

Impaired diastolic function in active rheumatoid arthritis. Relationship with disease duration

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Abstract

Objective

Using digitized M-mode and Doppler echocardiography, we evaluated left ventricular (LV) function in 54 patients (43 women and 11 men; mean age 50 years) suffering from active rheumatoid arthritis (RA) without obvious cardiovascular disease, and compared them with 54 age- and sex-matched normal subjects.

Results

No differences were found in LV end-diastolic diameter, systolic function and parietal thickness between the patients and controls. However, a significant reduction in various indexes of LV diastolic function was found, including E/A (ratio of early to late filling waves of mitral inflow Doppler) and the peak lengthening rate of the LV diameter (an index of LV relaxation evaluated by M-mode echocardiography). The former was correlated with patient age and was independent of disease duration, while the latter was more markedly correlated with disease duration than with patient age.

Conclusion

The relationship between diastolic impairment and disease duration in active RA may open new perspectives in the study of RA-associated cardiovascular disease.

Key words

Rheumatoid arthritis, diastolic function, echocardiography.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease involving several organ systems. Cardiac involvement has been well documented, and nodular granulomas may be found in pericardial, myocardial and endocardial tissue. These alterations may be responsible for rheumatoid pericarditis, myocarditis and endocarditis, with fibrotic and sclerotic alterations of the cardiac valves that may cause congestive heart failure and death. Moreover, rheumatoid vasculitis may affect the coronary arteries (causing myocardial ischemia and infarction) and the pulmonary arteries (leading to severe pulmonary hypertension and right heart failure). These alterations may well be responsible for the increased cardiovascular mortality observed in patients with RA (1), although cardiac involvement is often reported as an autopsy finding in otherwise asymptomatic patients (2). Overt heart failure and systolic dysfunction are often preceded by alterations in left ventricular diastolic function, which may be clinically silent for years or even decades. This underscores the importance of identifying early signs of cardiac involvement in multi-system diseases that may involve the heart. Indeed, several studies have recently reported alterations in left ventricular (LV) diastolic function in RA (3-5). Since some LV diastolic function parameters can be profoundly influenced by age (6, 7), as well as by the presence of hypertension (8),

hypertrophic cardiomyopathy, infiltrative cardiomyopathy and ischemic heart disease (9), these factors should be considered when evaluating the possibility that the observed alterations in LV diastolic function are due to RA.

The aim of the present study was therefore to evaluate LV diastolic function in patients affected by active RA without any evidence of hypertension or underlying cardiac disease by digitized M-mode and Doppler echocardiography, two diagnostic methods that should be considered as complementary rather than interchangeable since they focus on different aspects of LV diastolic function (10, 11).

Patients and methods

Fifty-four consecutive patients with active RA who were referred to a rheumatology out-patient clinic were admitted to the study. All of them fulfilled the 1987 revised criteria of the American College of Rheumatology for RA (12). The disease was considered to be active if the patient had at least two of the following features: (i) 6 or more tender joints; (ii) 3 or more swollen joints (68 joints were examined for tenderness and 66 joints were examined for swelling); (iii) morning stiffness lasting more than 45 minutes; and (iv) erythrocyte sedimentation rate (ESR) (Westergren) higher than 25 mm.

The main clinical data for our patients are reported in Table I. Patients with

Table I. Main clinical features of the RA patients studied for left ventricular diastolic function. Blood pressure and heart rate values were comparable with those of 54 age- and sex-matched healthy control subjects.

Variable	RA patients	Controls
No. of cases	54	54
Males/females	11 / 43	11/43
Mean age	50.3 ± 14.1	50.1 ± 13.9
Mean systolic blood pressure	128 ± 13.5	124 ± 13.9
Mean diastolic blood pressure	78 ± 6.9	77 ± 6.8
Mean heart rate	74 ± 7.3	76 ± 7.3
Mean disease duration (years)	5.9 ± 6	—
Mean ESR	53 ± 19	—
RF positive	41 (76%)	—
Treated with prednisone (< 5 mg/day)	27 (50%)	—
Treated with second-line drugs* (%)	48 (88%)	—

* Gold salts, hydroxychloroquine, methotrexate, sulphasalazine.

hypertension, diabetes mellitus and clinical, radiological, electrocardiographic or echocardiographic evidence of cardiac disease (such as congestive heart failure, ischemic heart disease, idiopathic or secondary cardiomyopathy, pericarditis or valvular heart disease) were excluded from the study. The patient evaluation included a complete history and physical examination and all participants underwent routine laboratory investigations. Each patient had complete M-mode and Doppler echocardiographic examinations performed using a Hewlett Packard Sonos 1000 and a 2.5 MHz transducer.

Fifty-four age- and sex-matched normal subjects, free of signs and symptoms of cardiovascular disease, were chosen as a control group.

M-mode echocardiography

LV M-mode echocardiograms were recorded (paper speed 50 mm/sec) under two-dimensional control, with a simultaneous electrocardiogram, and were subsequently digitized, following the method of Gibson and Brown (13) as previously described (14). The following parameters were evaluated for each patient:

- LV end-diastolic diameter;
- LV mass using the method of Devereux-Reichek (15);
- Peak systolic shortening rate of the LV diameter, i.e. the peak rate of change of the LV dimension in systole, normalized by the instantaneous systolic dimension;
- Peak diastolic lengthening rate of LV diameter, i.e. the peak rate of change of the LV dimension in diastole normalized by the instantaneous diastolic dimension (+dD/dt).

All echocardiograms were blindly evaluated by a single expert technician who digitalized 5 consecutive cardiac cycles for each echocardiogram. Care was taken to optimize this analysis, following previously suggested recommendations (16)

Doppler echocardiography

Standard Doppler examination of LV filling was performed to obtain the transmitral flow profile with subjects in the lateral decubitus position. Doppler trac-

ings were obtained in the apical four-chamber view and peak transmitral flow velocities were recorded in the pulsed mode with the sample volume placed level within the tips of the fully open leaflets. Diastolic function was measured by the peak velocity of early ventricular inflow (E), peak velocity in late diastole during atrial systole (A) and the ratio of these velocities (E/A) which is usually > 1 in young normal subjects.

Statistical analysis

Statistical evaluation of the results was carried out using the t-test for independent values, Pearson's linear correlation and logarithmic regression. Linear multiple regression was used to detect those parameters that were significantly and independently associated with the +dD/dt and E/A values (17).

Results

In our RA patients, both the LV diastolic diameter and LV systolic function (as measured by the peak shortening rate) were similar to those measured in the control group. No difference was observed in the LV mass or in the heart rate between the two groups.

The Doppler E/A ratio (the ratio of the early to late filling waves of mitral inflow Doppler) was reduced to < 1 in 21 patients and in 14 controls. According to linear multiple regression analysis, only the patient age was significantly associated with E/A in our patients, while the LV mass, disease duration and arterial blood pressure were not relevant (Table II). As reported in Figure 1, the E/A ratio decreased with age in both RA patients and in age-matched controls; however, RA patients had significantly lower values than control subjects (1.1 ± 0.34 vs 1.32 ± 0.43 ; $p = 0.003$).

Peak lengthening rate

The peak lengthening rate of the LV diameter (+ dD/dt) was significantly lower in RA patients than in controls (4.6 ± 1.59 vs 5.7 ± 1.15 $p < 0.0001$) and 17 patients had values < 3.4/sec, i.e. the mean - 2 SD of normal controls. Stepwise multiple regression analysis showed that both age and disease duration were significantly and independently associated with +dD/dt. Disease duration

proved to be more relevant than age, while LV mass and arterial blood pressure were not relevant (Table III). The distribution of +dD/dt values with respect to disease duration is shown in Figure 2.

E/A and +dD/dt were slightly correlated to each other ($p = 0.04$), while no significant correlation emerged between diastolic function and the corticosteroid treatment or treatment with second line drugs.

Discussion

Impaired diastolic function is often a clinically silent alteration preceding systolic dysfunction. Echocardiography is a relatively simple technique that allows a non-invasive evaluation of LV diastolic function and the presence of alterations in LV diastolic function has been reported in RA patients by several authors (3-5). However, the clinical relevance of diastolic dysfunction and its possible relationship to disease activity, disease duration or concurrent underlying heart diseases has not been yet clarified.

We investigated a group of carefully selected patients with active RA but no evidence of concomitant cardiovascular diseases. In spite of normal LV systolic function and normal LV mass, we found

Table II. Linear multiple regression for the dependent variable E/A ($r = 0.73$; $r^2 = 0.53$).

Parameter	Beta	Standard error	p-level
Age	-0.746	0.098	0.000000
Disease duration	-0.051	0.096	0.6
LV mass	0.077	0.096	0.4
Blood pressure	0.038	0.097	0.8
Intercept			0.000000

Table III. Linear multiple regression for the dependent variable +dD/dt ($r = 0.60$; $r^2 = 0.36$).

Parameter	Beta	Standard error	p-level
Age	-0.409	0.114	0.0008
Disease duration	-0.526	0.113	0.00002
LV mass	0.096	0.112	0.4
Blood pressure	0.055	0.112	0.7
Intercept			0.000000

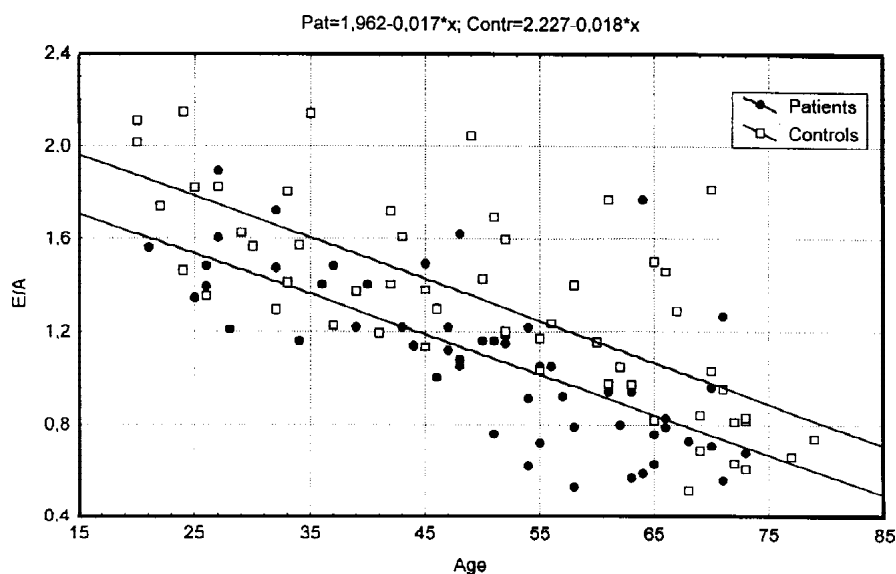


Fig. 1. Linear correlation between age and E/A ratio in 54 RA patients (lower line) and in 54 age- and sex- matched control subjects (upper line).

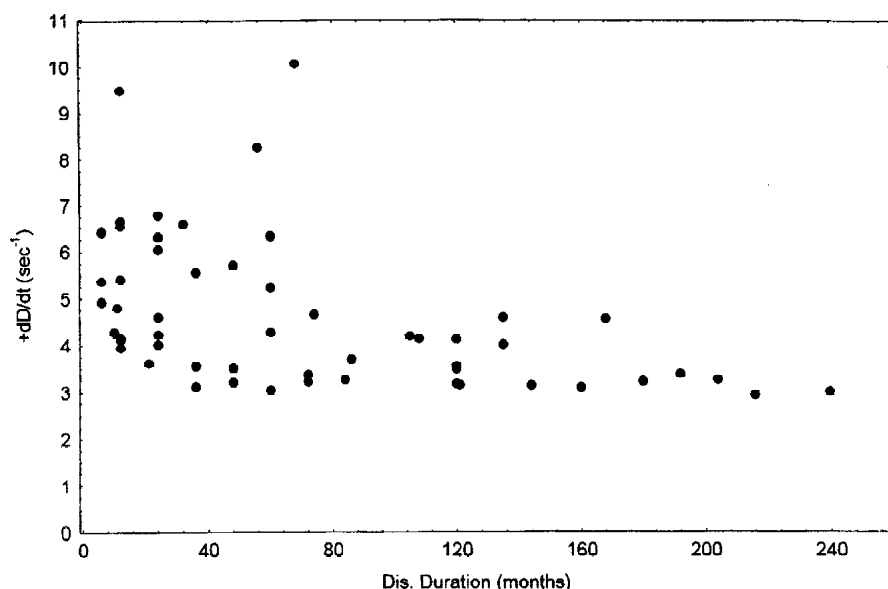


Fig. 2. Correlation between peak lengthening rate of left ventricular diameter (+dD/dt) and disease duration in 54 patients with active rheumatoid arthritis.

several alterations in LV diastolic function, with a reduction in the LV diameter peak lengthening rate (observed by digitized M-mode echocardiography) together with a reduction in the early filling wave of mitral inflow (by Doppler evaluation of mitral inflow). Besides confirming previous observations obtained by either Doppler (4) or M-mode echocardiography (3, 5), it is important to underscore that the simultaneous use of Doppler and digitized M-mode echocardiography in selected patients without the possible interference of underlying cardiac diseases may be able to add

important information to our current knowledge of cardiac involvement in active RA.

It has to be pointed out that the Doppler evaluation of mitral inflow and M-mode echocardiography investigate different aspects of LV diastolic function (10). Although the E/A ratio may be viewed as a simplistic and raw parameter in the analysis of diastolic function, there is little doubt that its alteration in patients matched for heart rate, age, sex, systolic function, LV mass and blood pressure may reveal possible signs of diastolic dysfunction (18). The well-known influ-

ence of age on the E/A ratio was confirmed by our results in both groups, although the inversion of the E/A ratio was observed at a younger age in the RA patients with respect to the control subjects, a finding which suggests the possibility of an earlier deterioration of diastolic function in active RA. A prospective study using a more complete Doppler echocardiographic analysis is now being carried out in our RA patients.

At variance with the E/A ratio, the other parameter of diastolic function, i.e. the peak lengthening rate of the LV diameter as measured by M-mode echocardiography (+dD/dt), was influenced not only by age, but also by disease duration. This further indicates that RA may accelerate the age-related progression of diastolic dysfunction. Indeed, +dD/dt was more markedly influenced by disease duration than by age.

Some controversy exists regarding the patient-to-patient variability of M-mode digitized echocardiography. However, when the analysis is optimized, as it was in this study, it represents a valuable tool to study diastolic and systolic function both in experimental models (19) and different clinical settings (20, 21).

To the best of our knowledge, ours constitutes the first report of a correlation between cardiac diastolic impairment and disease duration in RA. Two previous studies failed to find such a correlation. In the first, Rowe *et al.* (3) studied 22 RA patients with a mean disease duration of 13 years. This may be significant, since all our patients with RA lasting more than 6 years had low values (Fig. 2). In the second study, by Mustonen *et al.* (5), the lack of correlation between impaired diastolic function and disease duration could have been due to the small size of the sample (only 12 male patients were studied) and to the inclusion of patients with inactive disease (mean ESR 16 ± 3).

We still do not know the cause of diastolic impairment in RA patients. Necropsy studies occasionally reveal non-specific myocarditis (22), secondary amyloidosis (3, 5), rheumatoid granulomas within the heart (23) or vessel vasculitis (5, 24). Valvular disease is rarely detected in RA, while it is more frequent in systemic lupus erythematosus (25,

26). However, these events can not explain the very high frequency of diastolic impairment in RA patients and the presence of a similar impairment in other rheumatic diseases such as psoriatic arthritis and ankylosing spondylitis (3). Regarding the possibility of secondary amyloidosis, four of our patients with an abnormal peak lengthening rate of the LV diameter were further studied by means of Congo red staining of the periumbilical subcutaneous fat and in no cases were amyloid deposits found (data not shown).

Important factors underlying diastolic dysfunction are hypertension and LV hypertrophy (8). In our patient series the diastolic dysfunction could not be explained by LV mass differences since we selected patients with no evidence of hypertension and whose LV mass was comparable to that of the control group. Myocardial fibrosis has been detected at autopsy in RA, as well as in ankylosing spondylitis and systemic sclerosis, which are rheumatic conditions sharing with RA a high frequency of asymptomatic impairment of LV diastolic function (3, 27, 28). Inflammatory cytokines play an important role in the pathogenesis of RA and contribute to mediate not only local events but also the systemic acute phase response (29). Therefore, one can speculate that chronic cytokine release may lead to the deposition of connective tissue in the myocardium. Recent studies have suggested that inflammatory cytokines contribute to the development of atherosclerosis (30) as they can induce coronary intimal lesions and vasospastic responses in pigs' coronary arteries *in vivo* (31). Moreover, serum levels of all inflammatory cytokines were markedly higher in patients with atherosclerosis obliterans as compared with healthy subjects (32). This could contribute to explain the presence of a direct correlation between disease duration and echocardiographic abnormalities in our patients with active disease. This fact is of particular clinical interest as RA patients seem to suffer premature senescence with elevated mortality rates mainly due to cardiovascular diseases (1, 33, 34).

In conclusion, our study indicates a direct relationship between some of the

parameters of LV diastolic function and disease duration in patients with active RA. It is important to carefully evaluate diastolic function in such patients, looking for early modifications that may represent markers of cardiac involvement in this multi-system disease. Further prospective studies are needed to ascertain the prognostic relevance of diastolic dysfunction and to evaluate the role of disease control on the development of such abnormalities.

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