Concise report

Myocardial ischaemia without obstructive coronary artery disease in rheumatoid arthritis: hypothesis-generating insights from a cross-sectional study

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Abstract

Objective. RA is associated with increased cardiovascular events, reportedly to equal diabetes mellitus (DM). The presence of myocardial ischaemia was assessed in asymptomatic high-risk RA patients and compared with patients with DM and a healthy control group.

Methods. Eighteen consecutive non-diabetic RA patients without known cardiovascular disease who developed a new carotid atheromatic plaque during the last 3 years were matched 1:1 for traditional cardiovascular risk factors with asymptomatic type 2 DM patients and 1:2 with asymptomatic non-RA, non-DM control subjects. After dobutamine stress contrast echocardiography with wall-motion and perfusion evaluation, coronary angiography was performed in those with positive stress tests.

Results. Ischaemia by echocardiography was found in 67% of RA patients; this was significantly higher than controls (31%, $P=0.019$) but comparable to those with DM (78%, $P=0.71$). Angiography performed in eight consenting RA patients was normal in four, revealed non-flow-limiting coronary atheromatic lesions in two and significant lesions in two patients. RA patients with ischaemia had CRP serum levels significantly higher by six-fold compared with those with normal stress echocardiography.

Conclusion. Asymptomatic RA patients may display myocardial ischaemia at similar levels to DM patients but with low prevalence of obstructive coronary artery disease. Microvascular abnormalities associated with increased inflammatory response may account for these findings. Their exact nature and significance require further evaluation.

Key words: rheumatoid arthritis, myocardial ischaemia, cardiovascular risk, dobutamine stress contrast echocardiography, coronary angiography, optical coherence tomography, diabetes mellitus.

Introduction

RA is the commonest chronic systemic inflammatory musculoskeletal disease, affecting ~1% of the population. Cardiovascular morbidity is increased in RA [1] and large studies have suggested that cardiovascular risk in RA is similar to diabetes mellitus (DM) [2], a coronary artery disease (CAD) equivalent. Increased prevalence of traditional cardiovascular risk factors and accelerated atherosclerosis due to persistent systemic inflammation have been suggested as potential mechanisms [3, 4]. Whether coronary microvascular dysfunction may be an additional contributing factor is currently unknown.

Although an association of RA with subclinical atherosclerosis has been established [5, 6], no studies have investigated the prevalence and nature of actual cardiac ischaemia in patients with RA and subclinical atherosclerosis, and whether this is associated with obstructive CAD. Ischaemia can be identified by dobutamine stress
contrast echocardiography [7–9]. Myocardial ischaemia is associated with adverse prognosis in the general population and in DM [7, 10].

We investigated the presence and extent of myocardial ischaemia by dobutamine stress contrast echocardiography in asymptomatic high-risk RA patients; the presence of obstructive CAD was assessed angiographically in those with positive stress findings. Moreover, we compared the RA-derived echocardiography and angiography data with data derived from carefully matched asymptomatic patients with type 2 DM and an asymptomatic control group.

**Patients and methods**

**Study population**

We prospectively enrolled consecutive patients with RA [11], who had developed a new carotid plaque within 3 years in a follow-up US examination, without symptoms suggestive of CAD or heart failure. These patients underwent ischaemia evaluation due to high cardiovascular risk based on current recommendations [12].

This prospective RA cohort was matched 1:1 with asymptomatic patients with type 2 DM and 1:2 with asymptomatic apparently healthy subjects without RA or DM (Table 1). Patients with DM and control subjects were identified from a database of individuals referred for ischaemia evaluation by dobutamine stress contrast echocardiography between September 2010 and May 2011. The database contained information on 119 patients with DM and 797 controls. Matching was performed for age, gender, family history of CAD, smoking history, hypertension and dyslipidaemia. DM was defined as fasting plasma glucose >126 mg/dl, plasma glucose 2 h after 75 g oral glucose load >200 mg/dl, or anti-diabetic medication. Hypertension, dyslipidaemia and family history for CAD were defined as previously described [3].

Exclusion criteria for patients with RA were the presence of DM, uncontrolled hypothyroidism, renal impairment, malignancy or treatment with NSAIDs. Exclusion criteria for the other cohorts were the presence of any systemic inflammatory disease or malignancy. Patients previously diagnosed with CAD or presenting with typical anginal symptoms were also excluded.

**Study procedure**

Clinical evaluation and laboratory tests (cholesterol, low-density lipoprotein, ESR, high-sensitivity CRP) were performed in parallel with the stress echocardiography. All study participants underwent ischaemia evaluation using stress echocardiography. Patients with positive stress result were scheduled for diagnostic coronary angiography. In cases of diagnostic ambiguity after angiography, lesion severity was assessed by optical coherence tomography (OCT). Further interventional treatment was left to the operator’s discretion. The study was approved by the institutional ethics committee (ethics committee of Hippokration Hospital) and conforms to the Declaration of Helsinki.

**Stress echocardiography and echocardiographic image analysis**

All studies were performed using the Philips iE33 US system (Philips Medical Systems, Bothell, WA, USA) and the 2.5 MHz S5-1 transducer. Patients and controls underwent the accelerated dobutamine–atropine stress protocol as previously described [8]. Real-time myocardial contrast echocardiography was performed using low mechanical index (0.10–0.15). Images were obtained from the apical four-, two- and three-chamber views at rest and peak stress, and were interpreted off-line.

Acquired images were analysed for wall-motion and perfusion abnormalities by two independent investigators [13]. The wall-motion score index (WMSI) and number of segments with perfusion defects were assessed. The test was considered positive for ischaemia, if new or worsening wall-motion abnormalities and/or new perfusion abnormalities were observed in ≥2 contiguous myocardial segments [9]. Detailed methodology for stress echocardiography image acquisition and analysis are included in the supplementary data, available at Rheumatology Online.

**Table 1** Baseline clinical characteristics in the study cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA</th>
<th>DM</th>
<th>Control</th>
<th>RA vs DM, P-value</th>
<th>RA vs control, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>18</td>
<td>36</td>
<td>0.65</td>
<td>0.50</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>68.2 (6.7)</td>
<td>66.9 (5.4)</td>
<td>66.9 (6.9)</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>6 (33.3)</td>
<td>6 (33.3)</td>
<td>12 (33.3)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary risk factors, n (%)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Smoking history</td>
<td>13 (72.2)</td>
<td>13 (72.2)</td>
<td>26 (72.2)</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (72.2)</td>
<td>14 (77.8)</td>
<td>26 (72.2)</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>6 (33.3)</td>
<td>6 (33.3)</td>
<td>12 (33.3)</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>DM</td>
<td>0 (0)</td>
<td>18 (100.0)</td>
<td>0 (0)</td>
<td>0.001</td>
<td>0.99</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>4 (22.2)</td>
<td>4 (22.2)</td>
<td>7 (19.4)</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Disease duration, mean (s.d.), years</td>
<td>11.1 (7.2)</td>
<td>13.5 (4.0)</td>
<td>NA</td>
<td>0.22</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: not applicable.
Coronary angiography and OCT study

Significant coronary disease was identified at two cut-offs of stenosis severity, >50% and >70%, in a major epicardial artery. Plaques producing >70% stenosis were considered culprit, if the location of the lesions corresponded to the ischaemic territory, as previously described [13]. OCT was performed in cases of diagnostic ambiguity as previously described [14]. Detailed OCT methodology is included in the supplementary data, available at Rheumatology Online.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 19.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean (s.d.) or median [interquartile range (IQR)] for continuous variables and as percentages for categorical variables. Normality was assessed with the Kolmogorov–Smirnov test. Differences between groups were assessed pair-wise for categorical variables using Fisher’s test, and for normally distributed continuous variables using the Mann–Whitney test. Binary logistic regression, adjusting for age and gender, was used to assess the association of RA with the presence of significant angiographic lesions in subjects with positive stress test. A P < 0.05 indicated statistical significance.

Results

Dobutamine stress contrast echocardiography and coronary angiography in RA

Baseline echocardiographic parameters of the 18 RA patients who participated in this study were within normal limits. A positive dobutamine stress echocardiography result was found in 66.7% of RA patients. The mean WMSI of the cohort was 1.08 (s.d. 0.06), whereas among patients with positive stress results (n = 12), the mean WMSI was 1.12 (s.d. 0.04). The median number of segments with perfusion defect was 2 (IQR 2), while among subjects with positive stress test it was 2 (IQR 2). The association of anti-rheumatic medications, inflammatory biomarkers and disease activity with the stress findings is presented in Table 2.

Among the 12 patients with RA and positive stress result, in all of whom diagnostic catheterization was recommended, 8 consented to and 4 declined further investigation. Coronary angiography revealed the absence of macrovascular disease in four patients (50%), intermediate lesions with stenosis 50–70% in two patients (25%) and significant lesions in two patients (25%). In all patients with obstructive CAD the ischaemic territory corresponded to the culprit lesion. Supplementary Fig. S1 and supplementary Video S1, available as supplementary data at Rheumatology Online, present a patient with RA with positive stress test and absence of significant macrovascular disease.

RA- vs DM- and healthy control-derived stress echocardiography and coronary angiography results

Baseline characteristics of control patients with DM and of the healthy control group are listed in Table 1. Mean disease duration was 11.1 (s.d. 7.2) years for RA and 13.5 (s.d. 4.0) years for DM (P = 0.22). No significant differences were detected in the baseline echocardiographic parameters among the three groups.

A positive stress result was found in 14 DM patients (77.8%) and in 11 control subjects (30.6%) (P = 0.019 for RA vs control, P = 0.001 for DM vs control, P = 0.71 for RA vs DM). Mean WMSI was 1.10 (s.d. 0.07) in DM and 1.04

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA patients with negative stress echocardiography (n = 6)</th>
<th>RA patients with positive stress echocardiography (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>2 (33.3)</td>
<td>4 (33.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>64.7 (7.9)</td>
<td>68.7 (5.7)</td>
<td>0.225</td>
</tr>
<tr>
<td>RA duration, mean (s.d.), years</td>
<td>8.6 (4.1)</td>
<td>11.6 (8.5)</td>
<td>0.423</td>
</tr>
<tr>
<td>CRP, contemporary, mean (s.d.), mg/dl</td>
<td>0.2 (0.1)</td>
<td>1.2 (1.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>ESR, contemporary, mean (s.d.), mm/h</td>
<td>12.8 (9.8)</td>
<td>30.1 (11.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>CRP (AUC) during the past 3 years*, mean (s.d.), mg/dl x months</td>
<td>23.6 (15.7)</td>
<td>48.2 (37.4)</td>
<td>0.067</td>
</tr>
<tr>
<td>ESR (AUC) during the past 3 years*, mean (s.d.), mm/h x months</td>
<td>687.3 (381.8)</td>
<td>1154.2 (568.2)</td>
<td>0.058</td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>6 (100)</td>
<td>10 (83.3)</td>
<td>0.529</td>
</tr>
<tr>
<td>Anti-CCP positive, n (%)</td>
<td>4 (66.7)</td>
<td>10 (83.3)</td>
<td>0.569</td>
</tr>
<tr>
<td>Biologic DMARDs during the past 3 years, mean (s.d.), months</td>
<td>39.7 (2.9)</td>
<td>31.0 (15.0)</td>
<td>0.077</td>
</tr>
<tr>
<td>Prednisolone (daily &lt; 7.5 mg) during the past 3 years, mean (s.d.), months</td>
<td>30.3 (14.6)</td>
<td>32.1 (12.3)</td>
<td>0.807</td>
</tr>
<tr>
<td>Prednisolone (daily &lt; 7.5 mg) contemporary, n (%)</td>
<td>5 (83.3)</td>
<td>10 (83.3)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Derived from serial measurements performed every 3–6 months. AUC: area under the curve.
(s.d. 0.08) in the control group ($P = 0.006$; $P = 0.031$ for RA vs control, $P = 0.003$ for DM vs control, $P = 0.389$ for RA vs DM). Median number of segments with perfusion defect was 2 (IQR 3) in DM, and 0 (IQR 2) in the control group ($P = 0.004$; $P = 0.031$ for RA vs control, $P = 0.002$ for DM vs control, $P = 0.236$ for RA vs DM). Among subjects with positive stress results, the mean WMSI was 1.13 (s.d. 0.05) in DM and 1.14 (s.d. 0.07) in the control group ($P = 0.575$ for RA, DM and control comparison). Likewise, among subjects with positive stress results, the median number of segments with perfusion defect was 2 (IQR 2) for DM patients and 2 (IQR 2) for control subjects ($P = 0.50$ for RA, DM and control comparison).

In the group of DM, diagnostic catheterization was suggested to 14 patients, 2 of whom declined. Of these 12 patients, 4 did not have $\geq 50\%$ coronary artery stenosis, 2 had intermediate lesions with stenosis 50–70% and the remaining 6 had significant lesions. Finally, all 11 healthy control subjects consented to coronary angiography. Two of them had normal coronary vessels, eight had significant lesions and one had intermediate lesions, with stenosis 50–70%. RA was associated with a reduction in the risk for significant lesions compared with the other cohorts [odds ratio (OR) 0.125, 95\% CI 0.016, 0.999; $P = 0.050$] that remained significant after adjustment for age and gender (OR 0.076, 95\% CI 0.007, 0.789; $P = 0.031$).

**Discussion**

Despite the higher prevalence of cardiovascular risk factors in RA [3], traditional risk factor evaluation underestimates the cardiovascular risk in these patients [15]. Indeed, a number of studies has demonstrated an association of RA *per se* with subclinical atherosclerosis [6] and coronary microvascular dysfunction [5, 16]. Although there are studies demonstrating the link between inflammatory activation and atherosclerosis [17], this interaction has not been fully explored in patients with RA [4]. A recent prospective study provides evidence that inflammation is a contributor to the progression of subclinical atherosclerosis in RA [18].

The main findings of the present study are that: (i) high-risk asymptomatic patients with RA have significantly higher ischaemic burden than control subjects matched for traditional risk factors, but prevalence and extent of myocardial ischaemia comparable to matched asymptomatic patients with DM of similar duration; (ii) myocardial ischaemia is associated with increased and sustained systemic inflammatory response in RA; and (iii) in patients with RA and myocardial ischaemia, obstructive CAD may not be the main underlying pathology.

A retrospective study with exercise echocardiography has also shown higher ischaemia in an unselected group of patients with RA compared with a matched control group [19], with ischaemia being associated with adverse outcome during follow-up [19]. Therefore, the higher prevalence of ischaemia in RA patients with accelerated atherosclerosis might account for the higher cardiovascular morbidity compared with the general population. In the current study, RA was associated with similar prevalence and extent of ischaemia to DM. Given the prognostic significance of ischaemia in DM, our findings are in accordance with previous studies demonstrating similar cardiovascular morbidity in RA and DM [2]. Thus, our findings underscore the significance of continuous monitoring and intensive management of the cardiovascular risk in RA, as it is a condition associated with a high prevalence of ischaemia.

Interestingly, despite the high prevalence of ischaemia, patients with RA presented less often with obstructive disease. RA has been associated with reduced coronary flow reserve, a marker of microvascular dysfunction [5, 16], while microvascular impairment in RA has been documented by stress cardiac MRI [20]. Herein, we observed that only patients with increased and sustained inflammatory activation had microvascular dysfunction, as implied by the presence of ischaemia and the absence of macrovascular CAD, which was confirmed in the subset of patients with RA that underwent OCT examination.

**Study limitations**

Due to the small study sample and the cross-sectional design, there is no proof of causality or directionality for any of the associations found. Whether the abnormalities detected are surrogates of cardiovascular outcome in RA population can only be demonstrated in long-term follow-up studies. Furthermore, the limited study sample combined with the fact that cohorts were matched for stress echocardiography but not for angiography as well, mandates the cautious interpretation of these results, which should be regarded mainly as hypothesis-generating. Moreover, as only high-risk patients were studied, the exact impact of RA *per se* on myocardial ischaemia was not addressed, thus limiting the generalizability of our findings.

Another limitation is that subjects with a negative stress test were not evaluated by coronary angiography. Nevertheless, these patients had low probability for obstructive CAD, while the clinical impact of obstructive disease without ischaemia in asymptomatic patients would be limited. Finally, coronary flow reserve to confirm microvascular dysfunction was not measured during angiography in culprit arteries; however, the presence of occlusive lesions was excluded by OCT.

**Conclusions**

High-risk patients with RA have similar prevalence and extent of myocardial ischaemia to patients with type 2 DM, and higher than control subjects. Despite the similar ischaemic burden among patients with positive stress test in the different groups, fewer patients with RA had obstructive CAD in coronary angiography. These hypothesis-generating findings taken together with the association of myocardial ischaemia with inflammatory biomarkers, suggest that a process of inflammation-induced microvascular dysfunction may operate in some patients with RA, the exact nature and significance of which require further evaluation.
Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data
Supplementary data are available at Rheumatology Online.

References


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