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First cardiovascular magnetic resonance imaging study in individuals at-risk of rheumatoid arthritis detects abnormal aortic stiffness suggesting an anti-citrullinated peptide antibody mediated role for accelerated atherosclerosis

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Title: **First cardiovascular magnetic resonance imaging study in individuals at-risk of rheumatoid arthritis detects abnormal aortic stiffness suggesting an anti-citrullinated peptide antibody mediated role for accelerated atherosclerosis**

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Competing interests

The authors have no competing interests to declare.

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Patients with rheumatoid arthritis (RA) are at greater risk of major cardiovascular (CV) events, predominantly due to accelerated atherosclerosis, underpinned by inflammation and RA-disease factors, and also heart failure [1]. Overall modest event rate has necessitated the use of surrogate CV abnormalities of increased CV risk including arterial stiffness. Increased arterial stiffness is well-recognised in established RA [2], with early, similar reports using comprehensive and reliable cardiac magnetic resonance imaging (CMR) in our treatment-naïve, early onset RA cohort [3]. Autopsy, histopathological and clinical studies in general population and RA cohorts with and without CVD suggest citrullinated proteins as a mechanism for atherosclerosis, including presence of citrullination within the atherosclerotic plaque of subjects without RA [4, 5]. We hypothesised that individuals with circulating anti-CCP but no systemic inflammation (of RA typically associated with increased CV risk) also demonstrate CV abnormalities.

Anti-CCP positive individuals with any new musculoskeletal (MSK) symptoms but no clinical synovitis (subsequently termed at-risk individuals), and no prior history of CVD, were recruited from a tertiary centre Rheumatology outpatient clinic. Following informed consent, 18 at-risk individuals and 30 healthy controls (HC) matched for age and gender, underwent multi-parametric 3.0T CMR with late Gadolinium enhancement (Achieva, Philips, Best, The Netherlands) in an academic CMR centre. As part of our previously described cohort studies at at-risk individuals were classified as 'low' (<50%) or 'high' (>50%) risk of developing RA using a published clinical risk model [6] and followed up for 12 months to assess for progression to a clinical diagnosis of RA. CMR analysis was performed blinded to patient details. Using SPSS version 22, unpaired Student t-tests and Mann-Whitney tests compared continuous variables.

Of the at-risk individuals, 4 (22%) were male, the mean (±SD) age was 53 ±15 years, anti-CCP 136 ±136IU/ml and predicted absolute risk of RA 49 ±17%. There were no differences between at-risk individuals and HC for age, gender, blood pressure, CV risk factors (hypertension, diabetes, hypercholesterolaemia) and active smoking status, although at-risk individuals had a higher body mass index (29 ±5 and 25 ±5 kg/m^2 respectively) and proportion of ex-smokers (56% and 17% respectively). Table S1 details baseline demographic data of at-risk RA individuals and HC. Five of the 18 recruited patients progressed to RA over 12 months.

Analyses (table 1) revealed aortic distensibility was notably lower (indicating greater arterial stiffness) in at-risk individuals compared with HC (3.6 ±1.3 versus 4.9 ±2.1 x $10^{-3}$$mmHg^{-1}$ respectively); a finding most pronounced in the high-risk individuals (n=8) compared to low-risk (n=10) (3.1 ±0.6 and 4.2 ±1. x $10^{-3}$$mmHg^{-1}$ respectively), and in those who progressed to RA over 12 months (see Table 1). Similarly, sizeable differences in all other measures of aortic stiffness, including aortic compliance and aortic strain and aortic stiffness (β)was observed, again with greater aortic stiffness in high versus low at-risk individuals and in at-risk individuals progressing to RA.

To our knowledge this is the first study showing subclinical increase in aortic stiffness in at-risk individuals for RA, with values numerically close to those seen in early, treatment naïve RA. Our use of CMR as a research tool offers a particularly sensitive assessment of structural and functional changes to reflect micro- and macro-vascular pathological processes of RA. The key limitation of this pilot study is absence of control groups. Nevertheless, the abnormal aortic stiffness measures were most pronounced in the high at-risk cohort and those progressing to

RA (albeit with a trend for greater stiffness also seen in low risk patients), implying a particular role of CCP antibodies.

These data advance the concept of anti-CCP mediated atherosclerosis and support additional investigation in larger, and both anti-CCP positive and negative control populations.

Table 1: Baseline CMR findings for at-risk individuals and healthy controls.

Variable	Healthy Controls (n=30)	All At-Risk Individuals (n=18)	P value (controls vs all at risk)	<50% At-Risk Individuals (n=8)	P value (controls vs <50% risk)	>50% At-Risk Individuals (n=10)	P value (controls vs >50% risk)	Progressors to RA within 1 year (n=5)	P value (controls vs. progressors)	Non-progressors to RA within 1 year (n=13)	P value (controls vs non-progressors)
Aortic stiffness											
Aortic distensibility (10^{-3}mmHg^{-1})	4.9 ± 2.1	3.6 ± 1.3	0.001	4.2 ± 1.7	0.35	3.1 ± 0.6	0.001	3.2 ± 0.7	0.002	3.8 ± 1.5	0.048
Aortic compliance	17.4 ± 4.2	14.3 ± 3.6	0.15	15.2 ± 3.5	0.15	13.6 ± 3.8	0.15	13.8 ± 5.1	0.20	14.5 ± 3.1	0.017
Aortic strain	0.25 ± 0.08	0.20 ± 0.05	0.001	0.21 ± 0.08	0.23	0.19 ± 0.02	0.001	0.18 ± 0.02	0.001	0.21 ± 0.06	0.05
Aortic stiffness index (β)	2.7 ± 0.9	3.4 ± 0.9	0.005	3.1 ± 1.0	0.29	3.7 ± 0.8	0.005	4.0 ± 1.1	0.048	3.2 ± 0.7	0.06
LV structure											
LV Mass/BSA (g/m^2)	49 ± 8	46 ± 10	0.72	44 ± 7	0.16	48 ± 11	0.72	45 ± 13	0.57	46 ± 9	0.39
Measures of fibrosis											
Native T1 (ms)	1199 ± 35	1212 ± 34	0.39	1214 ± 40	0.37	1210 ± 32	0.39	1200 ± 21	0.98	1217 ± 38	0.19
ECV (%)	25.4 ± 2.5	27.7 ± 3.6	0.16	28.0 ± 3.7	0.1	27.4 ± 3.8	0.16	26.3 ± 1.7	0.35	28.3 ± 4.1	0.04
LGE	0/30	1/18	0.59	0/8	-	1/10 (10%)	0.59	0/5	-	1/13 (8%)	0.68
Function											
S'(seconds $^{-1}$)	1.16 ± 0.14	1.12 ± 0.12	0.23	1.16 ± 0.08	0.92	1.10 ± 0.14	0.23	1.12 ± 0.17	0.67	1.12 ± 0.10	0.31
LVEF (%)	62 ± 5	62 ± 4	0.95	61 ± 4	0.48	62 ± 4	0.95	63 ± 5	0.84	61 ± 4	0.49
LVEDV/BSA (ml/m^2)	78 ± 10	83 ± 12	0.42	84 ± 9	0.17	83 ± 15	0.42	80 ± 16	0.88	84 ± 11	0.11
Torsion (degrees)	15.1 ± -4.7	16.3 ± 4.6	0.76	17.1 ± 4.6	0.39	15.7 ± 4.8	0.76	13.7 ± 3.5	0.44	17.6 ± 4.7	0.19
Twist (degrees)	15.8 ± 4.6	17.1 ± 4.8	0.43	16.9 ± 5.2	0.66	17.3 ± 4.9	0.43	17.6 ± 5.5	0.53	16.9 ± 4.8	0.54

Mean (± SD) values presented unless otherwise stated.

BSA, body surface area; ECV, extracellular volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement

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