

Dr. Bathon

Project Abstract

Despite the recognition of the association of rheumatoid arthritis (RA) with accelerated cardiovascular disease (CVD) for over a century, little is known about the pathophysiologic mechanisms involved. Standardized mortality rates in RA remain up to 3 times higher than in the general population with CVD representing the leading cause of these excess deaths. Anti-cyclic citrullinated peptide antibodies (anti-CCP) have been extensively studied and found to be highly specific for RA. Our group previously reported a strong correlation of anti-CCP with an unusual cardiac phenotype in RA- i.e., low left ventricular (LV) mass by cardiac MRI. Moreover, we recently reported for the first time the presence of citrullinated substrates in RA myocardia (autopsy specimens). These data strongly suggest that autoreactivity to citrullinated peptides may constitute a critical link between autoimmunity and the increased incidence of atherosclerosis and myocardial dysfunction in RA. In my currently funded RO1 we are performing a cross-sectional study of 150 RA patients without clinical CVD to evaluate and identify factors that are associated with the phenotype of low LV mass by looking at RA-related specific characteristics, the degree of systemic and myocardial inflammation, and myocardial microvascular perfusion measured by cardiac PET-CT. This research supplement will contribute to and enhance this investigation by examining the ***specificities*** of anti-citrullinated peptide antibodies (ACPAs) in the enrolled RA patients and their associations with measures of LV structure and function and with atherosclerosis. Given the difficulty in obtaining myocardial and vascular tissue from RA patients to identify *in situ* specific citrullinated proteins, we will utilize an indirect approach in which we assay all 150 sera for autoantibodies against an array of proteins, and corresponding peptides, generated *in vitro* in their ***uncitrullinated and citrullinated*** forms. Thus, we will correlate a panel of ACPAs with: 1) measures of LV function and structure as well as with myocardial inflammation and microvascular perfusion, all assessed by cardiac PET-CT with NH3 and fludeoxyglucose (FDG), and with 2) vascular measures of atherosclerosis [coronary artery calcium (CAC) and vascular inflammation [FDG uptake in carotids and thoracic aorta]. The APCA antibody profile will be assayed by Dr. William Robinson at Stanford University.

There is considerable interest right now in understanding the epitope spreading of APCA reactivities and whether individual ACPAs identify or predict specific organ complications of RA. Our RA study population is unique in its multidimensional phenotyping of myocardial and vascular disease including measures of LV structure, function, inflammation and microvascular perfusion, as well as measures of atherosclerosis and vascular inflammation. Dr. Geraldino will have the opportunity to collect and examine novel sets of data in the context of a learning environment consisting of formal coursework and informal mentoring from an outstanding team of accomplished clinical and bench scientists. This Diversity Supplement will fulfill a critical need for protected training and research time to promote the career of this promising young investigator. Moreover, the results of this research project could provide a novel biomarker for early detection and management of those at high risk for CVD. Application of that knowledge could extend healthy life and reduce the burdens of illness and disability from RA.

The proposed studies will be performed using the study population, CVD measures and sera obtained in the parent grant, but they were not part of the original grant proposal. In the original proposal, the intent was to correlate only anti-CCP ***titer*** with myocardial inflammation and microvascular perfusion. Dr. Robinson has agreed to measure APCA reactivities in the 150 patients in this R01 (see *attached letter*). Of note, we also have an on-going collaboration with

Dr. Van Eyk, a CV proteomics expert at Hopkins, with whom we are taking a discovery approach to identify **myocardial proteins** that might be citrullinated in **non-RA** tissues.