# Myocardial Dysfunction in Rheumatoid Arthritis: A Controlled Tissue-Doppler Echocardiography Study

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***ABSTRACT.*** ***Objective.*** To determine the sensitivity and accuracy of tissue-Doppler echocardiography (TDE) to assess myocardial contractility. Heart failure is one of the determinants of the excess in mortality in patients with rheumatoid arthritis (RA).

***Methods***. Consecutive RA patients with normal clinical cardiac examination were prospectively included and compared to 27 controls. All underwent conventional echocardiography, and systolic and diastolic strain rate (SR) were determined by TDE.

***Results.*** Twenty-seven patients with RA were included (mean age 50 ± 10 yrs, disease duration 8 ± 6 yrs). Mean disease activity score was 4.3 ± 1.6, C-reactive protein 23 ± 32 mg/l. When compared to controls (50 ± 9 yrs), patients with RA had increased left ventricular mass (99 ± 24 vs 80 ± 25 $g/m^2$, p = 0.009), and there was a trend for left atrial enlargement (31 ± 3 vs 29 ± 6 mm, p = 0.06). Fractional shortening and systolic SR did not differ between groups. Diastolic function, as estimated by the E/A Doppler velocity ratio was similar in both groups (p = 0.18). However, diastolic SR was strikingly reduced in patients with RA versus controls (3.7 ± 1.3 vs 5.5 ± 1.1$s^{-1}$, p < 0.001) with 18/27 patients with RA having marked reduced diastolic SR (SR < 4$s^{-1}$). None of the RA characteristics was associated with significant differences in TDE measurements.

***Conclusion.*** TDE identifies impaired diastolic function in patients with RA that may not be detected by conventional measurements. (First Release Sept 1 2007; J Rheumatol 2007;34:2005–9)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS MYOCARDIAL DIASTOLIC FUNCTION
TISSUE-DOPPLER ECHOCARDIOGRAPHY

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, of unknown origin, affecting about 0.3-0.5% of the adult general population in different countries[1,2]. Among extraarticular features, the existence of a high risk of cardiovascular disease, particularly atherosclerosis, has emerged in recent years as a cause of morbidity and mortality[3,4].

Chronic heart failure (CHF) is a clinical syndrome that is the final manifestation of nearly all forms of heart disease[5]. As a consequence, its prevalence is increased in patients with RA when compared to non-RA patients[6]. Moreover, inflammation appears as a key underlying mechanism in the initiation and progression of both atherosclerosis and CHF[3,6]. Some echocardiographic studies have previously been performed in RA; the small number of patients and the absence of a control group in the majority of the studies did not allow clear conclusions but they suggested a higher prevalence of asymptomatic diastolic dysfunction associated with preserved systolic function[7,8]. Although easy to use, echocardiography has several limitations including the effect of loading conditions on measurements. Tissue-Doppler echocardiography (TDE) is a recent ultrasound technique allowing direct measurement of regional myocardial velocities and strain rate (SR). SR is a powerful indicator of myocardial function, independent of myocardial translational motion, less dependent on loading conditions, and far more sensitive than conventional measurements[9,10].

Our aim was to investigate left ventricular (LV) function in RA patients without symptoms of CHF using TDE.

## MATERIALS AND METHODS

Consecutive outpatients who were visited by one rheumatologist (YA) and fulfilled the revised criteria of the American College of Rheumatology for RA[11] were included after informed consent. Additional inclusion criteria included the absence of signs and symptoms suggesting CHF as judged by the investigator, ischemic heart disease, or previous systemic hypertension; patients treated with anti-tumor necrosis factor (TNF) drugs were also excluded. All patients with RA underwent examination, electrocardiogram (ECG), routine laboratory tests, conventional echocardiography, and TDE imaging; their results were compared to those of 27 age and sex matched controls. The protocol was approved by the appropriate ethics committee.

Atherosclerotic risk factors were defined in both groups as follows: hypertension was defined by a systolic blood pressure ≥ 140 mm Hg, dias-

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tolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medication. Diabetes was defined as fasting glucose ≥ 7 mmol/l (1.26 g/l) or current use of antidiabetic drug. Dyslipidemia included patients with low density lipoprotein-cholesterol ≥ 4.13 mmol/l (1.6 g/l), or current use of lipid lowering drugs, high density lipoprotein-cholesterol < 1.03 mmol/l (0.4 g/l), triglyceridemia ≥ 1.69 mmol/l (1.5 g/l), or current use of fibrate. Current smokers were defined as subjects reporting at least one cigarette/day.

All standard echocardiography and TDE (ATL HDI 5000 system- ATL, Bothell, WA, USA) were recorded by the same experienced cardiologist (CM); conventional measurements including LV cavity dimensions, left atrial (LA) diameter, wall thickness, fractional shortening (FR), and transmitral flow velocities were assessed as recommended. In addition, LV mass was measured according to Penn convention: [LV mass (g) = 1.04([LV end-diastolic diameter + septal thickness + posterior wall thickness]$^3$ – LV end-diastolic diameter) – 13.6]. An indexed LV mass was considered abnormal if > 111 g/m$^2$ in men and > 10 5g/m$^2$ in women, as recommended[12].

Radial LV thickening was assessed using color M-mode TDE as described[13,14]. Briefly, acquisitions were performed in posterior wall from a short axis view at the level of papillary muscle; myocardial wall motion velocities were extracted blindly in controls and subjects (HDI-Lab software) in the endocardium and epicardium to determine peak systolic, and early-diastolic SR: [SR = (endocardial-epicardial velocity) / distance between endocardium and epicardium]. Interobserver variability of TDE measurements in our laboratory has been described[15].

Data (mean ± SD) were compared in patients with RA versus controls using Student's t-test, chi-square analysis, or Fisher exact test as indicated ($p < 0.05$ for significance in all comparisons; Statview software).

## RESULTS

From November 2005 to March 2006, 29 consecutive patients with RA were screened. Two patients with previous hypertension were not included; results are therefore presented for 27 patients with RA and compared to 27 matched controls. Their baseline characteristics are presented in Table 1. Atherosclerosis risk factors were similar in patients with RA and controls; heredity was not investigated. Duration of the disease was 8.3 ± 5.7 years, and 15 patients had disease for more than 5 years. All patients had stable treatment with low-dose prednisone (< 10 mg/day) in association with methotrexate (15–20 mg/wk); none was treated with anti-TNF drugs (exclusion criterion) or nonsteroidal antiinflammatory drugs (NSAID). ECG showed no abnormality. Hemodynamic characteristics and echocardiographic and TDE results in both patients with RA and controls are shown in Table 2. Patients with RA had increased LV mass ($p = 0.009$) when compared to controls, and there was a trend for more patients having LV hypertrophy, as currently defined, when compared to controls (11/27 vs 4/27, respectively, $p = 0.06$). There was a trend for LA enlargement in patients with RA versus controls (31.4 ± 3.4 vs 29.0 ± 5.7 mm, $p = 0.06$). In addition, one patient with RA exhibited asymptomatic limited pericardial effusion. Systolic function assessed by fractional shortening did not differ between groups (Table 2). Transmitral flow velocities analysis by conventional Doppler showed no difference between groups regarding the E/A ratio (1.05 ± 0.26 vs 1.17 ± 0.41, $p = 0.180$), or the number of patients with an E/A ratio < 1 (10/27 vs 8/27, $p = 0.702$). Patients with RA had increased systolic pulmonary artery pressure although all values remain within normal range (Table 2).

*Table 1.* Demographic and baseline characteristics of patients with RA and controls.

| | RA Patients (n = 27) | Controls (n = 27) |
|---|---|---|
| Age, yrs | 50.4 ± 10.3 | 50.3 ± 9.5 |
| Male/female, n | 2/25 | 2/25 |
| Current smoker, n (%)* | 3 (11.1) | 4 (14.8) |
| Hypertension treated, n* | 0 | 0 |
| Abnormal lipid tests, n (%)* | 3 (11.1) | 4 (14.8) |
| Diabetes, n (%)* | 1 (3.7) | 0 |
| RA duration, yrs/n patients > 5 yrs (%) | 8.3 ± 5.7/15 (55.6) | NA |
| Disease activity score/n patients > 3.2 (%) | 4.3 ± 1.6/18 (66.7) | NA |
| C-reactrive protein, mg/l | 22.9 ± 31.7 | NA |
| Erythrocyte sedimentation rate, mm/h | 23 ± 19 | NA |
| Positive rheumatoid factor, ELISA, n (%) | 16 (59.3) | NA |
| Positive anti-CCP2 antibodies, ELISA, n (%) | 21 (77.8) | NA |

Unless otherwise indicated, numeric values are presented as mean ± SD; categorical variables are presented as n (%). * Atherosclerotic factors are defined in the text.

When regarding TDE measurements, no difference could be demonstrated between groups for systolic SR, whereas patients with RA had strikingly lower diastolic SR than controls (Table 2, Figure 1). Two patients with RA had reduced systolic SR < 2.0 versus none in controls (p = NS) and 18 had reduced diastolic SR < 4.0 s$^{-1}$ versus none in controls ($p < 0.0001$). Although no difference could be demonstrated between groups regarding hemodynamic and demographic data, we investigated the possible effect of these factors on diastolic SR. In univariate analysis, the existence of altered diastolic SR was not influenced by age ($p = 0.65$), heart rate ($p = 0.93$), systolic blood pressure ($p = 0.12$), or diastolic blood pressure ($p = 0.65$). Lastly, no correlation could be shown between RA characteristics and TDE measurements; duration of RA did not account for part of the observed differences.

## DISCUSSION

The main findings of our controlled study indicate that: (1) cardiac asymptomatic RA patients exhibit myocardial abnormalities: increased LV mass, a trend for LA enlargement, and mainly marked reduced diastolic function; and (2) TDE is an accurate and sensitive method to examine myocardial function and should be considered in this setting.

Assessment of LV function in patients with suspected cardiomyopathy is commonly performed by echocardiography. Some measurements such as fractional shortening, LV ejection fraction, transmitral flow velocity pattern by Doppler are used in routine clinical practice. These indexes are, however, load-dependent, and we believe that their measurement is not sensitive enough[10,13]. TDE is a recent method that allows the

*Table 2.* Hemodynamic, echocardiographic, and TDE results in patients with RA and controls.

| | RA Patients, n = 27 | Controls, n = 27 | RA vs Controls | Normal Values* |
|---|---|---|---|---|
| Systolic arterial pressure, mm Hg | 125 ± 10 [105–135] | 121 ± 8 [110–140] | 0.160 | < 140 |
| Diastolic arterial pressure, mm Hg | 73 ± 8 [55–80] | 76 ± 7 [60–85] | 0.336 | < 90 |
| Heart rate, beats/min | 73 ± 10 [53–95] | 73 ± 11 [53–95] | 0.944 | [60–90] |
| LV end-diastolic diameter, mm | 46 ± 4 [38–53] | 46 ± 4 [38–55] | 0.703 | [35–55] |
| Left atrial diameter, mm | 31 ± 3 [25–39] | 29 ± 6 [18–39] | 0.063 | [28–42] |
| Septum thickness, mm | 10 ± 1 [7–12] | 9 ± 2 [6–12] | 0.104 | [9–11] |
| Posterior wall thickness, mm | 9 ± 1 [7–11] | 9 ± 2 [6–12] | 0.610 | [9–11] |
| Myocardial mass/body surface, g/m$^2$ | 99 ± 24 [52–142] | 80 ± 25 [45–154] | 0.009§ | Men: < 111 g/m$^2$ Women: < 105 g/m$^2$ |
| LV hypertrophy, n | 11 | 4 | 0.06 | See upper |
| Fractional shortening, % | 37.9 ± 4.8 [31.9–53.2] | 37.8 ± 5.2 [29.3–51.2] | 0.935 | [28–42] |
| Transmitral E/A ratio | 1.05 ± 0.26 [0.64–1.57] | 1.17 ± 0.41 [0.55–2.11] | 0.180 | > 1 |
| Systolic pulmonary artery pressure, mm Hg | 31 ± 4 [23–39] | 28 ± 4 [20–37] | 0.015§ | < 40 |
| Systolic SR ($s^{-1}$) | 3.4 ± 1.0 [1.2–4.9] | 3.8 ± 1.4 [2.0–7.9] | 0.226 | [3–5] |
| Diastolic SR ($s^{-1}$) | 3.7 ± 1.3 [0.6–6.62] | 5.5 ± 1.1 [4.0–8.1] | < 0.001§ | [5–7] |

Unless otherwise indicated, numeric values are presented as mean ± SD [min–max]. *: expected values defined in normal population of similar age and considered as normal values. §: Statistically significant difference. Student's t-test for comparison.

direct and reliable measurement of myocardial velocities and SR that is calculated from the local difference in wall motion velocity. TDE has been extensively validated in animal models versus sonomicrometry and pressure-volume relations[16] and both controls and patients with myocardial infarction versus 3-dimensional Tagged magnetic resonance imaging ($r < 0.85$ for all comparisons)[17]; systolic and diastolic SR provide quantitative assessment of myocardial systolic and diastolic function respectively[9,18]. Indeed, systolic SR is able to detect subtle myocardial systolic dysfunction in various conditions, including ischemic and non-ischemic cardiomyopathies[10,13,15,19,20]; diastolic SR provides meaningful information concerning diastolic function and is useful to differentiate physiological from pathological pressure-overload in an animal model, and normal from abnormal diastolic function, as assessed in athletes versus patients with hypertension or hypertrophic cardiomyopathy[15,18,21,22].

Few echocardiographic studies have been performed in RA patients with or without clinical evidence of CHF[6,7]. Our results are in accordance with these studies, although our study used a more modern and accurate method for detecting cardiac involvement and a controlled study design that included patients who had no cardiac symptoms. In addition, systolic function was unaltered with increased age whereas diastolic function decreases progressively with age[9], pointing out the need for a control group. Lastly, the prognostic significance of abnormal cardiac function detected by TDE has been demonstrated in patients with cardiomyopathy[13,19,23].

We cannot comment on the exact mechanism of ventricular diastolic dysfunction, as it was not planned for in our study. In fact, diastolic function is a complex phenomenon, an active process that depends on a variety of factors[12].

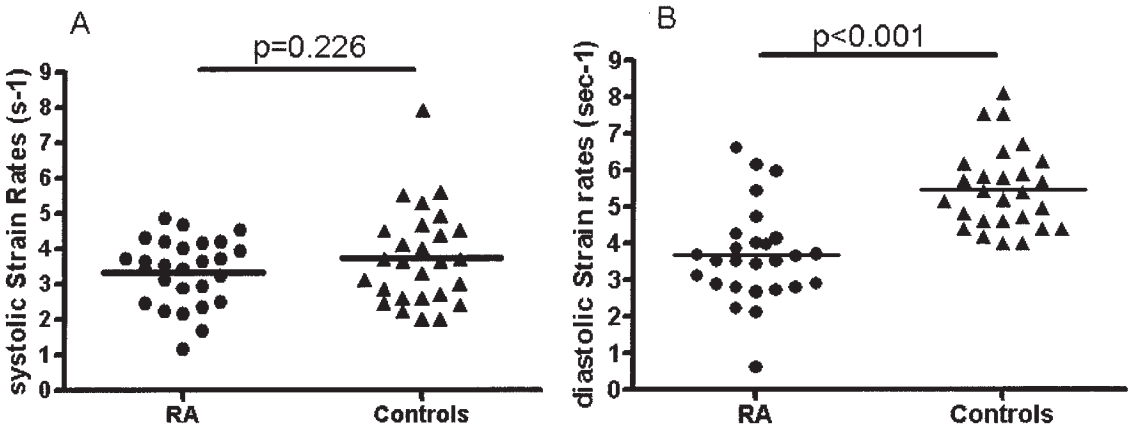


*Figure 1.* Systolic (A) and diastolic (B) strain rates determined by tissue-Doppler echocardiography in patients with RA and controls.

Hypertension is one of the most potent known risk factors for CHF; its prevalence may be increased in RA due to the chronic use of corticosteroids or NSAID. However, we excluded patients with previous hypertension and observed no difference in systolic or diastolic blood pressure when compared to controls, and blood pressure did not influence diastolic SR. Other well-known cardiovascular risk factors did not differ between groups. Myocardial ischemia is another potent risk factor for CHF; moreover, ischemia is known to alter diastolic myocardial wall motion earlier than systolic contraction[24]. Although our patients had no clinical or ECG abnormality, we can not affirm that myocardial ischemia may not account for part of the observed differences. Lastly, inflammation by itself may be involved in both myocardial ischemia and heart failure occurrence[5,6]. Levels of cytokine are indeed elevated in CHF and correlate with the severity of the disease[6], and there is experimental evidence that cytokines may cause myocardial injury. In patients with RA, inflammation may be considered a key determinant[6], and Wolfe and Michaud reported in a preliminary study a lower rate of CHF in RA patients treated with TNF inhibitors, even after adjustment for unbalanced clinical characteristics[25].

In our study, diastolic SR alterations did not correlate with inflammatory markers, severity of disease, presence of rheumatoid factors, or duration of disease. The absence of correlation between heart involvement and inflammatory markers is in accordance with previous studies[7,8]; however, cumulative inflammation rather than a single value should be investigated as a determinant of cardiac abnormalities. Literature concerning a possible link between heart involvement and duration of the disease is less clear[8].

TDE was limited to a section of the posterior wall of the LV, due to the angle-dependency of the method. However, as the left ventricle relaxes homogeneously, our results should be interpreted as global LV diastolic abnormality[18,24]. In our study, no correlation could be demonstrated between RA characteristics and TDE measurements; however, we acknowledge that the small sample size is a limitation and may account for the absence of any observed correlation. Lastly, these results demonstrate a striking rate of altered diastolic function; although TDE alterations are predictive of cardiac events in patients with cardiac involvement[13,19,23], the clinical consequence of a 1.8 $s^{-1}$ difference in diastolic SR in patients with RA is unknown; only longitudinal specific studies performed in patients with RA may determine exactly the impact of these early abnormalities on the progression of heart involvement and clinical events.

We observed in a controlled study that many patients with RA have altered diastolic function; these abnormalities are accurately detected by TDE whereas conventional methods failed at demonstrating such impairment. Patients with RA should be investigated very early in the course of the disease; predictive value of TDE in patients with RA remains to be established.

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