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

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. 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, with early, similar reports using comprehensive and reliable cardiac MRI (CMRI) in our treatment-naïve, early onset RA cohort. Autopsy, histopathological and clinical studies in general population and RA cohorts with and without CV disease (CVD) suggest citrullinated proteins as a mechanism for atherosclerosis, including presence of citrullination within the atherosclerotic plaque of subjects without RA. We hypothesised that individuals with circulating anti-cyclic citrullinated peptide (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 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 multiparametric 3.0T CMRI with late Gadolinium enhancement (Achieva, Philips, Best, The Netherlands) in an academic CMRI 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 model8 and followed up for 12 months to assess for progression to a clinical diagnosis of RA. CMRI analysis was performed blinded to patient details. Using SPSS V.22, unpaired Student t-tests and Mann-Whitney tests compared continuous variables.

Of the at-risk individuals, 4 (22%) were males, the mean (±SD) age was 53±15 years, anti-CCP 136±136 IU/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± kg/m², respectively) and proportion of ex-smokers (56% and 17%, respectively). Online supplementary 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 stiffness was notably lower (indicating greater arterial stiffness) in at-risk individuals compared with HC (3.6±1.3 vs 4.9±1.7 mm Hg⁻¹, respectively), a finding most pronounced in the high at-risk cohort and those progressing to RA (although 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 anti-CCP-negative control populations.

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**Table 1 Baseline cardiac MRI findings for at-risk individuals and HCs**

| Variable | HCs (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) | Nonprogressors to RA within 1 year (n=13) | P value (controls vs non progressors) |
|----------|------------|--------------------------------|----------------------------------|-------------------------------|--------------------------------|-------------------------------|----------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|----------------------------------|
| Aortic stiffness | 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 (ε) | 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/m²) | 49±8 | 46±10 | 0.72 | 44±7 | 0.16 | 48±11 | 0.72 | 45±13 | 0.57 | 46±9 | 0.39 |

LV function

| Variable | HCs (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) | Nonprogressors to RA within 1 year (n=13) | P value (controls vs non progressors) |
|----------|------------|--------------------------------|----------------------------------|-------------------------------|--------------------------------|-------------------------------|----------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|----------------------------------|
| 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/m²) | 78±10 | 78±10 | 0.12 | 84±9 | 0.17 | 83±15 | 0.42 | 80±16 | 0.88 | 84±11 | 0.11 |
| Torsion (degrees) | 15.1±4.7 | 15.1±4.7 | 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; HCs, healthy controls; LGE, late gadolinium enhancement; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction.

Letters
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