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RESEARCH LETTER

Relationship Between Risk of Atherosclerotic Cardiovascular Disease, Inflammation, and Coronary Microvascular Dysfunction in Rheumatoid Arthritis

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Inflammation is an independent risk factor for cardiovascular disease in the general population.[1] Patients with rheumatoid arthritis (RA) have ~1.5× excess risk[2] attributed to their chronic exposure to inflammation. Coronary flow reserve (CFR), a quantitative imaging biomarker, is one approach for assessing cardiovascular risk. In the absence of overt obstructive coronary artery disease, CFR provides information on the integrated hemodynamic effects of diffuse atherosclerosis and coronary microvascular dysfunction (CMD) on myocardial tissue perfusion.[3] CMD is associated with increased risk for cardiac mortality independent of traditional cardiovascular risk factors in the general population and in RA.[4,5] Current risk scores, for example, atherosclerotic CVD (ASCVD), underestimate cardiovascular risk in RA and the American College of Cardiology/American Heart Association now considers systemic inflammatory diseases as risk enhancers. Interleukin 6 (IL-6) is an inflammatory mediator implicated in RA pathogenesis, and its role in cardiovascular risk is increasingly recognized in the general population.[6,7] The objective of this study was to determine the relationships between ASCVD risk, inflammation, and CMD in RA. We hypothesized that CMD will be prevalent in patients with RA who have low estimated ASCVD risk and that CMD will be associated with higher levels of IL-6.

We analyzed baseline data from the LIIRA (Lipids, Inflammation and Cardiovascular Risk in RA) study, NCT02714881. The data that support the findings of this study are available from the corresponding author upon reasonable request. LIIRA included individuals with RA, age>35 years with active RA, not on a statin or biologic therapy. All subjects underwent assessment of cardiovascular risk factors, as well as the validated RA Disease Activity Score-28-C-reactive protein (CRP3), which includes tender, swollen joints, and hsCRP (high-sensitivity CRP); a stress myocardial perfusion positron emission tomography scan was performed to quantify CFR. Standard positron emission tomography imaging protocols were performed as previously described.[3] CFR was calculated as the ratio of myocardial blood flow (mL/min per g) at peak stress over that at rest; CMD was defined as CFR<2.5. Attenuation correction computed tomography scans were reviewed for semi-quantitative assessment of coronary artery calcium. HsCRP and IL-6 levels were measured in the clinical laboratory. A Wilcoxon rank-sum test was performed

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to test differences between median IL-6 and hsCRP among individuals with and without CMD; $P<0.05$ was considered significant (R version 3.6.3). The study was approved by the institutional review committee and all subjects gave informed consent.

LIIRA enrolled 74 subjects with mean age 54.5 (SD 10.6) years, 82% (N=61) female with mean RA duration of 7.4 (SD 8.4) years, 72% were on methotrexate, 42% on prednisone (mean dose 7.7 mg [SD 6.1]). The median Disease Activity Score 28-CRP3 was 4.0 (interquartile range [IQR] 3.1, 4.8], indicating moderate disease activity. Median hsCRP in the cohort was 4.1 mg/L (IQR 1.8, 8.6), with a mean low-density lipoprotein cholesterol of 115 mg/dL (SD 31.0). No subjects had coronary artery disease or hyperlipidemia. Cardiovascular comorbidities included diabetes, n=3 (4.1%), hypertension, n=18 (24%), and mean body mass index 30 kg/m^2 (SD 7.2).

The mean cohort CFR was 2.6 (SD 0.5) and CMD was present in 47% (N=34) of subjects. Coronary artery calcium was uncommon: 12% (N=9) had mild and 2.7% (N=2) had moderate coronary artery calcium. Clinically evident mild ischemia was detected on perfusion images in 3 subjects. The median ASCVD estimated risk for the entire cohort was 2.5% (IQR 0.9, 6.9); 54 (79%) subjects had ASCVD risk <7.5, considered low/borderline in the general population, among whom 41% (N=22) had CMD. The prevalence of CMD was 78.6% among patients with ASCVD risk >7.5, considered intermediate/high risk. Median IL-6 levels were 44% higher in subjects with CMD versus those without regardless of ASCVD risk (4.7 pg/mL [IQR 3.2, 23.9]) versus 3.2 pg/mL [IQR 1.6, 5.5], respectively, $P=0.01$) (Figure). No significant difference in hsCRP was observed among subjects with and without CMD (median hsCRP 5.6 mg/L [IQR 1.8, 14.6] versus 2.7 mg/L [IQR 1.5, 5.8], respectively, $P=0.07$).

The overall cohort had a median ASCVD risk below what is considered a threshold for primary prevention (ASCVD<7.5%) as well as low coronary artery calcium burden, yet had evidence for CMD, an independent risk factor for increased cardiovascular risk and mortality. CMD was associated with higher levels of IL-6 but not hsCRP; however, the lack of difference in hsCRP may be due to insufficient power because of the sample size. These findings provide insight into the mechanisms by which inflammation, and specific pathways, that is, IL-6 may mediate microvascular dysfunction and increased cardiovascular risk in RA,[7] with direct implications for individuals without RA. Indeed, the relationship between IL-6 and cardiovascular disease in the general population is being studied in the ZEUS (Zlitivekimab Cardiovascular Outcomes Study) trial, which will test whether targeting IL-6 will lead to a reduction in cardiovascular events.[6]

Limitations of this study include a relatively small sample size from 2 large academic centers; however, it is one of the largest studies performed with CFR and inflammatory biomarker data in RA. These findings suggest specificity of inflammatory pathways with CMD and the potential role of cardiac imaging in augmenting ASCVD estimated risk to identify excess

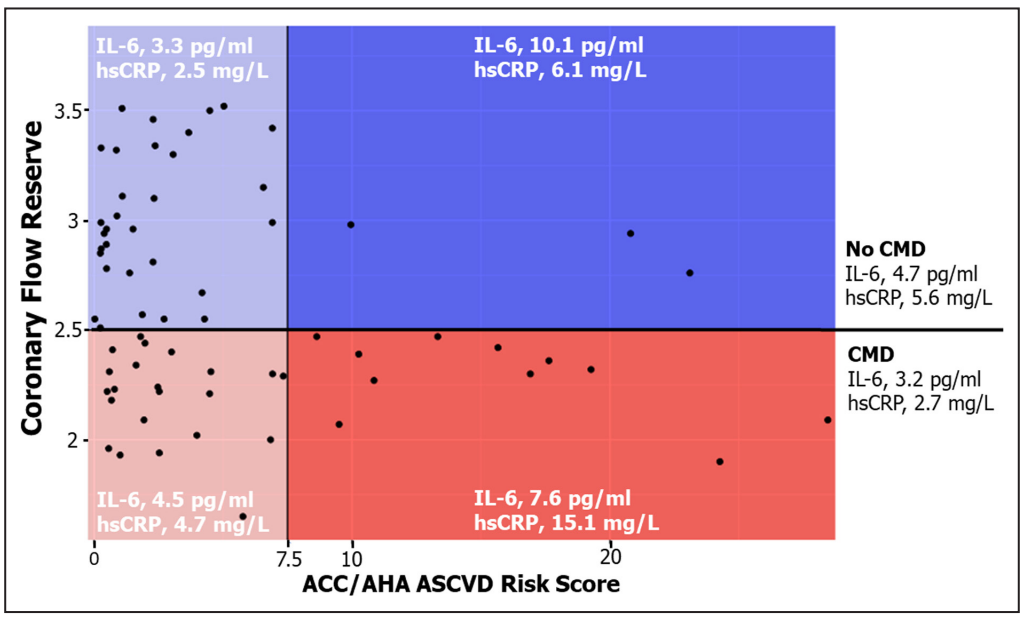

Figure. Relationship between baseline ASCVD estimated cardiovascular risk and CFR.
CMD defined as CFR<2.5, ASCVD <7.5% as low risk. Median levels of IL-6 and hsCRP shown in each quadrant. ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD. atherosclerotic cardiovascular disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; hsCRP, high-sensitivity C-reactive protein; and IL-6, interleukin 6.

cardiovascular risk among patients with chronic inflammatory conditions.

ARTICLE INFORMATION

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