Innovative Research Grant Application

DESCRIPTION

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Individuals with rheumatoid arthritis (RA) are at greater risk for developing incident heart failure (HF) and HF-associated morbidity and mortality than matched non-RA controls. **Little work has been done, however, to investigate pathophysiological mechanisms underlying myocardial dysfunction leading to HF in RA. A better understanding of these pathophysiological processes would promote the identification of biomarkers to predict risk for HF, and/or innovative approaches to treat or prevent HF, in RA.** Chronic elevations of inflammatory cytokines have been proposed as the primary mechanism of myocardial dysfunction in RA, but this is likely an *oversimplification* of the process. We hypothesize that additional mechanisms related to the overall rheumatoid process including autoantibody responses to citrullinated myocardial proteins, and specific monocyte and/or T cell subsets that can be detected in the periphery, may identify patients with subclinical myocarditis and/or microvascular dysfunction that may put them at risk for HF. In a currently enrolling cross-sectional study funded by NIAMS, 150 RA patients without history of clinical CV disease are undergoing cardiac PET-CT scanning to determine the prevalence of subclinical inflammatory myocarditis and microvascular perfusion. In the first 42 patients enrolled, a high percentage (~40%) of patients have evidence of myocarditis and/or microvascular dysfunction. We propose through the ACR grant mechanism to extend the study to eighteen months of followup in order to investigate several potential pathophysiological pathways and their potential contribution to myocardial dysfunction in RA. Our overall goal is to identify peripheral biomarkers that identify RA patients at risk for development of HF. Our specific aims are as follows:

Aim 1. To determine the longitudinal effect of imaging biomarkers of myocardial pathology (inflammatory myocarditis and microvascular dysfunction) on measures of left ventricular (LV) structure/function. Participants in the parent study will return in 18 months for a repeat echocardiogram, utilizing highly sensitive state-of-the-art measures of function via speckle tracking. Change in measures of LV structure/function will be compared to baseline.

Aim 2. To identify serum protein and cellular biomarkers associated cross-sectionally with subclinical myocarditis and microvascular dysfunction, and/or predictive of longitudinal change in measures of LV structure/function. Targeted biomarkers will include: a) measures of HF (brain naturetic protein [BNP]),myocardial damage (troponin-I) and myocardial fibrosis (galactin-3); b) antibodies against citrullinated myocardial proteins, using a novel myocardial peptide array; and c) subsets of monocytes and lymphocytes that are critically involved in the overall pathogenesis of RA.

The parent grant does not address biomarker assays other than anti-CCP2, C-reactive protein (CRP) and interleukin-6 (IL-6) measurements. By utilizing the cohort and biospecimens assembled for the parent R01 study, the proposed studies can be accomplished in a highly efficient and synergistic manner and with significant cost saving. **Understanding pathophysiologic mechanisms that contribute to the increased risk of HF in RA is essential to the development of targeted interventions aimed at reducing CV morbidity and mortality in RA.**

RELEVANCE:

INDIVIDUALS WITH RA SUFFER FROM AN INCREASED RISK OF DEVELOPING HEART FAILURE. THE CAUSES OF THIS INCREASED RISK ARE NOT WELL UNDERSTOOD. INVESTIGATING MARKERS BOTH IN BLOOD AND BY IMAGING TECHNIQUES NOT ONLY WILL PROVIDE CLUES REGARDING THESE PATHWAYS, BUT MAY ALSO REVEAL SENSITIVE BIOMARKERS FOR PREDICTING WHO WILL DEVELOP HF.