 132 healthy control subjects and 198 patients with rheumatoid arthritis were then defined by taking for every three close patients with rheumatoid arthritis the two closest healthy control subjects (selected from a pool of 186 patients). This large number ($n = 186$) of accessible patients made negligible the difference in all variables used for the matching between patients with rheumatoid arthritis and healthy control subjects.

Furthermore, a second control group, defined as the "non–rheumatoid arthritis group matched for comorbidities," was selected and compared with the study group of patients with rheumatoid arthritis; it was composed of 198 patients without rheumatoid arthritis, matched with those with rheumatoid arthritis for age, gender, body mass index, presence of hypertension, and presence of diabetes using the same statistical procedure described above. These 198 non–rheumatoid arthritis "control" patients were selected by taking the closest control subject for every patient with rheumatoid arthritis. These patients, who did not have rheumatoid arthritis, were selected from an original cohort of 437 consecutive patients who underwent clinical and echocardiographic evaluation at Villa Bianca Hospital during a CV assessment at a primary prevention clinic during the same recruitment period as for patients with rheumatoid arthritis. After the first selection, excluding 180 patients <35 or >80 years of age (to correspond to the age range of the study population with rheumatoid arthritis) and those with at least one risk factor for CV events, the 198 non–rheumatoid arthritis patients matched for comorbidities were selected from a final pool of 257 patients. Thus, the groups were matched on exposure (rheumatoid arthritis) and not heart structure and function (the end point of the study), so this cannot be considered a case-control study. Although prospective, it must be considered a study with a matched cross-sectional design.

All patients gave written informed consent, and the study was approved by ethics committees at all participating centers. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki as revised in 2000.