Concise report

Retinal vascular calibre is altered in patients with rheumatoid arthritis: a biomarker of disease activity and cardiovascular risk?

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Abstract

Objectives. Alterations in retinal vascular calibre, particularly wider venular calibre, have been independently associated with elevated markers of inflammation and cardiovascular risk in the general population. We hypothesized that retinal vascular calibre would be altered in patients with RA, who are known to have both elevated cardiovascular risk and chronic, systemic inflammation.

Methods. Retinal vascular calibre was measured from digital retinal photographs using computerized methods in 51 RA patients and 51 age- and gender-matched controls. Retinal vascular calibre was compared between RA and control patients with adjustment for relevant variables including cardiovascular risk factors and companion vessel calibre. The relationship between retinal venular calibre and inflammation was assessed by comparing controls and RA patients with high and lower disease activity.

Results. Retinal venular calibre [mean (s.d.)] was significantly wider in RA patients than in controls [235.9 (24.6) vs 211.6 (21.0) μm, P < 0.001]. After adjustment for all relevant variables, mean venular calibre remained 20.3 μm (95% CI 10.4, 30.3) wider in RA patients compared with controls. Retinal venular calibre [mean (s.d.)] also increased with increasing levels of systemic inflammation: 211.6 (21.0) μm in controls, 232.3 (22.4) μm in RA patients with moderate or lower disease activity and 255.5 (28.3) μm in RA patients with high disease activity (P for trend < 0.0001).

Conclusions. This study demonstrates that RA patients have dilated retinal venular calibre, reflecting systemic inflammation and possibly increased cardiovascular risk. Longitudinal studies correlating retinal vascular calibre with subsequent cardiovascular events will clarify the clinical utility of this test in patients with RA.

Key words: Rheumatoid arthritis, Cardiovascular, Atherosclerosis, Retinal vascular calibre, Inflammation, Ocular photography, Vascular, Risk.

Introduction

RA is a systemic inflammatory disease associated with endothelial dysfunction and increased cardiovascular morbidity and mortality [1, 2]. Inflammation is central to the pathogenesis of atherosclerosis [3] and it is likely that chronic systemic inflammation contributes to increased cardiovascular disease in RA. Traditional cardiovascular risk factors do not fully explain the increased cardiovascular risk in RA, so improved methods for identifying high risk patients are required [4].

Measurement of retinal vascular calibre is potentially a novel method for assessing cardiovascular risk. In epidemiological studies among the general population, changes in retinal vascular calibre, particularly wider...
venular calibre, have been independently associated with vascular risk factors and increased risk of cardiovascular events [5–13]. The pathophysiological determinants of retinal venular calibre are not completely understood; however, systemic inflammation and endothelial dysfunction appear to play an important role [8, 10, 14]. The aim of the present study was to compare retinal vascular calibre between RA patients and age- and gender-matched controls, and between RA patients with high and low disease activity levels. We hypothesize that alterations in retinal vascular calibre, particularly venular calibre, may reflect vascular dysfunction resulting from chronic systemic inflammation and may therefore be a biomarker of increased cardiovascular risk in RA patients.

Patients and methods
Fifty-one patients with RA as defined by the 1987 ACR criteria [15] were recruited at random from Royal Melbourne Hospital Rheumatology clinics. Exclusion criteria were acute glaucoma and inability to provide informed consent. Control patients were obtained from participants in the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, a population-based prospective cohort study of 11247 Australian adults [16]. Fifty-one age- and gender-matched healthy controls were randomly selected from AusDiab participants who had retinal photographs taken in 2004–05. Our study was approved by the Melbourne Health Human Research Ethics Committee and written informed consent was obtained from all participants according to the Declaration of Helsinki.

All participants underwent clinical assessment of cardiovascular risk factors. Hypertension was defined as blood pressure (BP) ≥140/90 mmHg or current use of anti-hypertensive medication. Diabetes was defined as fasting blood glucose ≥7.0 mmol/l or treatment with insulin or oral hypoglycaemic agents. Smoking status was defined as current smoker if smoking tobacco products at least daily, ex-smoker if previously smoked daily and never smoker if never smoked daily. Fasting lipid levels were determined using enzymatic methods. Disease activity in the RA subjects was measured using the 28-joint DAS (DAS-28), a validated composite score incorporating tender and swollen joint count, ESR and a patient global assessment of disease activity [17]. A DAS-28 >5.1 indicates high disease activity, while a DAS-28 <3.2 indicates low disease activity [17].

Measurement of retinal vascular calibre
Each subject in our study had digital retinal photographs taken according to standardized procedure with a 45-degree non-mydriatic fundus camera. The digital images of all RA and control subjects were analysed by a single trained assessor blinded to clinical information, using validated semi-automated software according to a standard protocol [18]. In brief, all the vessel calibres passing through the area between a half and one disc diameter from the edge of the optic disc were measured. The largest six calibres of arterioles and venules were summarized as the central retinal artery equivalent (CRAE) and the central retinal vein equivalent (CRVE), respectively. Reproducibility of this method is high, with intra-grader intra-class correlation coefficients of 0.97 and 0.96 for CRAE and CRVE, respectively.

Statistical methods
Descriptive data are summarized using mean (s.d.) or median (range) for continuous variables and n (%) for categorical variables. Baseline characteristics of the RA and control patients were compared using chi-squared test for categorical variables and the paired t-test for continuous variables. Normality of the variables was examined using boxplots, Kolmogorov–Smirnov and Shapiro–Wilks tests. CRAE and CRVE in RA and control patients were analysed by multivariable linear regression analysis adjusting for age, gender, BMI, BP, lipid levels, diabetes status, smoking status and companion vessel calibre. Pairwise comparisons of CRVE between control and RA groups were performed using the Tukey–Kramer test after analysis of variance (ANOVA). A P-value of 0.05 was used for significance testing. All statistical analyses were performed using Stata software, version 10.0 (Stata Corp., College Station, TX, USA).

Results
Demographic characteristics of the RA patients and controls are shown in Table 1. There were no significant differences between the two groups apart from mean diastolic BP and high-density lipoprotein (HDL) cholesterol, which were higher in the RA patients (77 vs 69 mmHg; \( P = 0.002 \) and 1.6 vs 1.3 mmol/l; \( P = 0.012 \), respectively). The RA patients had median (range) disease duration of 9 (0.3–55) years.

Mean retinal arteriolar and venular calibre were compared between the RA and control groups (Table 1). Mean (s.d.) CRAE was 152.3 (15.3) μm in the RA patients vs 143.7 (13.9) μm in the control patients (\( P = 0.004 \)). Mean (s.d.) CRVE was 235.9 (24.6) μm in the RA patients vs 211.6 (21.0) μm in the control patients (\( P < 0.001 \)).

The relative difference in CRAE and CRVE between RA patients and controls was calculated in an unadjusted model and in a model with adjustment for age, gender, BMI, systolic and diastolic BP, lipid levels, diabetes status, smoking status and companion vessel calibre. In the unadjusted analysis, both CRAE and CRVE were significantly wider in the RA group [mean CRAE 8.6 μm greater in RA vs controls (95% CI 2.8, 14.4 μm) and mean CRVE 24.3 μm greater in RA vs controls (95% CI 15.2, 33.2 μm)]. After adjustment for all relevant variables, as described above, the CRVE remained significantly larger in the RA patients [mean CRVE 20.3 μm greater in RA vs controls (95% CI 10.4, 30.3 μm)], while CRAE was not different between the groups [mean CRAE 2.4 μm greater in RA vs controls (95% CI −4.3, 9.1 μm)].
We also investigated the relationship between retinal venular calibre and severity of RA. Figure 1 shows CRVE in controls, RA patients with disease activity that was moderate or less (DAS-28 ≤ 5.1, n = 43) and RA patients with high disease activity (DAS-28 > 5.1, n = 8). Mean (s.d.) CRVE was larger as disease activity increased [211.6 (21.0), 232.3 (22.4) and 255.5 (28.3) μm in controls, RA with moderate or less activity and RA with high disease activity, respectively, \( P \) for trend <0.0001]. The differences remained significant after adjusting for potential confounders including age, gender, BMI, diabetes, BP, smoking status and lipid levels.

**Discussion**

In this comparison of RA patients and age- and gender-matched controls, we found that retinal venular calibre was significantly wider in the RA patients, especially in RA patients with high disease activity, while there was no difference in retinal arteriolar calibre between the two groups. This finding supports our *a priori* hypothesis and is consistent with recent data that suggest that retinal arteriolar and venular calibres are influenced by different vascular pathophysiological processes. Retinal arteriolar calibre is predominantly determined by BP, whereas retinal venular calibre has been associated with elevated markers of inflammation, endothelial dysfunction, obesity, diabetes and future risk of stroke and coronary heart disease [19]. After adjusting for BP, BMI, diabetes and other cardiovascular risk factors, our RA patients had similar retinal arteriolar calibre but wider retinal venular calibre compared with controls. This result, along with our observation that retinal venular calibre was highest in the RA patients with highest disease activity, suggests that retinal venular calibre in RA patients reflects systemic inflammation and possibly associated endothelial dysfunction.

After controlling for traditional cardiovascular risk factors, the RA patients had a mean retinal venular calibre that was 20.3 μm greater than that of the controls. In a meta-analysis of prospective studies in the general population evaluating the association between retinal venular calibre and incident coronary heart disease, a 20 μm increase in retinal venular calibre was associated with a coronary heart disease hazard ratio of 1.16 (95% CI 1.06, 1.26) in women [20]. Although it is not valid to directly translate the findings of this meta-analysis to our

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**TABLE 1** Demographic details of RA patients and controls

<table>
<thead>
<tr>
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<th>RA (n = 51)</th>
<th>Controls (n = 51)</th>
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</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>34 (67)</td>
<td>34 (67)</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>59.5 (12.5)</td>
<td>59.5 (12.5)</td>
</tr>
<tr>
<td>Systolic BP, mean (s.d.), mmHg</td>
<td>131 (19)</td>
<td>132 (22)</td>
</tr>
<tr>
<td>Diastolic BP, mean (s.d.), mmHg*</td>
<td>77 (11)</td>
<td>69 (11)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>5 (9.8)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>7 (13.7)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Ex-smoker, n (%)</td>
<td>8 (15.7)</td>
<td>14 (27.4)</td>
</tr>
<tr>
<td>Never smoker, n (%)</td>
<td>36 (70.6)</td>
<td>35 (68.6)</td>
</tr>
<tr>
<td>BMI, mean (s.d.)</td>
<td>29.7 (5.6)</td>
<td>29.2 (5.3)</td>
</tr>
<tr>
<td>Total cholesterol, mean (s.d.), mmol/l</td>
<td>5.2 (1.2)</td>
<td>5.3 (1.1)</td>
</tr>
<tr>
<td>HDL cholesterol, mean (s.d.), mmol/l*</td>
<td>1.6 (0.6)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>LDL cholesterol, mean (s.d.), mmol/l</td>
<td>2.9 (0.9)</td>
<td>3.3 (0.9)</td>
</tr>
<tr>
<td>Triglycerides, mean (s.d.), mmol/l</td>
<td>1.4 (0.6)</td>
<td>1.5 (0.8)</td>
</tr>
<tr>
<td>RA disease duration, median (range), years</td>
<td>9.4 (0.3–55)</td>
<td>NA</td>
</tr>
<tr>
<td>DAS, median (range)</td>
<td>3.4 (1.2–7.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Number of DMARDs, median (range)</td>
<td>2 (0–4)</td>
<td>NA</td>
</tr>
<tr>
<td>CRAE, mean (s.d.), μm*</td>
<td>152.3 (15.3)</td>
<td>143.7 (13.9)</td>
</tr>
<tr>
<td>CRVE, mean (s.d.), μm*</td>
<td>235.9 (24.6)</td>
<td>211.6 (21.0)</td>
</tr>
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</table>

*P < 0.05 for the comparison between RA and control patients. LDL: low-density lipoprotein; NA: not applicable.
study population, the comparison serves to place the magnitude of the difference in retinal venular calibre measurements in our RA and control patients into perspective.

To our knowledge, this is the first report of retinal vascular measurement in patients with RA. The strength of this study is the inclusion of RA patients and matched controls who are well characterized, with detailed information on cardiovascular risk factors and measures of systemic inflammation (in the RA patients). The methodology of retinal vascular calibre measurement used in this study is well established, widely accepted and has been extensively reported.

The main limitation is the cross-sectional nature of our study. It is not clear whether the observed increase in retinal venular calibre in RA patients is due to increased cardiovascular risk, high levels of systemic inflammation or a combination of the two. We are unable to draw conclusions about the relationship between increased retinal venular calibre in RA patients and subsequent risk of cardiovascular events from these data. Furthermore, our RA cohort included patients recruited from a tertiary hospital setting who had, on average, long-standing disease. Therefore, our findings may not be generalizable to patients with early or mild RA.

In summary, we have demonstrated that RA patients have wider retinal venular calibre, which is related to severity of disease. Longitudinal studies correlating retinal vascular calibre with disease activity progression and subsequent cardiovascular events will clarify the clinical utility of retinal vascular calibre measurement in patients with RA.

Rheumatology key messages

- Increased retinal venular calibre is associated with inflammation and cardiovascular risk.
- This study is the first to demonstrate wider retinal venular calibre in RA patients.
- Retinal venular calibre was widest in the RA patients with highest disease activity.

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References


