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The Assessment of Subclinical Cardiovascular Dysfunction in Treated Rheumatoid Arthritis

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ABSTRACT

Background and purpose: *Rheumatoid arthritis (RA) causes frequently cardiovascular complications, probably determined by early atherosclerosis in connection to chronic systemic inflammation. Purpose of our study was to assess subclinical cardiac and vascular dysfunction, and to evaluate the mechanisms of ventriculo-arterial interaction, in patients with correctly treated RA vs. normal subjects.*

Methods: *We evaluated 46 subjects (55±10 years, 2 men): 29 patients with seropositive treated RA (mean duration of 11±9 years), without documented cardiovascular or pulmonary disease, and 17 control subjects, matched for age, sex, and distribution of conventional major risk factors. All RA patients were under long-term treatment (more than 6 months) with Methotrexat + Sulfasalasine (22 patients) or Methotrexat + Sulfasalasine + Infliximab (7 patients). We determined biomarkers of inflammation (P-selectin, interleukines 1, 6, 10, 18, seric amiloid A, α-TNF, γ-interferon, C-reactive protein, anti-oxidated LDL antibodies), myocardial fibrosis (β-crosslaps) and ventricular overload (BNP). We assessed the parameters of cardiac function by standard and tissue Doppler echocardiography, intima-media thickness and arterial stiffness by "e-tracking" and "wave intensity analysis" (at the level of the right carotid artery), endothelial function by flow mediated dilation (FMD), and carotid-femoral pulse wave velocity by the Complior method.*

Results: *Biological parameters of inflammation, markers of myocardial fibrosis and of ventricular overload were not different between the 2 study groups. Also, parameters of subclinical cardiac and vascular function were similar between the two groups. RA patients had subclinical RV dysfunction, correlated to the duration of the disease. They also tended to have higher values of systolic pulmonary artery pressure than normals.*

Conclusion: *Correctly treated patients with RA, with controlled systemic inflammation, have normal LV, endothelial and arterial function. However, in the absence of documented pulmonary disease, they do have subclinical RV dysfunction, correlated with the duration of disease. This suggests an intrinsic RV myocardial involvement but, since pulmonary artery pressure was also higher, a secondary mechanism might be also involved.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease of uncertain cause. Although it has many general symptoms, the characteristic feature of the disease is persistent inflammatory synovitis, which affects usually peripheral joints and evolves symmetrically, causing alterations of the joint cartilage and bone erosions. Despite its destructive potential, RA has variable outcomes. Some patients develop only a slight joint discomfort of short duration, while others have progressive disease, with significant functional impairment.

The prevalence of RA in the general population is of approximately 0.8% (0.3 -2.1%), women being affected 3 times more frequently than men. The prevalence grows with age, while frequency differences between sexes decrease with the increase of age. The first signs of the disease appear usually during the 4th and 5th decades of life and 80% of patients develop the disease between the age of 35 and 50 (1, 2).

RA associates a cardiovascular risk and mortality rate 3-5 times higher than the general population matched for sex and age. Cardiovascular disease is responsible for 35-50% of the mortality excess in patients with rheumatoid arthritis (RA), being followed by cerebrovascular disease as second cause of mortality in these patients (3-5). Traditional atherosclerosis risk factors don't explain this excess of cardiovascular mortality and morbidity, indicating that other mechanisms may be involved, among which chronical inflammation is the most studied. Major cardiovascular events, such as myocardial infarction, unstable angina pectoris or sudden cardiac death occur approximatively 10 years earlier in patients with RA, suggesting that this disease, similarly to diabetes mellitus, represents a significant independent risk factor for early atherosclerosis (6). The immunological disorder and the systemic inflammation in RA play a major role in the development of early atherosclerosis and premature mortality. Factors determinating high cardiovascular mortality in patients with RA appear early in the natural history of the disease, because patients with newly diagnosed sero-positive RA have already elements of endothelial dysfunction (7) .

Consequently, the adequate control of chronic inflammation in RA might reduce cardiovascular risk. Many studies have demonstrated the fundamental role of inflammation in the pathogenesis of atherosclerosis. The presence of high grade systemic inflammation in RA might explain the development of cardiovascular disease (8). A series of similarities between atherogenic lesions and chronical synovitis have been underlined. Inflammation mediators from the synovial joint tissue reach systemic circulation in high concentrations and thus might affect the vascular endothelium and also the myocardium – generating proatherogenic lesions and myocardial fibrosis (9).

Despite the accumulated data regarding cardiovascular risk factors in RA, they mainly result from retrospective, not prospective studies.

The purpose of our study was to assess subclinical cardiac and vascular dysfunction, and to evaluate the mechanisms of ventriculo-arterial interaction, in patients with correctly treated RA versus normal subjects. ❑

METHOD

Subjects

46 subjects (55±10 years, 2 men) were enrolled into the study: 29 patients with seropositive treated RA (mean duration of 11±9 years), without documented cardiovascular disease or pulmonary disease, and 17 control subjects, matched for age, sex, and distribution of conventional major risk factors. All RA patients were under long-term treatment (more than 6 months) with Methotrexat + Sulfasalasine (22 patients) or Methotrexat + Sulfasalasine + Infliximab (7 patients).

Before measurements, all subjects refrained from alcohol consumption and intensive physical activity for 24 hours, and from caffeine consumption for 5 hours, in order to avoid the acute effects on endothelial function and oxidative stress (10, 11). All measurements were performed in a constant room temperature (25°). Subjects were evaluated by conventional echocardiography, tissue Doppler imaging, integrated assessment of endothelial and arterial function and ventriculo-arterial coupling, and biological assessment. All individuals gave their informed consent before participation, and the study protocol was approved by the Local Research Ethics Committee. All measurements were averaged from at least 3 consecutive cardiac beats.

Biological assessment

We determined biomarkers of inflammation (P-selectin, interleukins 1, 6, 10, 18, seric amyloid A, α-TNF, and γ-interferon, C - reactive protein, and anti-oxidated LDL antibodies), myocardial fibrosis (β-crosslaps) and ventricular overload (BNP).

Echocardiography

Conventional echocardiography was performed on a commercially available ultrasound machine (General Electric VIVID 7), using a 1.5-5 MHz transducer and consisted of M-mode, 2D, and Doppler blood flow measurements. M-mode tracings from the parasternal long axis view were used to measure aortic root, left atrium diameter, systolic and diastolic septal and posterior wall thickness, left ventricular diameters, fractional shortening, and left ventricular mass index (method of Devereaux with the application of Penn convention). Cross sectional images were recorded from the apex, and end-diastolic and end-systolic areas and left ventricular lengths were measured for the calculation of ejection fraction (modified biplane Simpson's method). For the evaluation of right ventricular systolic function we assessed, using the apical 4 chamber vue, the right ventricular fractional area change (FAS), as: (RV end-diastolic area- RV end-systolic area)/RV end-diastolic area (12)

Diastolic function was assessed by pulsed-wave Doppler of the transmitral flow; E/A ratio being calculated. Left ventricular inflow was recorded by color M-mode echocardiography, and flow propagation velocity was measured.

Tissue Doppler recordings were made in 4 incidences: parasternal long axis, apical four chambers, apical two chambers and apical three chambers, and were interpreted offline at the level of seven myocardial segments in order to assess longitudinal function from the mean velocities of six basal segments (from the apical four-chamber, two-chamber, and three-chamber view). Peak myocardial velocities in systole (STDI) and diastole (ETDI – early and ATDI – late diastolic waves) were measured.

On-line pulsed-wave tissue Doppler recordings were made at the level of the medial and lateral mitral annulus, as well as the lateral tricuspid annulus.

For the evaluation of the right ventricular function, we determined also, at the level of the lateral tricuspid annulus isovolumetric acceleration (IVA) and we calculated the RV myocardial performance index- RVMPI, according to current guidelines (12) as:

$$RVMPI = (IVCT + IVRT)/EjT$$

where *IVCT- isovolumic contraction time, IVRT- isovolumic relaxation time, EjT-ejection time*

2D - speckle tracking imaging was used in order to assess longitudinal myocardial deformation, according to the current recommendations (13). A frame rate of 70–80 frames/s was used during the whole examination, with an optimal sector width and image depth, without a dual-focusing option. Using off-line analysis, global longitudinal strain was obtained– a negative percent of deformation. We identified the frame in which LV endocardium was best defined and we traced manually the border of the endocardium, in order to identify the region of interest (ROI) between the endocardial and epicardial borders. All LV walls were divided into 3 sites: basal, medial, and apical. Cardiac cycle intervals were measured using pulsed wave tracing from the LV outflow tract (aortic valve opening – AVO, and aortic valve closure – AVC). Global longitudinal strain (GLS) was calculated from 18 ventricular sites from the apical chamber views.

We also calculated RV GLS, from 6 right ventricular sites, using the 4 chamber apical view.

Arterial structure and function

After resting supine for 15 minutes, arterial assessment was performed at the right common carotid artery (RCCA) level, using another ultrasound machine (ALOKA SSD 5500, α 10), with a high resolution ultrasound transducer (7.5 MHz linear array probe). *Intima-media thickness* (*IMT*), was measured 1 cm bellow the bulb of the RCCA.

Echo-tracking and wave intensity analysis were used to assess arterial stiffness, forward and backward waves propagation, and ventriculo-arterial coupling. Measurements were taken as mean of five beats. RCCA diameter waveforms change was obtained, and by calibration for blood pressure, ***augmentation index*** (***AIx***), an index of arterial stiffness was calculated according to the formula:

$$AIx = AP/PP \times 100\%$$

where AP is augmentation pressure (difference between the second and the first systolic peak on the arterial trace) and PP is pulse pressure.

Wave intensity (WI) was calculated according to the formula:

$$WI = (dP/dt)\,(dU/dt)$$

where P is blood pressure and U flow velocity, in respect to time (t). This is a validated method (14) that allows estimation of the forward and backward traveling arterial waves in the early and late systole (compression and expansion waves, respectively). As an index of ventriculo-arterial coupling, we measured the ***amplitude of the forward, compression wave*** (***CW***).

Finally, we assessed ***pulse wave velocity*** (***PWV***), using a validated non-invasive automated device (Complior, Artech Medical, Paris, France). After placing the transducers on the carotid and femoral arterial sites, carotid-femoral transit time (dt) has been measured. Distance (dD) traveled by the pulse wave was assessed with a zero-length measurement over the surface of the body, with a non-elastic tape. Pulse wave velocity was calculated as the distance divided by the transit time (dD/dt).

Simultaneously with arterial assessment, brachial arterial blood pressure was measured by an automated sphygmomanometer (Omron 705CP, Tokyo, Japan).

Endothelial function

Endothelial function was assessed with the same ALOKA 5500 α 10 machine. Internal diameter of the right brachial artery was monitored for 10 minutes: 1 min at rest, 5 min during a forearm ischemia induced by inflation up to 250 mmHg of a pneumatic forearm cuff, and 4 min after deflating the cuff. In order to minimize operator dependent error, a mechanical probe holder was used. Measurements were taken as a mean of five beats of every phase. ***Flow-mediated dilation*** (***FMD***) was calculated as the percent of maximal diameter change at the right brachial artery level, observed during reactive hyperaemia following deflation of the forearm occluding-cuff, according to the formula:

FMD = [(diameter after cuff deflation – resting diameter)/resting diameter] x 100%

also measured.

Reproducibility

We have reported detailed studies of reproducibility of tissue Doppler data elsewhere (15-17). Reproducibility of ultrasound assessment of arterial and endothelial function in our laboratory was measured in 20 subjects by two observers; intra-, and inter- variability are reported as standard deviation divided by its corresponding mean value, to give a coefficient of variation (CV in %) (18). ❑

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS software (version 16.0) (SPSS Inc. Chicago, Illinois). Results are presented as mean value ±standard deviation. Differences between groups were tested for significance using the independent samples t-test. Linear regression was used to investigate the relation between two parametric variables in the total population. ANCOVA univariate analysis of variance was used with heart rate as a covariate, to assess influence of heart rate on the arterial stiffness parameters (19). A $p<0.05$ for a two-tailed test was considered significant. ❑

RESULTS

Subjects

General characteristics of the study groups are shown in Table 1 and 2. There were no significant differences between the two groups for age, height, weight, body mass index, or distribution of classical cardiovascular risk factors. The incidence of already diagnosed chronic heart

	Control	RA
Age (yrs)	55.1 ± 10.1	55.5 ± 9,6
Sex (% male sex)	5.8%	3.4%
BMI	27.9 ± 5.3	27.0 ± 5.2
Systolic BP (mmHg)	125 ± 15	127 ± 19
Diastolic BP (mmHg)	77 ± 9	73 ± 11
Pulse pressure (mmHg)	50 ± 9	54 ± 12
Heart rate (bpm)	64 ± 9	67 ± 8
* BP = blood pressure		

TABLE 1. Demographical characteristics of the study groups

Parameter	Smoking	Diabetes	Hypertension	Dyslipidemia	Obesity	CHD
Total	5/46	4/46	26/46	23/46	14/46	8/46
Control	5/17	3/17	10/17	10/17	5/17	4/17
RA	0/29	1/29	16/29	13/29	9/29	4/29

TABLE 2. Distribution of classical risk factors and known chronic heart disease (number of patients)

Parameter	Control	RA	p	Reference values
P selectin	80.5 ± 23.7	88.2 ± 22.5	NS	14.9±1.3 ng/ml
Il 1	20.2 ± 11.6	22.4 ± 14.7	NS	36.1±21.7 pg/ml
Il 6	15.9 ± 6.4	20.9 ± 11.7	NS	0.9 - 4.3 pg/ml
Il 10	161.1 ± 339.2	443.8 ± 806.7	NS	0 - 13. 7 pg/ml
Il 18	253.1 ± 162.3	318.7 ± 174.9	NS	250.3±76.5 pg/ml
SAA	64.6 ± 49.1	72.1 ± 52.3	NS	9.6±7.30 µg/ml
TNF α	107.5 ± 28.9	171.9 ± 201.9	NS	1.2 -15.3 pg/ml
γ Ifn	20.8 ± 9.4	73.7 ± 183.5	NS	15.4 ± 3.8 pg/ ml, very high >100
Ac anti oxidated LDL	232.9 ± 54.1	197.3 ± 63.5	NS	483 ± 79 nEq/ml
Beta cross-laps	0.7 ± 0.3	0.6 ± 0.3	NS	≤ 0.85 ng/ml
BNP	3.03± 0.7	3.6 ± 0.4	<0.05	0.5 - 30 pg/ml
C reactive protein	13.9 ± 1.4	30.6 ± 61.7	NS	1.08±9 mg/l

*Il - interleukin, SAA-serum amyloid A, TNF-tumor necrosis factor, Ifn-interferon, BNP-brain natriuretic peptide

TABLE 3. Biological assessment- RA *vs*. control group

disease was similar in the 2 study groups. None of the RA patients had known family history of rheumatoid arthritis or other systemic disease.

Biological assessment

There was no significant difference between biological markers of inflammation, myocardial fibrosis and ventricular overload between controls and RA (Table 3). We noticed in both groups elevated values of some markers of inflammation (P selectin, interleukin 6 and 10, serum amyloid A, TNF α, γ interferon and C reactive protein).

	Controls	RA	p
Aortic root diameter (mm)	30.9 ± 2.5	31.1 ± 3.6	NS
Left atrium diameter mm)	37.9 ± 4.5	37.6 ± 5.5	NS
Septal thickness (mm)	8.5 ± 1.5	9.4 ± 1.6	NS
PW thickness (mm)	8.6 ± 0.9	9.0 ± 1.5	NS
LVEDD (mm)	45.1 ± 4.6	46.1 ± 5.2	NS
LVESD (mm)	31.1 ± 5.4	31.0 ± 5.3	NS
LVMI (g/m^2)	101.7 ± 115.7	86.6 ± 31.1	NS
EF (%)	58.5 ± 3.9	59.6 ± 5.0	NS
FS (%)	31.5 ± 5.3	32.6 ± 7.8	NS
E/A ratio	1.0 ± 0.2	1.1 ± 0.3	NS
FVP (cm/s)	52.4 ± 16.7	54.0 ± 15.6	NS
IVRT (ms)	95.7 ± 9.8	90.3 ± 12.4	NS
E/ETDI	11.1 ± 2.9	10.3 ± 3.8	NS
E/FVP	1.5 ± 1.0	1.4 ± 0.6	NS
Longitudinal function			
Mean STDI	5.2 ± 0.8	5.7 ± 0.7	NS
STDI medial mitral annulus (cm/s)	5.8 ± 0.9	7.2 ± 1.5	NS
STDI lateral mitral annulus (cm/s)	7.1 ± 2.1	8.7 ± 2.2	NS
Mean ETDI	6.5 ± 1.6	6.9 ± 1.8	NS
Mean ETDI/ATDI	1.1 ± 0.5	1.1 ± 0.4	NS
Global LS (%)	-20.3 ± 3.6	-19.2 ± 1.3	NS

*PW = posterior wall; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVMI = left ventricular mass index; EF = ejection fraction; FS = fractional shortening; FVP = flow propagation velocity; IVRT = isovolumic relaxation time; STDI = systolic velocity; ETDI = early diastolic velocity; ATDI = late diastolic velocity; Global LS = global longitudinal strain;

TABLE 4. Standard echocardiographic data and myocardial velocities (cm/s) assessed by tissue Doppler imaging in the study groups (mean ± SD)

Markers of myocardial fibrosis were in normal limits in both study groups. BNP had significantly higher values in the RA group, but both values were in normal range.

There were no statistical significant correlations between biological markers and the echocardiographic parameters (standard, Tissue Doppler) or those of vascular function.

Parameter	Controls	RA	p
Transversal diameter of RV (mm)	27.4 ± 4.0	28.3 ± 4.8	NS
TAPSE (mm)	22.6 ± 4.5	26.0 ± 3.3	NS
FAS (%)	42.8 ± 5.6	40.7 ± 6.5	NS
S TDI tricuspid annulus (cm/s)	9.4 ± 1.9	8.2 ± 1.9	0.04
IVA lateral tricuspid annulus (cm/s2)	3.1 ± 0.9	2.3 ± 1.0	0.04
RV TDI MPI	0.66 ± 0.3	0.52 ± 0.2	0.04
RV GLS (%)	-18.6 ± 3.8	-21.9 ± 4.8	0.03
SPAP (mm Hg)	20.9 ± 10.1	28.8 ± 10.7	0.02
*TAPSE = tricuspid annular systolic excursion; SPAP = systolic pulmonary artery pressure			

TABLE 5. RV structural and functional parameters (standard echocardiography and TDI, mean ± SD)

Echocardiography

Conventional echo data are listed in Table 4. There were no statistical significant differences between the 2 groups and the values obtained were in the normal range. Myocardial systolic and diastolic velocities, as well as GLS, assessed by tissue Doppler and speckle tracking, are also shown in Table 4.

Regarding the evaluation of the right heart, standard echocardiography parameters were not different between the 2 study groups. TDI tricuspid annular velocities, IVA, MPI and RV GLS were significantly lower in the RA group. RVGLS inversely correlated with the duration of the disease (r=-0.45, p=0.04) (Figure 1). Although SPAP was normal in both study groups, SPAP values were significantly higher in the RA group (Table 5).

None of the examined patients presented hemodynamic significant valvular heart disease. We detected only mild or medium regurgitation, with no valvular stenosis (Table 6).

Parameter	Controls	RA	p
IMT (mm)	0.7 ± 0.1	0.6 ± 0.2	NS
β index	7.3 ± 1.7	13.1 ± 13.9	NS
Arterial compliance	0.8 ± 0.3	0.6 ± 0.2	NS
Augmentation index (%)	17.1 ± 9.5	18.0 ± 7.9	NS
FMD (%)	11.6 ± 3.6	12.1 ± 6.6	NS
PWV carotid-femoral (m/s)	10.1 ± 1.5	9.9 ± 2.0	NS
*IMT = intima media thickness; FMD = flow mediated dilatation; PWV = pulse wave velocity.			

TABLE 7. Vascular function parameters (mean ± SD)

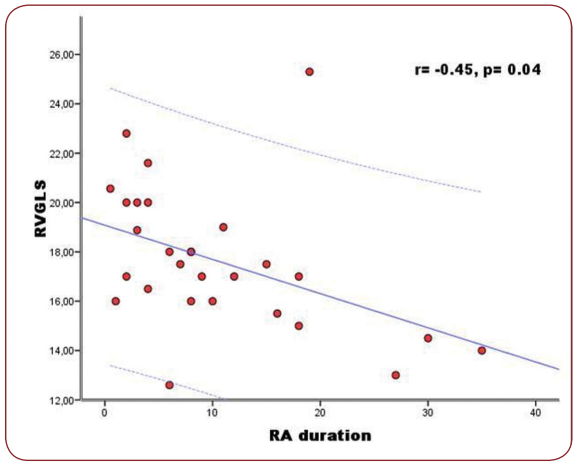

FIGURE 1.

Arterial and endothelial function

The results of the assessment of arterial and endothelial functions are shown in Table 7. The vascular function parameters were in normal ranges for the age of the patients, with no statistical significant values between the 2 groups.

Reproducibility

Reproducibility of tissue Doppler data was previously reported (14-16); interobserver variability was ± 6.8% for the radial velocities, and

Parameter	Controls					RA				
Grade of regurgitation	Gr.0	Gr.1	Gr.2	Gr.3	Gr.4	Gr.0	Gr.1	Gr.2	Gr.3	Gr.4
Mitral regurgitation	2	5	1	0	0	9	11	2	0	0
Aortic regurgitation	6	2	0	0	0	18	4	0	0	0
Tricuspid regurgitation	1	5	2	0	0	2	16	4	0	0

TABLE 6. The presence and grading of valvular regurgitation in the 2 study groups

Parameter	Intraobserver variability	Interobserver variability
IMT	±3.7%	±4.3%
AIx	±17.8%	±8.4%
AC	±6.2%	±6.6%
β index	±3.8%	±1.2%
FMD	±2.5%	±1.7%
PWV	±3.3%	±2.6%

TABLE 8. Reproducibility of vascular function parameters (Bland Altman coefficient) (17)

Parameter	MTX + SSZ	MTX+SSZ+antiTNF	p
Il6	17.6 ± 11.1	29.7 ± 8.7	0.044
SAA	58.3 ± 45.5	110.8 ± 55.3	0.05
Beta crosslaps	0.5 ± 0.2	0.9 ± 0.3	0.015
LVSF	29.8 ± 7.4	39.1 ± 5.1	0.012

TABLE 9. Subgroup analysis of the RA patients (statistically significant differences, mean ± SD)

between ± 2.0% and ± 6.1% for the longitudinal velocities, while intraobserver variability was ± 2.7% for the radial velocities, and between ±1.8% and ± 2.5% for the longitudinal velocities. Reproducibility of the assessment of arterial and endothelial functions is shown in Table 8 (18).

Subgroups

Regarding the subgroups analysis of the RA patients, there were no statistical relevant differences between most of the biological parameters, excepting Il6, SAA and beta-crosslaps. Concerning echocardiographic parameters, the LVEF was significantly higher in the subgroup treated with anti TNF agents. Differences between subgroups are shown in Table 9. ❑

DISCUSSION

RA is a chronic inflammatory disease, with headquarters at the joint level, but which can affect most of the main inner organs. Having similar mechanisms with those of atherosclerosis (Table 10) and being frequently associated with classical atherosclerosis risk factors (Table 11), RA comes with high cardiovascular morbidity and mortality (4-6, 9). Recent studies have suggested a much higher cardiovascular affectation in RA than in normals matched in sex and age,

Parameter	Atherosclerosis	RA
Activation of macrophages		
• TNFα	↑	↑
• Metalloproteinase	↑	↑
• Interleukin 6	↑ (unstable angina pectoris)	↑
Activation of mastocytes		
Activation of T cells		
• Interleukin 2 soluble receptor	↑ (unstable angina)	↑
• CD3+DR+	↑(unstable angina)	↑
• CD4+CD28-	↑(unstable angina)	↑
• CD4+IFNγ+	↑(unstable angina)	↑
• Th1/Th2 balance	↑ Th1	↑ Th1
Activation of B cells		
• Autoantibodies (LDLox, HSP)	0 or ↑	0 or ↑
• Rheumatoid factor	0	↑
C reactive protein	↑(unstable angina)	↑↑
Adhesion molecules (VCAM-1, ICAM-1, E selectin, P selectin)	↑	↑
Endothelin	↑	↑
Neoangiogensis	↑	↑
Possible antigenes	HSP, LDLox, infectious agents	collagen II, cartillage antigenes, HSP, infectious agents

TABLE 10. Similarities between atherosclerosis and RA (9)

Cardiovascular risk factors	Implication in RA	The association between metabolic disorders and inflammatory response in RA	Risk reduction through inflammation supression
Obesity/insulin resistence			Steroids and sulfasalasine raise pradoxically insulin sensitivity in RA
• Redistribution of adipose tissue	+	No data	
• Hyperinsulinemia	+	+	
• Insulin resistance	++	+	
Dyslipidemia			Antiinflammatory therapy raises HDL-cholesterol; there are no data on the effects of the rest of the lipid profile
• Free fatty acids	+	+	
• Triglycerides	+/0	+	
• ↓ HDL chol	++	++	
• Small and dense LDL	+	+	
• Lipoprotein (a)	++	+	
Endothelial dysfunction			sICAM lowers at Sulfasalasine; terapia Anti TNFα therapy ameliorates FMD
• sICAM 1	++	+	
• vWF	+	+	
• Microalbuminuria	+	+	
• Low vascular reactivity	++	+	
• Arterial stiffness	++	+	
Oxidative stress			There are no studies in RA, but ibuprofene raises the levels of antioxidants in neoplasy
• Malonyldialdehyde (MDA)	+	+	
• ↓ Vitaminic antioxidants	+	+	
Hemostasis alterations			Limited data
• Fibrinogen	++	++	
• PAI 1	+	0	
Blood pressure	+	No data	No data.
Hemostasis alterations			Steroids lower homocysteine levels in RA
• ↓ Vitamin B6	++	+	
• Homocysteine			

TABLE 11. Cardiovascular risk factors in RA, their association with inflammatory response and the effects of inflammation supression on them (26)

even similar to that in diabetes mellitus (6, 20). There are multiple therapeutic alternatives in RA, which act through antiinflammatory and immunosupressive mechanisms and often lead to a limitation of joint disease and augmentation of the quality of life (Table 12) (1, 2, 21-25). Their effects on subclinical cardiovascular dysfunction has been little studied until now (21-25, 26).

Our study has aimed to perform an extensive cardiovascular evaluation in patients with long term (over 6 months) treated RA, through biological methods, quantifying inflammation, myocardial fibrosis and cardiac dysfunction, as well as through modern ultrasonographic methods, compared to normal subjects, matched in sex, age, and distribution of classical cardiovascular risk factors. The purpose was to verify the efficacy of antirheumatoid therapies on subclinical atherosclerotic disease.

The biological parameters used were those mentioned in literature to be associated with inflammation in RA as well as in early atherosclerosis (8, 9, 27). We also used markers of myocardial fibrosis and ventricular overload (BNP). Concerning the echocardiographic examination, we have extended beyond standard parameters, using new methods, such as Tissue Doppler Imaging or Speckle Tracking, which allow the de-

Therapy	Characteristics
Lifestyle changes	Joint rest, physiotherapy, diet (including omega3 rich principles, with antiinflammatory effect through interference with the metabolism of arachidonic acid).
NSAIDs	They determine the inhibition of COX enzymes and lower the production of prostaglandines, prostacyclines and tromboxane, having antiinflammatory, analgesic and antipiretic effects.
DMARDs	Methotrexate, gold salts, D-penicilamine, synthetic antimalarics, sulfasalasine.They belong to different medication classes, but have many similar therapeutic effects. They determine clinical amelioration, but can also modify some serological parameters, such as levels of rheumatoid factor, C reactive protein and ESR.
Systemic corticosteroids	In monotherapy or low doses (< 7.5 mg/day), in association with DMARDs.
Anticytokines and anti-Il	Etnarecept (Type II TNF receptor, attached to IgG1), Infliximab (monoclonal antiTNF antibody), Adalimumab (monoclonal antiTNF antibody), Anakinra (Il1 receptor antagonist). Parenteral administration has important effects in patients in whom DMARD therapy has failed.One of the major side effects is diminishing the resitance to infections.
Immunosupression	Azathioprine, Leflunomide, Cyclosporin, Cyclophosfamide. Have similar effects with DMARDs.
Surgery	In patients with severe joint disease (arthroplasty, joint prosthesis, synovectomy).
* NSAIDs = Non Steroidal AntiInflammatory Drugs; DMARDs = Disease Modifying Antirheumatic Drugs; anti-Il = antiinterleukines; COX = Cyclooxigenase	

TABLE 12. Therapeutic strategies in RA (1, 29)

tection of early systolic or diastolic dysfunction. We also focused on the ultrasonographic evaluation of ventriculo-arterial coupling, because arterial stiffness induced by atherosclerotic determinations may lead over time to cardiac dysfunction. (28). Endothelial function was determined through vascular ultrasound using the method of flow mediated dilation. Also, we have included in our examination the measurement of pulse wave velocity (COMPLIOR method), as supplementary marker of arterial rigidity, mainly of great arteries.

The right heart was also evaluated, because of the frequent occurence of pulmonary hypertension and consequent right ventricular dysfunction in autoimmune disease with associated vasculitis (29, 30).

The results of our study have shown that in treated RA there are no significant differences compared to normals. Biological parameters of inflammation, myocardial fibrosis and ventricular overload, as well as ultrasonographic determination of systolic and diastolic function, were similar in the 2 study groups and were situated in normal range. Both subjects with RA and normals, had an endothelial function (assessed through FMD) and an arterial stiffness, according to their age.

An important finding of our study concerns the right heart: RA patients, although correctly treated, have subclinical RV dysfunction, correlated to the duration of the disease. Also, RA patients tend to have higher values of systolic pulmonary artery pressure than normals. This should be taken into consideration for the follow up of patients with RA and also when implementing prevention therapies.

Regarding the 2 subgroups of RA patients (Methotrexate + Sulfasalasine vs. Methotrexate +Sulfasalasine +AntiTNF-Infliximab) the studied biological and ultrasound parameters were in their majority similar, with some exceptions. In the infliximab group, we have noticed significantly higher values of interleukine 6 and SAA (suggesting less control of inflammation) as well as of β crosslaps (as markers of subclinical myocardial fibrosis). On the other hand, the infliximab group had a higher LV shortening fraction, probably acting as an early compensatory mechanism for myocardial fibrosis.

The results of our study indicate that current therapeutic methods in RA are efficient not only regarding the control of joint disease, but also of systemic inflammation and cardiovascular morbidity. ❑

CONCLUSION

Patients with correctly treated RA and controlled systemic inflammation, regardless of the disease duration, do not have subclinical cardiac and vascular dysfunction. Being considered a disease with significant cardiovascular risk, similar to diabetes, RA needs quick implementa-

tion of cardiovascular prevention and an early start of treatment. ❑

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