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ABSTRACT

Individuals with rheumatoid arthritis (RA) are at 50% greater risk for developing heart failure (HF) and HF associated morbidity and mortality than non-RA controls. This risk persists even after adjustment for coronary artery disease, implying that immunologic and inflammatory factors intrinsic to RA contribute to the increased risk of HF. Our overall hypothesis is that myocardial inflammation and microvascular ischemia are prevalent in RA patients, are mediated by antibodies to myocardial citrullinated proteins, promote impairment of left ventricular (LV) structure/function, and are attenuated with RA therapies. Indeed, in 128 RA patients without clinical CVD who underwent [18fluoro-deoxyglucose] positron emission-computed tomography (FDG PET-CT) (the RHYTHM study), we observed FDG uptake (inflammation) in 35% and impaired myocardial blood flow reserve (MFR) in 29%. Both myocardial inflammation and impaired MFR were strongly associated with clinical and laboratory measures of RA disease activity; impaired MFR was also associated with higher LV mass, a known precursor of HF. These data suggest that myocardial inflammation and impaired MFR mediate, in part, early changes in LV structure/function that predate clinical HF; but it is critical to confirm these relationships in longitudinal studies. Proximal events that mediate myocardial pathology in RA are unknown. We hypothesize that antibodies against citrullinated myocardial proteins (APCAs) mediate, in part, this abnormal myocardial phenotype (inflammation and impaired MFR), leading to myocardial remodeling and ultimately to functional decline. Our preliminary data demonstrating seroreactivity in 30% of RHYTHM sera in a novel myocardial protein array support this hypothesis. A related question is whether tumor necrosis inhibitors (TNFi's) affect myocardial inflammation. This is a far from insignificant question as TNFi's were associated with increased HF hospitalizations and death in non-RA HF patients and their risk for HF in RA is still unclear despite widespread use. In the next funding period, we seek to extend the study period for the RHYTHM cohort for aims 1 and 3, and to utilize an independently funded study (TARGET) for aim 2, in order to investigate the following aims:

1) To determine if imaging indicators of myocardial pathology at baseline (inflammation, impaired MFR) are predictive of longitudinal (adverse) change in measures of LV structure and function over 4-6 years in RA patients without clinical cardiovascular disease (CVD) at baseline.

2) To determine, in a currently enrolling NIH-NIAMS funded randomized clinical trial (the TARGET study), if RA therapies reduce myocardial inflammation.

3) To determine if seroreactivity to citrullinated myocardial antigens in RHYTHM participants is associated with baseline myocardial inflammation and impaired MFR and/or with change over time in parameters of LV structure/function. These investigations will advance understanding of mechanisms that contribute to and mitigate increased risk of myocardial dysfunction in RA.