Noninvasive Cardiovascular Imaging in Rheumatoid Arthritis: Current Modalities and the Emerging Role of Magnetic Resonance and Positron Emission Tomography Imaging

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Objectives: Rheumatoid arthritis (RA) is associated with premature atherosclerosis and increased prevalence of cardiovascular disease. The objective of this review is to summarize current and emerging imaging modalities for the evaluation of subclinical atherosclerosis in RA, with an emphasis on potential application of novel modalities, high-resolution magnetic resonance imaging and positron emission tomography, as screening tools for early cardiovascular disease risk stratification.

Methods: A PubMed literature search was undertaken using the search terms "rheumatoid arthritis" AND "cardiovascular disease" OR "atherosclerosis" OR "plaque" and including all relevant terms for imaging modalities.

Results: Two noninvasive imaging modalities have been widely adopted for direct visualization of arterial wall: carotid ultrasonography and cardiac computed tomography. Published studies in the RA population using these 2 modalities are reviewed. Novel cardiovascular imaging modalities are described, with an emphasis on high-resolution magnetic resonance imaging and positron emission tomography. Emerging research tools in vascular imaging, including dynamic and cardiac stress perfusion contrast-enhanced magnetic resonance imaging, are presented. The incremental imaging capabilities to characterize plaque composition and vessel wall inflammation as well myocardial abnormalities and published studies are systematically reviewed.

Conclusions: An increasing number of cardiovascular imaging modalities with improved characterization of features associated with plaque vulnerability have been developed. Given the heightened cardiovascular risk profile of the RA population, these novel imaging modalities offer promise for risk stratification and drug safety evaluation.

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Cardiovascular disease (CVD) is an important extra-articular comorbidity in patients with rheumatoid arthritis (RA), with a 2- to 3-fold increased prevalence compared with the general population (1,2). Early CVD identification, along with ongoing CV risk factor monitoring and management, has been advocated to be incorporated as part of the standard of care for RA patients (3). Proposed mechanisms for acceleration of atherosclerosis include traditional cardiovascular (CV) risk factors (4-7) and systemic inflammation-related mechanisms (8). Multiple studies have supported the latter hypothesis, demonstrating markers of RA severity and inflammation to predict the incidence of CV events (7,9-14).

The Framingham risk score (15) and other risk scoring models apply a combination of clinical risk factors to predict risk of future CV events in the general population. These clinical risk factors ("traditional" CV risk factors) typically include age, gender, hypertension, hyperlipidemia, diabetes, and smoking status. These prediction models do not account for any RA-related risk factors, and their utility has not been validated for the RA population. Indeed, application of the Framingham score in patients with RA has been suggested to markedly underestimate CV risk (16). The Reynold's risk score may improve CV risk prediction for RA patients, because it also includes high-sensitivity C-reactive protein (CRP) and family history of premature CVD (17). However, most large cohort studies conducted in RA do not have complete Framingham and Reynold's risk score variables measured at baseline.

Atherosclerosis is a progressive, multifocal disease of the arterial wall, initiated by lipid accumulation in the intima layer, sustained by chronic inflammation, and resulting in plaque formation. The underlying molecular and immunological mechanisms of atherosclerosis share similarities with those of RA (18). Patients with RA have been observed to have distinct characteristics of morphological and functional vascular abnormalities compared with non-RA patients. Histologic evidence in patients with CVD reveals increased inflammation in the walls of coronary arteries and increased prevalence of vulnerable plaque characteristics in RA patients compared with non-RA controls (19). Patients with RA have a higher prevalence and severity of subclinical atherosclerosis, detected by different vascular imaging and functional modalities, compared with healthy controls with similar CV risk profiles (20). Because plaque rupture is the most frequent cause of arterial thrombosis, identification of rupture-prone or "vulnerable" plaques represents a promising screening strategy for patients with subclinical atherosclerosis. Key features of the vulnerable plaque include a lipid-rich necrotic core, a thin fibrous cap, inflammatory cellular infiltrate, and plaque neovascularization (21,22).

Noninvasive atherosclerotic plaque imaging and visualization of vascular inflammation are new potential surrogates of CV risk that open novel opportunities for studying the biology and mechanisms of CVD in rheumatic diseases (23). In this article, we review the currently available noninvasive techniques for evaluation of atherosclerotic plaque. We then introduce emerging molecular imaging techniques, including positron emission tomography (PET), high-resolution magnetic resonance imaging (HR-MRI), dynamic contrast-enhanced (DCE) MRI, stress perfusion contrast-enhanced MRI (CMR), followed by a discussion of their potential applicability to patients with rheumatic diseases. Emerging data from our group and others suggest that blocking proinflammatory cytokines, particularly tumor necrosis factor, may reduce CV risk in RA (24,25). Thus, identification of clinical subsets with evidence of plaque inflammation and other characteristics of plaque instability may help to refine stratification and intervention strategies.

METHODS

A PubMed literature search was undertaken for studies published between 1963 and June 2011, using the following index terms, alone or in combination: "rheumatoid arthritis," "cardiovascular disease," "atherosclerosis," "plaque," and including all relevant imaging terms for carotid ultrasound, Doppler, carotid intima media thickness, ankle-brachial index, computed tomography, coronary calcification, Agatston score, magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI, stress perfusion MRI, positron emission tomography, and fluorodeoxyglucose (FDG). Preference was given to clinical studies, meta-analyses, and guidelines. References noted in relevant articles were also assessed.

Carotid Intima-Media Thickness (CIMT)

Carotid ultrasonography (US) is a noninvasive, accurate, and reproducible imaging modality that provides quantitative measurements of CIMT, widely used to identify subclinical vascular disease, evaluate cardiovascular risk, and monitor drug-related changes in clinical trials (26). Application of carotid US to clinical research began in the mid 1980s, when a histology study confirmed the feasibility of direct measurement of carotid artery wall thickness with in vivo B-mode real-time imaging (27). CIMT is defined as the distance between the inner and outer lines, corresponding to lumen-intima and media-adventitia interfaces, respectively. Current US technology is limited in distinction between intima and media layers.

CIMT can be measured at either the near (ie, closest to the transducer) or the far wall of the arterial segment at 3 anatomical locations: the extracranial common carotid artery (CCA), the most accessible and recommended approach (28); the bifurcation or carotid bulb; and the proximal internal carotid artery (ICA). CIMT can be expressed as a maximum thickness over a length or as a maximum thickness measured at the specific location (29). CIMT is influenced by age, sex, race, and systolic blood pressure, as well as anatomic location (30). Due to