# Letters to the Editors

## Prognostic value of diastolic dysfunction in asymptomatic rheumatoid arthritis patients without cardiovascular risk factors

Sirs,

Cardiovascular (CV) disease represents the leading cause of mortality in patients with rheumatoid arthritis (RA), but its pathogenesis is still not clear (1). An increased left ventricular (LV) diastolic dysfunction (LVDD) without clinically evident cardiac disease is reported in patients with RA (2-4), representing one of the earliest findings of cardiac subclinical involvement. On the other hand, LVDD is usually attributable to common structural abnormalities, such as hypertrophy, interstitial fibrosis, or impaired myocyte relaxation resulting from ischaemia (3, 4). Anyway, how LVDD should evolve during time remains to be elucidated in RA.

We previously reported a LVDD prevalence of 76% in 93 consecutive RA outpatients (5). We then aimed at evaluating the prognostic significance of this finding in the same patients. Among the 93 RA patients, 23 were excluded due to known cardiopathy (n=8) or lost to follow-up (n=15). The remaining 70 patients were retrospectively re-analysed after a 7-year follow-up (2006-2013) and divided into 2 groups, with (LVDD+: n=55) and without (LVDD-: n=15) LVDD. Patients of each group were also divided in two other subgroups, according to the presence of previous CV risk factors (*i.e.* diabetes mellitus, arterial hypertension, smoke, obesity, hypercholesterolaemia, family history): LVDD+/CV+ (n=36); LVDD+/CV- (n=19); LVDD-/CV+ (n=6); LVDD-/CV-group (n=9). Patients were compared with age- and sex-matched healthy controls (n=9). CV events were defined as major (ischaemic cardiopathy, heart failure, arrhythmias, pulmonary hypertension or embolism, ischaemic vascular complications) or minor (new onset hypertension). Echocardiograms, as reported in our previous paper (5), were performed by Vivid 7 (GE) with a 3.5 MHz transducer. The subjects' written consent was obtained according to the Declaration of Helsinki and the study was conducted in compliance with standards currently applied in our country.

CV events were found in 25% LVDD+ cases (14/55). No CV events occurred in LVDD- patients. To evaluate the potential effect of LVDD on the onset of CV events, we compared LVDD+/CV- (n=19) and LVDD-/CV- groups (n=9) (Table I). CV events occurred only in LVDD+/CV- group (37% *vs.* 0%, $p$=0.043): 1 congestive heart failure, 1 coronary bypass graft surgery, 1 transient ischaemic attack, 4 new onset hypertension. Kaplan-Meier curve (not shown) showed a trend to a different outcome according to LVDD presence or absence ($p$=0.212) in CV- patients. About 40% of CV events occurred within the first 10 years since RA onset. A multivariate analysis of those parameters significantly different between LVDD+/CV- and LVDD-/CV- groups revealed that CV events were associated only with LVDD ($p$=0.036); age quite reached significance ($p$=0.051), while RA duration, age at symptoms onset and diastolic blood pressure were not significant. Among 50 age- and sex-matched healthy controls CV-, we found 9 LVDD+ cases. Comparing LVDD+/CV- RA patients with LVDD+/CV- healthy controls followed-up for the same period, we found that CV events occurred only in RA cases (7 *vs.* 0 cases, $p$=0.06, Table I).

**Table I.** Comparison between LVDD+/CV- (n=19), LVDD-/CV- (n=9) and healthy controls (n=9).

| | CV- patients (n=28) | LVDD+/CV- patients (n=19) | LVDD-/CV- patients (n=9) | *p*-value (19 *vs.* 9 cases) | LVDD+ healthy controls (n=9) | *p*-value (19 *vs.* 9 controls) |
|---|---|---|---|---|---|---|
| Age (years) | 53 ± 15 | 60 ± 11 | 39 ± 13 | <0.001 | 46 ± 18 | 0.082 |
| Male sex | 5 (18%) | 3 (16%) | 2 (22%) | 1.000 | 10 (20%) | 1 |
| RA duration (years) | 11 ± 8 | 12 ± 9 | 7 ± 4 | 0.030 | - | - |
| Age at symptoms onset (years) | 43 ± 14 | 48 ± 10 | 32 ± 16 | 0.004 | - | - |
| DAS 28 | 3.55 ± 1.79 | 3.54 ± 1.77 | 3.55 ± 1.93 | 0.990 | - | - |
| RF+ | 20 (71%) | 14 (74%) | 6 (67%) | 1.000 | - | - |
| Anti-CCP+ | 12 (43%) | 8 (42%) | 4 (44%) | 0.457 | - | - |
| ANA+ | 12 (43%) | 7 (37%) | 5 (56%) | 0.398 | - | - |
| CRP (mg/L) | 0.8 ± 0.9 | 0.8 ± 1.0 | 0.7 ± 0.6 | 0.723 | - | - |
| Steroids | 21 (75%) | 16 (84%) | 5 (56%) | 0.165 | - | - |
| Metothrexate | 21 (75%) | 14 (74%) | 7 (78%) | 1.000 | - | - |
| Anti-TNF-α drugs | 19 (68%) | 12 (63%) | 7 (78%) | 0.670 | - | - |
| SBP (mmHg) | 130 ± 14 | 132 ± 13 | 125 ± 15 | 0.230 | 123 ± 21 | 0.212 |
| DBP (mmHg) | 75 ± 7 | 77 ± 7 | 70 ± 5 | 0.006 | 73 ± 10 | 0.067 |
| E wave (m/s) | 0.64 ± 0.21 | 0.58 ± 0.20 | 0.78 ± 0.17 | 0.017 | 0.75 ± 0.19 | 0.039 |
| A wave (m/s) | 0.78 ± 0.27 | 0.90 ± 0.20 | 0.53 ± 0.20 | <0.001 | 0.67 ± 0.21 | 0.002 |
| E/A | 0.96 ± 0.56 | 0.64 ± 0.19 | 1.62 ± 0.49 | <0.001 | 1.12 ± 0.36 | <0.001 |
| DT (ms) | 236 ± 60 | 265 ± 50 | 175 ± 25 | <0.001 | 192 ± 36 | <0.001 |
| E' wave (m/s) | 0.07 ± 0.04 | 0.05 ± 0.02 | 0.11 ± 0.04 | 0.002 | 0.12 ± 0.05 | 0.001 |
| A' wave (m/s) | 0.08 ± 0.03 | 0.09 ± 0.03 | 0.06 ± 0.03 | 0.007 | 0.07 ± 0.03 | 0.038 |
| E/E' | 11.0 ± 5.8 | 12.4 ± 6.3 | 8.0 ± 3.1 | 0.057 | 6.5 ± 4.1 | 0.001 |
| Diastolic pattern | Grade I: 19 (68%) | Grade I: 19 (100%) | Normal: 9 (100%) | <0.001 | Grade I: 9 (100%) | <0.001 |
| CV events | 7 (25%) | 7 (37%) | 0 | 0.043 | 0 | 0.06 |

CV: cardiovascular; RA: rheumatoid arthritis; DAS: disease activity score; RF: Rheumatoid factor; CCP: cyclic citrullinated peptides; ANA: nti-nuclear antibodies; CRP: C-reactive protein; TNF: tumour necrosis factor; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Although many medical conditions associated with LVDD (*e.g.* hypertension, coronary artery disease, increasing age, obesity, and diabetes mellitus) are predictors of mortality, LVDD alone was demonstrated to be responsible of increased adverse CV event in the general population (6) and in cardiologic patients (7). This is the first study evaluating the role of LVDD alone regarding the CV prognosis of RA patients. The natural history of LVDD in RA is not known. In the general population it predicts the evolution into congestive heart failure in about 2% in 2-year follow-up (8). In our RA cases (but not in controls) LVDD alone is responsible of onset of CV adverse events. Since these patients were free from CV risk factors during follow-up, the only underlying pathophysiological mechanism could be the inflammatory burden of RA, responsible of myocardial stiffening, as previously demonstrated (9). In conclusion, our study could give the rheumatologist an important message about how to manage LVDD in RA patients even without any CV risk factor. LVDD displays an impact on the onset of CV events during the first years of RA. Therefore, a closer cardiologic and rheumatologic follow-up could prevent or delay adverse CV events even in RA patients free from CV risk factors.

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