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 Reynolds’ 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
different hemodynamics along the carotid tree, carotid bulb and ICA are more predisposed to atherosclerotic plaque formation rather than CCA (31). Although the cutoff point for abnormal CIMT varies, carotid plaque has been defined as an isolated CIMT of ≥1.5 mm or an isolated CIMT >50% of the surrounding intima-media thickness (IMT), regardless of the absolute dimension (32). In general, the presence of carotid plaque, or IMT ≥75th percentile for the patient’s age, sex, and race, is indicative of increased CVD risk (28). To date, there is still no universally accepted carotid scanning protocol, resulting in heterogeneous data collection and analysis across published observational and intervention studies.

CIMT as a Surrogate Measure of General and Coronary Atherosclerosis in the General Population

Autopsy studies conducted in the 1960s revealed a moderate correlation between the extent of carotid and coronary atherosclerosis that was subsequently replicated by cross-sectional studies employing coronary angiography, intravascular US, and computed tomography (CT) (29). Prospective studies further established the association of CIMT with traditional CV risk factors, prevalent CVD, atherosclerosis in other arterial beds, and most importantly, future CV events (26). A landmark Cardiovascular Health Study prospectively followed 4476 asymptomatic adults aged 65 years and older using a composite measure of the maximal CCA and ICA IMTs (33). The cumulative 7-year rate of myocardial infarction (MI) or stroke was above 25% for subjects in the quintile with the highest IMT versus 5% for the lowest quintile (relative risk 3.87, 95% confidence interval 2.72–5.51). A systematic review and meta-analysis of 8 prospective studies, including a total of 37,197 subjects followed up for a mean of 5.5 years, showed that for an absolute CIMT difference of 0.1 mm, the future risk of MI increases by 10 to 15%, and stroke risk increases by 13 to 18% (34). However, the risk effect of CIMT for both end points decreased with adjustments for other CV risk factors. In view of these relationships, CIMT has been used as a surrogate endpoint for assessing the effect of pharmacological treatment on systemic atherosclerosis in clinical trials (35) with lipid-modifying, glucose-lowering, antihypertensive, and hormone-replacement therapies (26). Whether reduction of CIMT progression is a valid surrogate endpoint remains controversial.

Carotid US in Patients with RA

Carotid US has become the most commonly applied noninvasive imaging modality to detect subclinical atherosclerosis in patients with rheumatic diseases. A recent systematic review and meta-analysis concluded that CIMT is significantly increased in a wide spectrum of rheumatic diseases versus healthy controls, an overall absolute mean difference of 0.06 mm (95% confidence interval, 0.05–0.06 mm) (36). Specifically in RA patients, a new meta-analysis of 22 studies demonstrated an increased CIMT in RA patients versus controls (37). However, a variety of CIMT measurement protocols and lack of technical information related to the protocols used across the studies should be taken into account while interpreting the data. Overall, increased CIMT correlated with RA severity and duration (38–41). Conflicting results regarding plaque prevalence rates in RA were reported (11,40,42,43). Of particular note, a cross-sectional study of RA and control patients found that the prevalence of carotid plaque was 3-fold higher in RA versus controls, whereas CIMT was not increased (42). These findings might be explained by a more adverse profile of CV risk factors in the controls. Moreover, another study of RA patients versus healthy controls found comparable CIMT values between the groups (11). Of note, both carotid plaque presence and CIMT were associated with markers of systemic inflammation: erythrocyte sedimentation rate and CRP (11). A longitudinal follow-up of CIMT in RA patients, treated with a variety of nonbiologic DMARD regimens, revealed an increased annual CCA CIMT progression in RA patients versus healthy controls (44). The discordant results of CIMT measurements in RA suggest that vessel wall thickness progression may not be the primary mechanism by which RA incurs increased CV risk.

As in the general population, CIMT has been reported to predict the development of future CV events in the RA population. A small prospective study of RA patients, free of traditional CV risk factors at enrollment, examined incident CV events over a 5-year period (45). Patients who experienced CV events, 17% of the cohort, all had carotid plaques and significantly higher baseline CIMT than the rest of the cohort. The study concluded that CIMT >0.91 mm was independently associated with a high risk of subsequent CV event during the follow-up (45). Most recently, a prospective study of 636 RA patients confirmed that both CIMT and carotid plaque presence independently predict the incidence of acute coronary syndromes in RA (46). The incidence of new acute coronary syndromes was 2.3- and 4-fold higher for unilateral and bilateral plaque, respectively, compared with patients with no plaque.

Carotid US Limitations

Although carotid US is clearly helpful in identifying subclinical atherosclerosis, several important limitations must be acknowledged. Carotid US performance and interpretation is operator-dependent and, therefore, subject to intra- and interoperator measurement variability, making serial assessments of carotid US difficult, unless baseline and follow-up scans are read at the same time. US accessibility is anatomically limited to specific segments of the carotid tree. Although most CIMT measurements are acquired at the CCA, advanced atherosclerosis predominantly develops downstream from the ICA (47). US does
not differentiate smooth muscle hypertrophy or age-related sclerosis from the atherosclerotic process (47), does not directly inform about plaque burden, and does not define plaque composition (eg, presence of a necrotic core) or presence of vascular inflammation, both important for identification of vulnerable plaque.

In contrast to the general population, the extent of correlation between carotid US images and degree of histopathologic coronary atherosclerosis in RA patients has not been studied. Indeed, only a limited amount of information is available regarding the histopathology of atherosclerosis in RA patients. In 1 study, the features of coronary artery atherosclerosis in RA patients versus non-RA controls were examined postmortem (19). Overall, there was no difference in severity and extent of atherosclerosis between both groups, except for increased vessel wall inflammation observed in the RA group. In the subset of patients with established CVD, RA patients showed less severe CAD, reflected by extent of atherosclerosis and overall grade of stenosis, versus non-RA controls. However, RA patients with CVD were found to have a higher number of vulnerable plaques and more medial inflammation of the main coronary arteries. The results suggest that the phenotype of CVD in RA patients may be different than non-RA patients, and that simple anatomical imaging by US may not be adequate. New imaging techniques, able to provide more accurate information about plaque structure, composition, and metabolic activity, may therefore be required for risk stratification of early CVD in RA patients.

Ankle-Brachial Index
Ankle-brachial index (ABI) is a noninvasive, cost-effective test recommended by the American College of Cardiology/American Heart Association (ACC/AHA) for the diagnosis of peripheral artery disease (48), commonly applied in clinical practice for over 2 decades. The ABI represents a ratio of Doppler-recorded systolic blood pressure (BP) in the lower and upper extremities, measured in the posterior tibial and/or dorsalis pedis and brachial arteries, respectively. In addition to the assessment of peripheral artery disease, the ABI measured at rest has been shown to correlate with generalized and coronary atherosclerosis (49,50). In the general population, lower levels of the ABI (below 0.9) have been independently associated with an increased risk of all-cause and CVD-related mortality, MI, and stroke (51–54). A meta-analysis of 16 population-based studies found that ABI could improve the prediction of CV events when combined with the Framingham risk score (55).

In the RA population, a case-control study detected an increased prevalence of peripheral artery impairment measured by the ABI versus healthy controls (56). However, this difference was decreased with adjustment for inflammatory markers and joint damage. Interestingly, patients with an advanced RA (≥20 deformed joints) had more incompressible and obstructed arteries, independently of other covariates. Data from the Johns Hopkins RA cohort have also demonstrated a higher prevalence of arterial incompressibility in RA versus controls (57). Emerging evidence further suggests that application of the ABI in RA can be useful for CV risk stratification in patients with RA. Incompressibility of the peripheral arteries was found to be independently associated with an increased all-cause and CV mortality in a large prospective RA cohort (58).

The main advantages of the ABI examination include the fact that the test can be easily performed at the bedside or an outpatient setting. Among the limitations is the possibility of inaccurate BP measurements and calculation of the index that has been observed in the primary care setting (59). The ABI may be inaccurate when systolic BP cannot be abolished by BP cuff inflation, ie, in the elderly or patients with diabetes, or other diseases that result in arterial calcification.

Coronary Artery Calcification (CAC)
Electron beam CT (EBCT) and multidetector CT (MDCT) are fast CT methods designed to detect and assess CAC, a marker of subclinical CAD and a predictor of coronary events in the general population (60,61). CAC occurs almost exclusively in atherosclerotic arteries and seems to originate from the healing mechanism of subclinical plaque rupture events (62). Coronary calcification characterizes a late stage of atherosclerosis, corresponding to a healed plaque rather than to a vulnerable plaque (61). The rationale behind CAC measurement as a surrogate marker of atherosclerosis is based on a high correlation between CAC and total atherosclerotic plaque burden confirmed by histopathologic, sonographic, and angiographic studies (63).

EBCT uses a rotating scanning electron beam to produce serial, thin-section scans, synchronized with the heart cycle (60). The design of EBCT permits acquisition of cross-sectional images of the heart with no constraints of mechanical motion. The most widely used method to quantify the amount of coronary calcium is the Agatston score, calculated by multiplication of the area of calcified coronary lesion and CT attenuation coefficient (64). The sum of the scores for all coronary-artery lesions represents the overall Agatston score (64). In recent years, EBCT has been replaced by an advanced mechanical high-resolution MDCT, capable of acquiring up to 128 slices simultaneously and producing high-quality images. Because EBCT preceded MDCT technology, the majority of studies to date on CAC and atherosclerosis have employed EBCT and reported the Agatston scores.

CAC as a Surrogate Measure of Coronary Atherosclerosis in the General Population
Large prospective studies, based on population cohorts, have demonstrated the incremental prognostic
value of CAC, beyond traditional risk factors (61). A meta-analysis of 4 studies published before 2003 examining asymptomatic subjects with baseline EBCT CAC score measurements and longitudinal follow-up of CV events incidence concluded that CAC score is an independent predictor of CHD events (65). A subsequent meta-analysis of 6 studies published between 2003 and 2005 showed that the presence of any CAC quantity increases CV events risk by 4-fold over 3 to 5 years (61). The Multi-Ethnic Study of Atherosclerosis, a population-based cohort of individuals without known CVD, found that a CAC score $>300$ was associated with a hazard ratio for future CHD events of nearly 10.4, and the independent predictive value of CAC was equal across ethnicities (66). CAC was found to predict not only CHD-related but also all-cause mortality (66–68). Currently, both American and European societies of cardiology support CAC screening in patients at intermediate risk of hard events (corresponding to Framingham score 6–20%) (60,69).

**Coronary Arterial Calcium (CAC) Measurement in Patients with RA**

A number of observational studies have determined a higher prevalence of CAC in the RA population versus healthy controls (70–73). Increased prevalence and severity of coronary calcification was detected by EBCT in patients with established (disease duration $>10$ years) but not early (disease duration $<5$ years) RA versus controls in a cross-sectional study (70). RA patients with coronary calcifications also had higher Framingham scores than patients with no calcifications, even after adjustment for age and gender (74). In addition, higher CAC scores were also correlated with the presence of metabolic syndrome (75) as well as serum tumor necrosis factor-alpha and interleukin-6 levels in the RA patients (76). The latter observation supports the concept of inflammation promoting CAC in RA patients. Other studies have demonstrated an association between RA duration and RA severity with CAC scores (72,77).

The prevalence, extent, and distribution of atherosclerosis have also been studied by MDCT in 85 RA patients and 85 controls, including imaging of the thoracic aorta and coronary and carotid arteries (73). RA cohort demonstrated earlier onset, greater prevalence, and more diffuse calcification over multiple vascular beds, as well as a preferential involvement of the thoracic aorta versus coronary arteries as compared with controls. Interestingly, discordance between measures of subclinical atherosclerosis in carotid and coronary arteries has been recently reported in RA (78). High CAC scores were found not only in RA patients with carotid plaque and increased CIMT but also in those without plaque and low CIMT. In contrast, a higher correlation between carotid measures and CAC score was found in non-RA controls.

In summary, visualization of coronary arteries by means of EBCT or MDCT has consistently demonstrated a higher prevalence and severity of CAC in longstanding RA as compared with healthy controls.

**Cardiac CT Limitations**

Cardiac CT has been described to have limitations in identifying nocalcified and rupture-prone coronary plaques. Cardiac CT angiography based on 64-slice MDCT can be used to detect nocalcified plaques (79), but requires intravenous contrast agent injection and uses a significant dose of radiation. Exposure to ionizing radiation is an important limitation of cardiac CT. The estimated effective dose from a single CAC screening by MDCT widely varies from 0.8 to 10.5 mSv (1 mSv = 1 mGy in the case of radiographs), with the mean value of 3.1 mSv (80). This can be compared with an annual effective dose from natural background radiation in the USA of about 3 to 3.6 mSv (81). New imaging techniques aim to substantially reduce the radiation dose from cardiac CT. Finally, cardiac CT imaging is a more expensive procedure than carotid US (82).

**High-Resolution Magnetic Resonance Imaging**

HR-MRI has recently emerged as superior to other noninvasive modalities technology to characterize atherosclerotic plaque and depict arterial wall (83). MRI differentiates tissue structure on the basis of proton magnetic resonance properties with a wide range of image contrast, without using ionizing radiation. In vivo plaque image acquisition requires a multicontrast approach with black-blood and bright-blood sequences. In the black-blood technique, the signal from the flowing blood is suppressed and turned black to better image the adjacent vessel wall (84). (Fig. 1) The bright-blood sequence can be used to assess the thickness of the fibrous cap and the morphological integrity of atherosclerotic plaques (85). Advantages of HR-MRI include excellent soft-tissue contrast and sensitivity to flow, applicable to most vascular beds. However, the potential to image the human coronary artery wall is still limited, due to blood flow, motion, and spatial artifacts (86,87).

In large arteries such as the carotids, HR-MRI can provide comprehensive information about plaque size, composition, morphology, and biology (88). Most importantly from the clinical point of view, HR-MRI can reliably detect and quantify the key histopathologic correlates of plaque vulnerability: the presence of a lipid-rich necrotic core, fibrous cap thickness, intraplaque hemorrhage, calcification, and thrombus, with high resolution and reproducibility (85,89–94).

A close correlation between HR-MRI classification of the carotid atherosclerotic lesions and histologic findings, based on the American Heart Association classification, was confirmed in a study of 60 patients imaged before endarterectomy (95). This study demonstrated that HR-
MRI could distinguish advanced lesions from early and intermediate atherosclerotic plaque, with a high degree of sensitivity and specificity. A cross-sectional study of carotid MRI imaging in subjects with and without angiographically proven obstructive CAD revealed a distinct structure and composition of carotid artery walls in the disease group versus controls (96). Accordingly, HR-MRI has a broad range of potential applications, including atherosclerosis assessment from preclinical evaluation to clinical detection, diagnosis, and prognosis (97,98). A summary of vulnerable plaque histologic features and correlated imaging modalities outcomes is summarized in Table 1.

DCE-MRI offers an additional parameter for evaluating plaque vulnerability by providing information on plaque vascularity (99). Neovascularization, the formation of new capillaries within the atherosclerotic plaque, is a hallmark of vulnerable atherosclerotic lesions (22). The presence of neovessels has been linked with extravasation and activation of inflammatory cells, as well as lipid deposition in the vessel wall (100). Neovessels also seem to play a key role in the progression of atherosclerotic plaques, plaque inflammation, and rupture.

DCE-MRI has been used extensively to study tumor vascularity. This technique takes advantage of the administration of a contrast agent (ie, Gadolinium chelates) to quantify the extent of blood supply and its associated physiological characteristics (99). Several gadolinium uptake parameters correlate with the extent of plaque vascu-
larity, macrophage burden, and neovessel density (confirmed by staining of histological specimens). The use of DCE-MRI in conjunction with standard approaches offers further insight into biologic processes associated with plaque vulnerability.

The noninvasive nature of HR-MRI facilitates serial assessments of atherosclerotic lesions in the setting of intervention trials. MRI has been shown to be useful in prospective quantification of changes in carotid atherosclerotic plaque size and morphology (101). Regression of carotid and aortic atherosclerosis lesions after lipid-lowering therapy with statin therapies has been demonstrated (97,98,102,103).

Recent advances in the development of novel targeted molecular contrast agents, such as superparamagnetic iron oxide nanoparticles (SPION), significantly broaden the capabilities of vascular HR-MRI to identify specific cell types within atherosclerotic plaque. Experimental studies in animals have shown that SPIONs are internalized by macrophages and thus accumulate in high-risk plaques with a high macrophage content, inducing magnetic resonance signal changes (104). Application of

<table>
<thead>
<tr>
<th>Type of Lesion (Modified AHA Classification)</th>
<th>Plaque Characteristics</th>
<th>Histological Correlates</th>
<th>Expected Findings on Imaging (MRI and FDG-PET)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type III Intermediate lesion (pre-atheroma)</td>
<td>Pathological intimal thickening. SMCs in a proteoglycan-rich matrix with areas of extracellular lipid accumulation without necrosis</td>
<td>Increased plaque burden on multicontrast MRI</td>
<td></td>
</tr>
<tr>
<td>Type IV Early fibroatheroma</td>
<td>Increased macrophage content</td>
<td>Increased plaque burden on multicontrast MRI Increased SUV/TBR on PET</td>
<td></td>
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<tr>
<td>Type Va Fibroatheroma (type V lesion)</td>
<td>Well-formed necrotic core with an overlying fibrous cap</td>
<td>Increased plaque burden on multicontrast MRI Increased SUV/TBR on PET Increases size of LRNC Fibrous cap thickness measured by multicontrast MRI (fibrous cap enhanced postcontrast)</td>
<td></td>
</tr>
<tr>
<td>Type Vb Calcific lesion (type VII lesion)</td>
<td>A thin fibrous cap infiltrated by macrophages and lymphocytes with rare SMCs and an underlying necrotic core</td>
<td>Increased plaque burden on multicontrast MRI Calcification size detected by CT or multicontrast MRI Increased plaque burden on multicontrast MRI Fibrous cap thickness measured by multicontrast MRI (fibrous cap enhanced postcontrast)</td>
<td></td>
</tr>
<tr>
<td>Type Vc Fibrotic lesion (type VIII)</td>
<td>Thick fibrous cap</td>
<td>Changes in measures of DCE-MRI</td>
<td></td>
</tr>
<tr>
<td>Type VI lesion Lesion with surface defect and/or hematoma/hemorrhage and/or thrombotic deposit</td>
<td>Fibroatheroma with cap disruption; luminal thrombus with or without communication with the underlying necrotic core; erosion</td>
<td>Increased plaque burden on multicontrast MRI Changes in measures of DCE-MRI</td>
<td>Hemorrhage detected by multicontrast MRI</td>
</tr>
</tbody>
</table>


LRNC, lipid rich necrotic core; SMC, smooth muscle cell; SUV, standardized uptake value; TBR, target-to-background ratio.
SPION-enhanced MRI permits not only measurement of macrophage burden in atherosclerotic plaque but also monitoring of statin-induced changes in plaque inflammation in animal models (105). A preliminary study employing SPION-enhanced MRI in 11 patients with carotid disease has confirmed the predominant accumulation of SPION in macrophages within prone-to-rupture or ruptured carotid plaques (106). This modality also shows promise in the functional imaging of atherosclerotic plaque.

In summary, HR-MRI has been shown to be a useful tool for clinical detection, diagnosis, and follow-up of atherosclerotic disease. Application of HR-MRI to study atherosclerosis in patients with RA and other rheumatic diseases would be promising for the study of atherosclerosis progression and evaluation of CV safety of new drugs.

In addition to vascular applications of HR-MRI, cardiac contrast-enhanced MRI (CMR) has been used to provide information about myocardial perfusion deficits, ventricular function, and myocardial viability. This modality has the advantage of high spatial and temporal resolution. Visualization of delayed contrast appearance in myocardial layers provides valuable diagnostic information. Late myocardial enhancement that appears as an area of high signal intensity localized to the subendocardial layer is the best current technique to discriminate scarred versus viable myocardium in patients with ischemic CAD (107). Different patterns and distribution of late enhancement might be helpful in diagnosing other myocardial diseases, including myocarditis (108). CMR with pharmacologically induced stress (eg, adenosine) has been established as a noninvasive diagnostic tool with high sensitivity and specificity for detecting subendocardial perfusion defects. This modality also permits the identification of microvascular dysfunction in the absence of significant coronary stenosis (109,110).

Myocardial abnormalities by stress perfusion CMR have been detected in a pilot study of 18 RA patients without history of cardiac disease (111). A high prevalence of delayed enhancement was observed and was associated with higher RA disease activity. Similar findings of a high prevalence of delayed enhancement on CMR were demonstrated in a study of 16 patients with Takayasu arteritis, suggesting the possibility of silent ischemia or myocardial scarring (112). These studies demonstrate the utility of late gadolinium enhancement and stress perfusion CMR in assessment of clinically silent myocardial disease in patients with rheumatic diseases. Further studies are required to validate these preliminary findings in larger RA cohorts.

**18F-Fluorodeoxyglucose-Positron Emission Tomography**

FDG-PET is a metabolic technique that provides functional images of glycolytic activity to detect localized inflammation with high sensitivity and reproducibility (23,113,114). The primary clinical use of FDG-PET has been historically in the field of oncology, where FDG-PET in combination with CT (PET-CT) is the gold standard for monitoring tumor response to therapy. In the context of cardiovascular imaging, FDG-PET is an emergent modality for the identification of plaque inflammation (23,113).

In FDG-PET a radioactive tracer (FDG) is administered intravenously to circulate within the body and accumulate at the site of interest. FDG is a labeled modified glucose analog that transports into cells by glucose transporters and accumulates intracellularly. The degree of its cellular uptake is dependent on the cellular metabolic rate and the number of glucose transporters, which are up-regulated in inflammatory conditions (119). Radiotracer uptake is semi-quantitatively expressed as a “standardized uptake value.” To date, FDG has been the most commonly used PET agent in vascular imaging (114–116).

Histopathological data have confirmed the relationship between plaque inflammation and plaque rupture, including an abundance of macrophages within ruptured plaques (117,118). Correlations between the degree of arterial FDG uptake and the density of macrophages determined histologically have been documented in both animal models of atherosclerosis (119–121) and patients with carotid disease ($r = 0.70–0.85$) (116,122).

In 2002, FDG-PET was used for the first time to visualize and quantify human carotid plaque inflammation in patients scanned shortly after transient ischemic attack. A higher FDG uptake was recorded within “culprit” carotid plaques compared with their asymptomatic contralateral counterparts (116). Subsequent examination of the excised plaques showed FDG accumulation mainly in plaque macrophages (116). Subsequently, an FDG-PET study of 17 patients with severe carotid artery stenosis demonstrated a strong correlation between FDG uptake and plaque macrophage content (as determined from endarterectomy specimens) (122). Accordingly, FDG-PET was established as a noninvasive in vivo measure of carotid plaque inflammation severity. Another study reported that FDG-PET uptake in 1 vascular bed served as a biomarker for inflammation in other vascular beds, particularly when those beds were anatomically adjacent (123). No overlap between plaque inflammation and plaque calcification was found (123). Recently, FDG-PET was shown to be useful as a robust surrogate marker of efficacy in serial plaque imaging. Short scan time, small variability in plaque FDG uptake, and excellent intra- and interobserver agreement represent the multiple advantages of FDG-PET for interventional trials.

Several studies have demonstrated a correlation between measures of systemic inflammation, in particular, high-sensitivity CRP, and vascular inflammation detected by FDG-PET in the general population (123,124). In a pilot study conducted in patients with psoriasis, FDG-PET/CT detected diffusely increased inflammation of the
aortadescribed above 10 years, and presence of certain extra-articular features. There are no evidence-based guidelines regarding the two modalities has been conducted. Extrapolating from the guidelines targeted to the general population, carotid US to evaluate for the presence of carotid plaque and CIMT measurement and/or cardiac CT to assess CAC seems a reasonable approach to refine the CV risk in patients at intermediate CVD risk (28,60). However, the definition of intermediate risk in RA patients has not been clearly defined as in the general population (where it corresponds to Framingham risk score of 6%-20% without established CVD) and should require further study and validation.

In recognition of the need for better risk stratification, alternative imaging modalities have been developed over the last decade. Valid and reliable data on plaque inflammation and burden, correlating with vulnerable plaque characteristics on a histopathological level, can be obtained through FDG-PET and MRI, respectively. Early experience further supports a multimodality imaging approach (129). In RA, these new technologies appear to be promising for the detection of early subclinical CVD, and for monitoring the CV effects of antirheumatic therapies. Future studies will clarify the role of these novel modalities and their utility for clinical research and patient care.

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