Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease

Alejandro Recio-Mayoral¹, Justin C. Mason¹, Juan C. Kaski², Michael B. Rubens³, Olivier A. Harari¹, and Paolo G. Camici¹*

¹Medical Research Council Clinical Sciences Centre and National Heart and Lung Institute, Imperial College School of Medicine, Du Cane Road, London W12 0NN, UK; ²Division of Cardiac and Vascular Sciences, St George’s Hospital Medical School, London, UK; and ³Department of Radiology, Royal Brompton Hospital, London, UK

Aims
To demonstrate that exposure to chronic inflammation results in coronary microvascular dysfunction (CMD).

Methods and results
Using positron emission tomography, resting and hyperaemic (adenosine, 140 μg/kg/min) myocardial blood flow (MBF) was measured in 25 patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). Coronary flow reserve (CFR) was calculated as adenosine/resting MBF. Patients had normal or minimally diseased (i.e. ≤20% luminal diameter) coronary arteries at angiography and no cardiovascular risk factors. Twenty five age- and gender-matched healthy volunteers served as controls. Resting MBF was similar in patients and controls (1.25 ± 0.27 vs. 1.15 ± 0.24 mL/min/g; P = 0.15) while patients had lower hyperaemic MBF (2.94 ± 0.83 vs. 4.11 ± 0.84 mL/min/g; P < 0.001) and CFR (2.44 ± 0.78 vs. 3.81 ± 1.07; P < 0.001). CFR was inversely related to disease duration (r = −0.65; P < 0.001) and SLE disease activity (r = −0.69; P = 0.01). Seven patients showed ischaemic electrocardiographic changes during adenosine. They had longer disease duration (21 ± 7 vs. 14 ± 5 years; P = 0.03) and lower CFR (1.76 ± 0.81 vs. 2.49 ± 0.54; P = 0.006) when compared with patients without changes.

Conclusion
A reduced CFR in the absence of significant coronary disease is suggestive of CMD. We speculate that this is the consequence of prolonged systemic inflammation, which may precede and contribute to premature coronary artery disease in these patients.

Keywords
Coronary circulation  •  Myocardial blood flow  •  Inflammation  •  Rheumatoid arthritis  •  Systemic lupus erythematosus  •  Positron emission tomography

Introduction
Patients with systemic inflammatory, autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), suffer from increased cardiovascular morbidity and mortality owing to accelerated atherosclerosis and premature coronary artery disease.¹ ² This is especially pronounced in younger women and frequently silent and subclinical. Moreover, RA and SLE are independent risk factors for the development of atherosclerosis.³ ⁴ The excess risk observed in these diseases appears to be driven by the damaging effects of systemic inflammation on the vasculature,⁵ and thus the concept has arisen of inflammation as a cardiovascular risk factor (CVRF).⁶ Furthermore, a complex role for inflammation in the pathogenesis of atherosclerosis has been demonstrated both experimentally and clinically.⁷ ⁸ Atherosclerosis is seen as an active inflammatory and immune-mediated process in which leucocytes and soluble factors (antibodies, activated complement, cytokines) play a role in accelerating vessel pathology. The term coronary microvascular dysfunction (CMD) has been introduced to describe abnormalities in the regulation of myocardial blood flow (MBF) which are not explained by disease of the epicardial coronary arteries.⁹ As this type of dysfunction is, at least in part, reversible,¹⁰ ¹¹ its assessment can be used to guide interventions aimed at reducing risk factor burden and progression.

* Corresponding author. Tel: +44 20 8383 3186, Fax: +44 20 8383 3742, Email: paolo.camici@csc.mrc.ac.uk
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to established epicardial atherosclerosis. Regional abnormalities in coronary blood flow velocities using transthoracic echocardiography have been previously demonstrated in patients with RA and SLE.\textsuperscript{12,13} However, in these studies patients did not undergo coronary angiography to exclude epicardial disease.

We therefore hypothesized that exposure to chronic systemic inflammation in patients with RA or SLE, but without traditional CVRF or angiographic evidence for coronary artery disease results in CMD, an early marker of accelerated coronary atherosclerosis and that the degree of CMD is directly related to disease duration.

**Methods**

**Study population**

We prospectively studied 25 patients, 13 SLE and 12 RA, recruited between January 2006 and December 2007. All patients fulfilled American College of Rheumatology revised diagnostic criteria for SLE and RA.\textsuperscript{14,15} All patients underwent coronary angiography using multi-slice (64 slices) computed tomography (Siemens Somaton, SLE and RA.\textsuperscript{14,15} All patients underwent coronary angiography using multi-slice (64 slices) computed tomography (Siemens Somaton, Siemens Medical Systems, Erlangen, Germany). Patients were included only if they had normal or minimally diseased coronary arteries (\(\leq 20\%\) luminal reduction). Furthermore, patients with one of the following CVRF, smoking, arterial hypertension (defined as blood pressure over 140/90 mmHg or taking antihypertensive drugs at the time of inclusion), diabetes mellitus (defined by a fasting glucose level over 141 mg/dL (7.8 mmol/L) or a random-sample glucose level over 200 mg/dL (11.1 mmol/L)) and hypercholesterolaemia [defined by total cholesterol level over 240 mg/dL (6.2 mmol/L) and/or with previous or current use of lipid-lowering therapy] were excluded from the study. All patients had normal renal function calculated by applying the Cockcroft-Gault formula\textsuperscript{16} to the serum creatinine value (Table 1).

High-sensitivity C-reactive protein was measured in all patients. The activity of rheumatic disease at the time of the study was determined using disease-specific activity indices. For RA, the Disease Activity Score 28 index (DAS-28)\textsuperscript{17} was used, which is based on the analysis of 28 joints, considering the number of painful and swollen joints, global evaluation of the disease by the patient and C-reactive protein levels. For SLE, the Safety of Estrogen in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI),\textsuperscript{18} which evaluates SLE activity considering 24 clinical and laboratory variables, was used. We obtained information on current and previous treatment and disease duration. Time-averaged corticosteroid daily dosage, and total cumulative corticosteroid dose was calculated (Table 2).

### Table 1  Disease characteristics in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>RA (n = 12)</th>
<th>SLE (n = 13)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>33 (\pm) 8</td>
<td>30 (\pm) 8</td>
<td>0.37</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>16 (\pm) 11</td>
<td>11 (\pm) 7</td>
<td>0.16</td>
</tr>
<tr>
<td>Range (years)</td>
<td>2–36</td>
<td>1–22</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)\textsuperscript{b}</td>
<td>0.84 (\pm) 0.18</td>
<td>0.85 (\pm) 0.17</td>
<td>0.86</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min)\textsuperscript{c}</td>
<td>94.4 (\pm) 17.8</td>
<td>104.3 (\pm) 22.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Prednisone current use, n (%)\textsuperscript{d}</td>
<td>8 (61.5)</td>
<td>5 (41.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Prednisone total cumulative dose (g)</td>
<td></td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Median</td>
<td>2.6</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0–22.6</td>
<td>2.1–15.9</td>
<td></td>
</tr>
<tr>
<td>Prednisone mean daily dosage (mg/day)</td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Median</td>
<td>3.5</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0–6.6</td>
<td>2.6–7.4</td>
<td></td>
</tr>
<tr>
<td>NSAID current use, n (%)\textsuperscript{d}</td>
<td>6 (50)</td>
<td>0 (0)</td>
<td>0.005</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2.5–16.3</td>
<td>1.2–5.9</td>
<td></td>
</tr>
<tr>
<td>SLEDAI Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>–</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>–</td>
<td>0–2.0</td>
<td></td>
</tr>
<tr>
<td>DAS-28 Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.7–2.5</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Plus–minus values indicate means \(\pm\) SD, unless otherwise indicated. SLEDAI Index, Systemic Lupus Erythematosus Disease Activity Index; DAS-28, Disease Activity Score 28 joins index; NSAID, non-steroidal anti-inflammatory drugs.

\textsuperscript{b}To convert values for serum creatinine to mmol/L, multiply by 88.4.

\textsuperscript{c}Glomerular filtration rate estimated by applying the Cockcroft-Gault formula.\textsuperscript{16}

\textsuperscript{d}Current use’ indicates use of medication at the time of study or in the previous month.
Table 2  Main clinical characteristics and haemodynamic parameters during positron emission tomography scanning of patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 25)</th>
<th>Controls (n = 25)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLE (n = 13)</td>
<td>RA (n = 12)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 ± 12</td>
<td>47 ± 7</td>
<td>44 ± 9</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>13 (100)</td>
<td>10 (83)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.4 ± 4.6</td>
<td>24.6 ± 2.7</td>
<td>23.9 ± 4.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>173.3 ± 36.1</td>
<td>195.6 ± 26.9</td>
<td>173.0 ± 21.3</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>93.9 ± 35.6</td>
<td>115.2 ± 32.6</td>
<td>113.4 ± 33.0</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>59.1 ± 24.3</td>
<td>60.8 ± 15.1</td>
<td>55.7 ± 14.3</td>
</tr>
<tr>
<td>Basal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>118 ± 17</td>
<td>119 ± 15</td>
<td>117 ± 11</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 10</td>
<td>71 ± 7</td>
<td>70 ± 8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87 ± 12</td>
<td>87 ± 8</td>
<td>86 ± 9</td>
</tr>
<tr>
<td>HR (b.p.m.)</td>
<td>74 ± 9</td>
<td>72 ± 9</td>
<td>65 ± 8</td>
</tr>
<tr>
<td>RPP (mmHg x b.p.m.)</td>
<td>8832 ± 2007</td>
<td>8531 ± 1464</td>
<td>7693 ± 1690</td>
</tr>
<tr>
<td>CR (mmHg/mL/min/g)</td>
<td>67.9 ± 10.1</td>
<td>76.1 ± 18.6</td>
<td>79.1 ± 17.0</td>
</tr>
<tr>
<td>Adenosine stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 13</td>
<td>125 ± 13</td>
<td>118 ± 15</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 8</td>
<td>70 ± 9</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>88 ± 9</td>
<td>88 ± 10</td>
<td>86 ± 9</td>
</tr>
<tr>
<td>HR (b.p.m.)</td>
<td>109 ± 8</td>
<td>108 ± 10</td>
<td>97 ± 13</td>
</tr>
<tr>
<td>RPP (mmHg x b.p.m.)</td>
<td>13137 ± 1936</td>
<td>13582 ± 2413</td>
<td>11 604 ± 2474</td>
</tr>
<tr>
<td>CR (mmHg/mL/min/g)</td>
<td>31.1 ± 10.2</td>
<td>36.5 ± 10.8</td>
<td>21.1 ± 4.4</td>
</tr>
</tbody>
</table>

*Plus–minus values indicate means ± SD. The body mass index is the weight in kilograms divided by the square of the height in meters. HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; b.p.m., beats/min; RPP, rate–pressure product; and CR, coronary resistance.

1To convert values for total cholesterol, LDL, and HDL to mmol/L, multiply by 0.02586.

2Rate–pressure product is systolic blood pressure multiplied by heart rate.

3Coronary resistance is the median blood pressure divided by myocardial blood flow.

Twenty-five gender- and age-matched healthy controls were also included (Table 2). None of the subjects had a history of cardiovascular disease or coronary risk factors. Entry criteria included normal heart rate, blood pressure, electrocardiogram, and two-dimensional echocardiogram as well as low clinical probability for coronary artery disease. None of the study subjects were receiving cholesterol-lowering agents or oestrogens at time of the study.

Study protocol

The coronary microcirculation is not visible on angiography and its study is indirect and relies on measurement of parameters such as MBF and coronary flow reserve (CFR). These are principally regulated by the coronary microcirculation and thus, in the absence of coronary stenoses, their measurement provides an index of microvascular function.

MBF (mL/min/g of tissue) at rest and during pharmaco logically induced hyperaemia (adenosine 140 μg/kg/min, infused over 7 min) was measured non-invasively using positron emission tomography (PET) (ECAT 962 Exact HR+ scanner, CTI/Siemens, Knoxville, TN, USA) with oxygen-15 labelled water, as previously reported. Blood pressure and 12-lead electrocardiogram were recorded at baseline and every minute during adenosine infusion. CFR was calculated as hyperaemic MBF divided by resting MBF. Because the latter is closely related to the heart rate–systolic blood pressure product, an index of myocardial oxygen consumption, resting MBF data were also corrected for the respective rate–pressure product. CFR corrected for rate–pressure product was calculated by dividing hyperaemic MBF by resting MBF corrected for rate–pressure product.

The study protocol was approved by the Research Ethics Committee of Imperial College Healthcare Trust and radiation exposure was licensed by the UK Administration of Radioactive Substances Advisory Committee. All patients gave informed and written consent before the study.

Statistical analysis

Results are presented as percentages for categorical data and analysed using χ² test or Fisher’s exact test as appropriate. Continuous normally distributed variables are expressed as mean ± 1 standard deviation (SD) and compared with Student’s two-tailed unpaired t-test. Continuous non-normally distributed data are expressed as median and interquartile range and analysed by Mann–Whitney U test. The Kolmogorov–Smirnov test was used to check normal distribution. The data for resting and hyperaemic MBF and CFR were examined using one-way ANOVA and Bonferroni’s test to localise the source of any difference. Bivariate correlations between study variables were calculated using Spearman’s rank correlation coefficients. All statistical analyses were performed with the Statistical Package for the
There were no differences between patients and controls with regard to age, gender, body mass index, and lipids (Table 2). RA and SLE patients had comparable disease duration and corticosteroid regimens. Current use of traditional non-steroidal anti-inflammatory drugs and cyclo-oxygenase 2 inhibitors was confined to six RA patients. C-reactive protein levels were higher in RA compared with SLE patients although the difference fell short of statistical significance. Mean disease activity scores indicated low levels of disease activity both in RA and SLE (Table 1). Coronary angiography showed mild coronary artery disease in 7 of 25 patients while the angiogram was completely normal in the remainder.

Myocardial blood flow

At the time of PET scanning, blood pressure, heart rate, and rate–pressure product were similar in patients and controls (Table 2). As shown in Figure 1, there was no difference in global (whole left ventricle) resting MBF between patients and control subjects (1.25 ± 0.27 vs. 1.13 ± 0.27 mL/min/g, P = 0.10). By contrast, MBF during adenosine hyperaemia (2.94 ± 0.83 vs. 4.24 ± 0.95 mL/min/g, P < 0.001) and CFR (2.44 ± 0.78 vs. 3.87 ± 0.92; P < 0.001) were severely blunted in patients compared with controls. There were no changes in regional MBF and CFR in patients and controls. After correction of resting MBF for rate–pressure product, the resulting values for CFR were 2.55 ± 0.85 and 3.60 ± 1.04 (P < 0.001) for patients and normal controls, respectively. There was no difference in corrected CFR between RA and SLE patients (2.54 ± 0.92 vs. 2.55 ± 0.81; P = 0.89) (Figure 2). Corrected CFR in RA patients receiving non-steroidal anti-inflammatory drugs and cyclo-oxygenase 2 inhibitors was comparable to that in patients not receiving these medications (2.61 ± 1.26 vs. 2.48 ± 0.52; P = 0.83). None of the patients with minimal coronary disease at angiography showed differences in MBF or CFR in the regions subtended by the diseased arteries when compared to regions with no disease. However, patients with minimal coronary disease had lower CFR compared with other patients (1.95 ± 0.85 vs. 2.59 ± 0.71; P = 0.08) although this difference fell short of statistical significance.

Electrocardiographic changes and myocardial blood flow

Seven of the 25 patients, but no controls, developed ischaemic electrocardiographic (ECG) changes during adenosine stress. Dark blue bar represents patients with ischaemic ECG changes. Light blue bar represents patients without ischaemic ECG changes. Error bars indicate standard deviation.
depression at 80 ms after the J point in two or more contiguous leads) on the electrocardiogram during adenosine stress. The patients with electrocardiographic changes had longer disease duration compared to those without (19 ± 7 vs. 11 ± 9 years, \( P = 0.03 \)) and more severe reduction in CFR (1.76 ± 0.81 vs. 2.70 ± 0.59; \( P = 0.004 \); Figure 3). There was no relationship between evidence of disease at angiography and occurrence of electrocardiographic changes during adenosine stress (\( P = 0.30 \)).

**Figure 4** Relation between coronary flow reserve and disease duration. Scatter plot showing linear regression between coronary flow reserve and disease duration (years) in patients. Dark blue circles represent SLE patients. Light blue squares represent RA patients. The solid lines represents the point estimated and the upper and lower lines the 95% confidence intervals. Coronary flow reserve \( = 3.16 - 0.06 \times \) years of disease.

### Disease activity, disease duration, and microvascular dysfunction

CFR was inversely related to SLE disease activity as measured by the SELENA-SLEDAI index (Spearman’s \( \rho = -0.69; P = 0.01 \)). In RA there was a trend towards a negative correlation between CFR and disease activity as measured by the DAS-28 index (Spearman’s \( \rho = -0.55; P = 0.06 \)). When patient data were pooled, a significant inverse correlation between disease duration and CFR was demonstrated (Spearman’s \( \rho = -0.67, P < 0.001 \); Figure 4) and between CFR and high-sensitivity C-reactive protein levels (Spearman’s \( \rho = -0.48, P = 0.02 \)). No significant association was found between CFR and age (Spearman’s \( \rho = -0.37, P = 0.12 \)), prednisone total cumulative dose (Spearman’s \( \rho = -0.28, P = 0.18 \)), and prednisone mean daily dose (Spearman’s \( \rho = -0.19, P = 0.36 \)).

### Discussion

Premature, accelerated coronary atherosclerosis is an established complication of SLE and RA.\(^{2,4,23,24}\) We now report a novel finding, namely that abnormalities in absolute MBF and CFR are present in patients with RA and SLE in the absence of significant coronary artery disease and conventional CVRF. These findings are suggestive of CMD,\(^9\) which may represent an early marker of accelerated coronary atherosclerosis and contribute to the increased cardiovascular morbidity and mortality in these patients.

In seven patients (28%), the dysfunction of the microvasculature was severe enough to induce ischaemic-like changes on the electrocardiogram and in one MBF during adenosine stress was even lower than resting MBF.

### Comparison with previous studies

CMD has been previously reported in cross-sectional studies in patients with RA and SLE using alternative techniques such as Doppler ultrasound and transthoracic echocardiography which, however, do not permit absolute quantification of MBF.\(^{12,13}\) However, in these studies coronary angiography was not performed and therefore the changes in coronary flow velocity cannot be ascribed necessarily to abnormal microcirculatory function.

This is the first report demonstrating the utility of PET scanning in the identification of CMD in patients with RA and SLE without CVRF in whom significant epicardial coronary artery disease was excluded angiographically. Because of its quantitative nature, PET allows global and regional CFR measurements in the territories of all three major coronary arteries. In our study, no patient or control showed regional changes in MBF or CFR. No control had CFR < 2 allowing exclusion of significant epicardial coronary artery disease.

### Impaired endothelial function in rheumatic disease

Previous studies have demonstrated impaired flow-mediated dilatation in the peripheral circulation of patients with chronic inflammation including RA and SLE.\(^{25–27}\) However, data from flow-mediated dilatation in the brachial artery cannot be necessarily extrapolated to the coronary circulation.\(^{28}\) Increased aortic stiffness as measured by pulse wave velocity has also been associated with an increased risk of coronary atherosclerosis and demonstrated in RA\(^{29}\) and SLE.\(^{30}\) Furthermore, analysis by ultrasound of carotid artery intima-media thickness has been reported as an early indicator of atherosclerotic risk in patients with RA\(^{31}\) and SLE.\(^{26}\) These data are supported by the increased incidence of carotid atherosclerotic plaques in patients with RA\(^{32}\) and SLE,\(^{33}\) with a recent longitudinal study demonstrating significant progression of disease in women with SLE.\(^{34}\)

### Inflammation and atherosclerosis

Available data suggest that intensive management of inflammation combined with traditional CVRF modification and treatment is required to minimize cardiovascular risk in RA and SLE.\(^{35}\) Anti-tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) therapy may enhance flow-mediated dilatation\(^{36,37}\) although this benefit may be transient.\(^{25}\) Notwithstanding, the risk of myocardial infarction in patients with RA who respond to treatment with anti-TNF-\(\alpha\) agents is markedly reduced when compared with non-responders, supporting the notion that inflammation plays a pivotal role in atherosclerotic disease.\(^{38}\)

Likewise, statins and angiotensin-converting enzyme inhibition may have similar beneficial effects on flow-mediated dilatation\(^{39,40}\) and may also reduce aortic stiffness.\(^{11}\) Studies of cardiovascular mortality and progression of atherosclerosis have also revealed
encouraging results for methotrexate and mycophenolate mofetil, agents commonly used in the management of RA and SLE. In particular, methotrexate has been shown to reduce cardiovascular mortality by 70%. We speculate that the positive effects of these treatments on cardiovascular risk might also be achieved through a reduction of CMD.

To explore the mechanisms underlying these findings, we considered the relationship between the derangement of MBF and disease activity. A significant inverse correlation between SLEDAI and CFR was present although only a trend between DAS-28 and CFR was observed.

Our findings are also consistent with the concept of inflammation as a risk factor for coronary artery disease. We hypothesize that chronic inflammation impairs coronary microvascular function, which in turn is responsible for the abnormalities in MBF and CFR. Of note we demonstrated a correlation between CFR and disease duration in patients with low grade inflammation. In this context, a disease-specific element has been reported to contribute to the increased cardiovascular risk associated with SLE and RA, although the precise nature of this remains to be determined. Soluble factors including increased levels of the pro-inflammatory cytokines—TNF-α and interleukin-6—may be important. Endothelial injury associated with immune complexes, complement activation, antiphospholipid, and anti-endothelial antibodies are particularly relevant in SLE. In RA, increased numbers of CD4+CD28- T cells capable of secreting Th1 cytokines resulting in macrophage activation and endothelial injury have been associated with accelerated atherosclerosis. It is likely that at least some of these factors may play a causative role in CMD.

Limitations and future directions

This is a proof of principle study and its main limitations, i.e. the relatively small sample size, its cross-sectional design, and lack of follow-up data, do not make it possible to prove that the severity of CMD predicts major adverse cardiovascular events and precedes established epicardial atherosclerotic disease. Multi-slice (64 slices) computed tomography has been demonstrated to have a high negative predictive value, although its accuracy in measuring the degree of minor coronary lesions is less clear. The current challenge to clinicians is to identify those patients at higher risk early in the course of the disease such as those with evidence of ischaemic-like changes on the electrocardiogram during stress. In addition to a longitudinal study to establish the relationship between CMD and overt atherosclerosis, the effect of therapeutic intervention on MBF and CFR needs to be investigated.

Conclusions

In summary, we provide evidence that chronic inflammation in the absence of epicardial stenoses and traditional coronary risk factors is associated with severe abnormalities of the coronary microcirculation. This may represent an early marker of cardiovascular disease which precedes and contributes to accelerated atherogenesis in patients with RA and SLE.

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Conflict of interest: none declared.

References


