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Myocardial perfusion values of early, pre-treatment rheumatoid arthritis do not differ from healthy controls: A CADERA sub-study.

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Conflicts of interest

The authors declare no conflicts of interest

Ethics

The single- centre study was undertaken at Leeds Teaching Hospitals NHS Trust rheumatology and cardiology departments according to the Declaration of Helsinki, with approval from the National Research Ethics Service (Leeds (West) Research Ethics Committee (reference 10/H1307/138; Current Controlled Trials (registration number: ISRCTN50167738))). All participants provided informed, written consent.

Dear Editor,

Rheumatoid arthritis (RA) is a chronic inflammatory condition associated with an increased risk of coronary artery disease. Inflammation leading to myocardial microvascular dysfunction (MVD) is considered to be a key mechanistic factor. Although reduced myocardial perfusion reserve has been demonstrated in patients with established RA [1], it has not yet been investigated in early, treatment naïve, RA patients. The CADERA trial (Coronary Artery Disease Evaluation in RA) [2] was a randomized trial to determine if patients with early, treatment naïve RA have cardiovascular disease, and if it is modifiable with therapy. Here, we present the myocardial perfusion analysis of CADERA.

Consecutive patients diagnosed with new-onset RA provided written informed consent before undergoing cardiovascular magnetic resonance imaging (CMR) in this study, which was approved by the National Research Ethics Service (Leeds (West) Research Ethics Committee (reference 10/H1307/138) All patients were randomized to either 'Early ETN': first- line tumour necrosis factor inhibitor (TNFi), etanercept (ETN) + Methotrexate (MTX) (15 mg weekly, optimised to 25 mg weekly by week 8); or 'delayed ETN': first- line MTX-treat-to-target (TT) (MTX monotherapy 15 mg weekly increased to 25 mg weekly at 2 weeks +/- additional sulphasalaine/hydroxychloroquine, with escalation to ETN+MTX at week 24 if not in in DAS28-ESR remission) [2]. The primary outcome measure for CADERA was aortic distensibility, but a subgroup of CADERA patients underwent additional rest and adenosine induced stress quantitative perfusion imaging. Patients were invited to return for a second scan following 1 year of treatment. Thirty healthy volunteers, matched to the first thirty study patients by age and sex, also underwent a single CMR scan. Myocardial blood flow (MBF) values at rest and stress were estimated using a previously described model-independent deconvolution method [3], and myocardial perfusion reserve (MPR) values were calculated.

Of the 70 patients recruited to the main CADERA study, 32 underwent rest and stress perfusion at both visits. Of these one was excluded leaving 31 patients. Of the 23 healthy controls that underwent stress and rest perfusion, 21 had analysable perfusion data (Table 1).

There was no difference in perfusion measurements between healthy controls and early, pre-treatment RA patients: MPR (mean difference: 0.17; 95%CI: -0.39, 0.73; p=0.54) or stress MBF (mean difference 0.18 ml/min/g; 95% CI: -0.05, 0.40 ml/min/g; p=0.13), figure 1. There was no difference in perfusion measurements between pre-treatment patients and 1 year post-treatment: MPR (mean difference 0.23; 95%CI: -0.16, 0.63; p=0.24), stress MBF (mean difference: 0.12 ml/min/g, 95% CI: -0.21, 0.45 ml/min/g, p=0.45), (Figure 1). There was no substantive difference in MPR or stress MBF between the treatment groups and no evidence of an intervention-time interaction.

Our data did not show evidence of reduced myocardial perfusion in treatment naïve RA, compared with normal controls. Perfusion did not increase after 1 year of RA-directed treatment, and there was no difference in perfusion between treatment groups, although this study was not powered to detect differences in perfusion and our sample size may have been too small to detect differences adequately. These early RA data differ from studies in established RA, which show reduced perfusion compared to healthy controls [1]. These results could suggest possible differences in the time course of large and small vessel disease in RA, with macrovascular changes occurring before measurable myocardial microvascular disease.

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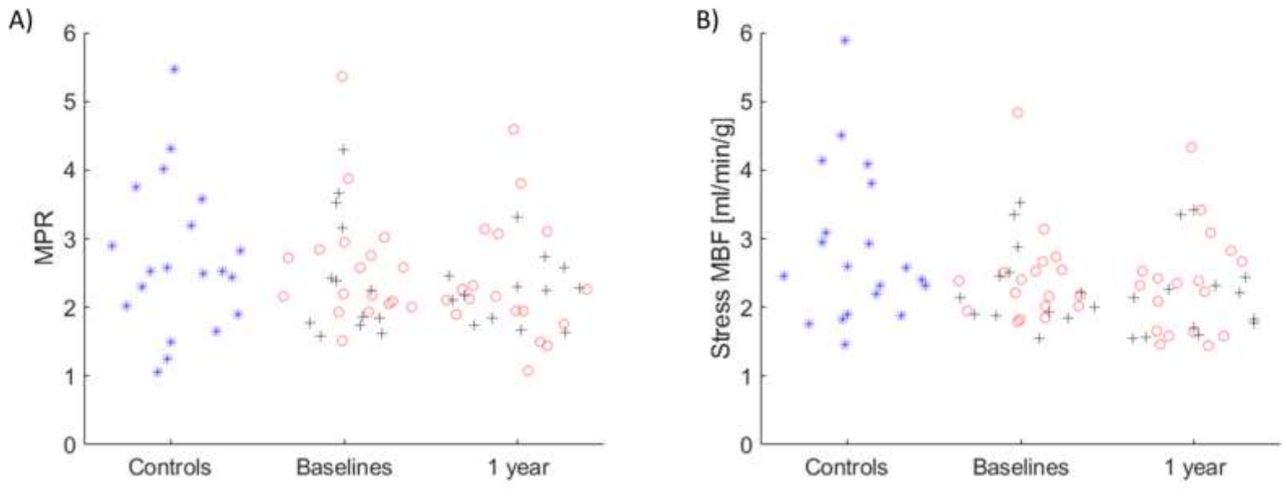
Figure 1: The d*istributions of A) MPR and B) stress MBF values for healthy controls (blue stars) and patients who received Early ETN treatment (black crosses) delayed ETN treatment (red circles) therapy at baseline and at 1 year follow up.*

Table 1: Summary of baseline demographic, disease activity and comorbidity data for controls and patients.



Variable	Healthy Volunteers n=21	Patients n=32
Demographics		
Female % (n/N)	63 (13/21)	72 (23/32)
Age, years median (IQR)	56 (11)	56.5 (14.3)
BMI, median (IQR)	27.7 (7.5)	24.7 (4.6)
RA profile, % (n/N)		
ACPA positive	N/A	81 (26/32)
RF positive	N/A	66 (21/32)
RA disease activity profile, median (IQR)		
Baseline DAS28	N/A	6.1 (1.4)
ESR	N/A	42 (32.5)
CRP	N/A	10.5 (24.7)
Traditional CV risk factors, % (n/N)		
Hypertension	0 (0/21)	12.5 (4/32)
Hypercholesterolaemia	0 (0/21)	3 (1/32)
Diabetes	0 (0/21)	0 (0/32)
Family History IHD	0 (0/21)	2.9 (1/32)
Smoking status, % (n/N)		
Current	14 (3/21)	17 (5/29)
Former	19 (4/21)	41 (12/29)
Never	67 (14/21)	41 (12/29)
Perfusion, median (IQR)		
Stress MBF [ml/min/g]	2.51 (1.39)	2.21 (0.61)
Rest MBF [ml/min/g]	1.10 (0.58)	0.92 (0.38)
MPR	2.53 (1.42)	2.25 (0.99)

Denominator less than n indicates missing data.
BMI, body mass index; ACPA, anti-citrullinated protein/peptide antibody; RF, rheumatoid factor; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; CRP, C- reactive protein; IHD, ischaemic heart disease; MBF, myocardial blood flow; MPR, myocardial perfusion reserve.