Why Currently Used Diagnostic Techniques for Heart Failure in Rheumatoid Arthritis Are Not Enough: The Challenge of Cardiovascular Magnetic Resonance Imaging

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Rheumatoid arthritis (RA) is a multiorgan inflammatory disorder affecting approximately 1% of the population that leads to progressive joint destruction and disability. Patients with RA exhibit a high risk of cardiovascular disease, which results in premature morbidity and mortality and reduced life expectancy, when compared with the general population. Among various guises of myocardial involvement, heart failure (HF) has been recently recognized as an important contributory factor to the excess cardiovascular mortality associated with RA. HF in RA typically presents with occult clinical symptomatology and is mainly associated with structural and functional left ventricular abnormalities leading to diastolic dysfunction, while systolic myocardial performance remains well preserved. As isolated diastolic dysfunction is a predictor of high mortality, the evaluation of patients in early asymptomatic stages, when treatment targeting the heart is more likely to be effective, is of great importance. Although patient history and physical examination remain the cornerstones of HF evaluation, noninvasive imaging of cardiac chambers, coronary arteries, and great vessels may be necessary. Echocardiography, nuclear techniques, and invasive coronary angiography are already established in the routine assessment of HF; however, many aspects of HF pathophysiology in RA remain obscure, due to the limitations of currently used techniques. The capability of cardiovascular magnetic resonance (CMR) to capture early tissue changes allows timely

detection of pathophysiologic phenomena of HF in RA, such as myocardial inflammation and myocardial perfusion defects, due to either macrovascular (coronary artery disease) or microvascular (vasculitis) disease. Therefore, CMR may be a useful tool for early, accurate diagnosis and research in patients with RA.

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KEY WORDS

Rheumatoid arthritis • Myocarditis • Vasculitis • Coronary artery disease • Heart failure • Echocardiography • Nuclear cardiology • Computed tomography • Cardiac magnetic resonance

Rheumatoid arthritis (RA) is a multiorgan inflammatory disorder affecting approximately 1% of the population. Disease presentation and course vary widely; although some patients present with mild arthritis, in the majority, the disease leads to progressive joint destruction and disability. Among extra-articular features, cardiovascular disease (CVD) has the greatest clinical impact as the main cause of premature morbidity and mortality.[1-3] Despite remarkable therapeutic advances resulting in better control of systemic and joint inflammation, RA-associated mortality has not improved over the past few decades, in contrast to what has occurred in the general population.[4] The widening mortality gap has been largely attributed to cardiovascular (CV) comorbidity, as CV events seem to be approximately 50% higher in those with RA[5] and are associated with worse outcomes compared with the general population.[6,7]

The determinants of CV risk in patients with RA have not yet been clarified. Traditional CV risk factors such as male sex, hypertension, dyslipidemia, insulin resistance, body composition changes, and physical inactivity have received much attention and have been extensively analyzed[8-10]; however, they cannot completely explain the excess CV morbidity and mortality.[11] They do contribute, but in a different way or to a lesser extent in comparison with other individuals. For example, adjustment for classic CV factors in observations demonstrating enhanced CV risk in RA patients compared with the general population did not significantly change the results of the analysis,[12,13] suggesting that RA itself represents an important independent risk factor.[14] Although the cause-and-effect relationship between inflammation and CV risk in RA is still unclear, striking pathophysiologic similarities between preclinical atherosclerosis and rheumatoid synovitis strongly suggest a link underlining these processes, and a potential inflammatory etiology for accelerated atherosclerotic disease. In addition, recent reports indicating a common genetic background for atherosclerosis and RA[15,16] highlight the complexity of the interrelation between traditional CV risk factors, immune activation, and high-grade local and systemic inflammation, all of which may trigger pathways leading to diverse clinical presentations of CVD in patients with RA.[17-20]

Myocardial involvement in RA is typically clinically silent[21] and can manifest as coronary artery disease (CAD), heart failure (HF), pericarditis, myocarditis, or valvular disease. Even in the absence of obstructive CAD, RA patients may display levels of myocardial ischemia similar to those of patients with diabetes.[22] Although cardiac complications with underlying ischemic pathology were initially considered to pose the greatest CV risk, the contribution of HF to excess morbidity and mortality has been recently demonstrated and recognized. It is now well established that the burden of HF is greater in patients with RA. Even after adjusting for CV risk factors and ischemic heart disease, the prevalence of HF is twofold higher in patients with RA than that in the general population,[23] representing a major contributor to mortality.[24] The clinical presentation of HF in RA is atypical, with fewer classic symptoms and signs and higher mortality compared with patients without arthritis.[25] Thus, more vigilant screening and, if possible,

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preclinical identification of HF is important, as the early initiation of cardioprotective treatment may diminish the number of CV events and improve the natural history of the disease. In that respect, a number of noninvasive assessments such as biochemical markers,[26,27] modern echocardiographic techniques,[28] and cardiovascular magnetic resonance (CMR)[29] have been suggested for CV risk stratification in patients with RA. We discuss the limitations of conventional imaging techniques to determine subclinical myocardial involvement and focus on the emerging role of CMR in this clinical field with clear unmet diagnostic needs. Pathophysiology aspects of HF in the general population and individuals with RA are also briefly presented.

Currently Used Techniques for Diagnostic Assessment of HF in RA

According to the American College of Cardiology (ACC) Foundation/American Heart Association (AHA) Task Force on Practice Guidelines, HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. HF may be the endpoint of a wide spectrum of left ventricular (LV) functional abnormalities, which range from normal LV size and preserved ejection fraction (EF) to severe dilatation and/or markedly reduced EF. There is no single diagnostic test for HF, because it is largely a clinical diagnosis that is based on careful history and physical examination; however, identification of the structural abnormality, leading to HF, generally requires invasive or noninvasive cardiac imaging.[30] HF is currently a major health issue worldwide, with an incidence of 1% to 2% and a prevalence of > 10% among persons age > 70 years in developed countries.[31]

CAD, hypertension, myocarditis leading to dilated cardiomyopathy, valvular diseases, and diffuse subendocardial vasculitis are the main causes of HF in rheumatic diseases.[32] Currently used imaging techniques for the evaluation of HF are discussed next.

Echocardiography

The single most useful diagnostic test in the evaluation of patients with HF is the comprehensive two-dimensional (2D) echocardiogram coupled with Doppler flow. The echocardiographic information should be quantified with a numerical estimate of EF, measurement of ventricular dimensions and/or volumes, wall thickness, evaluation of chamber geometry, and regional wall motion. All valves should be evaluated for anatomic and flow abnormalities to exclude the presence of primary valve disease. Secondary changes in valve function, particularly the severity of mitral or tricuspid valve regurgitation, should also be assessed. Noninvasive hemodynamic data acquired at the time of echocardiography are an important parameter for patients with preserved or reduced EF.[33] Although echocardiography is a first-line and gold standard noninvasive technique for HF,[34] it has several limitations, including the following:

(a) It is operator dependent and has the limitation of acoustic window[35]
(b) It suffers lack in reproducibility of measurements (> 10% confidence intervals of EF measured with 2D echocardiography suggest that this may not be a useful tool for identification of subtle changes)[36]
(c) It cannot perform tissue characterization and therefore does not contribute toward clarifying the pathophysiologic background leading to HF and disease acuity[29]

New echocardiographic techniques, such as strain rate and speckle tracking echocardiography (STE), are currently used as sensitive tools to diagnose early myocardial involvement in different diseases, including hypertrophy, CAD, and myocardial dysfunction. A recent evaluation of RA patients without a history of CVD proved that they have impaired LV and right ventricular systolic longitudinal strain, as measured using STE, in comparison with matched individuals with normal cardiac function and without RA, CVD, or CVD risk factors. Strain abnormalities were associated with markers of RA disease severity and suggest that subclinical myocardial disease may be present in RA prior to the development of symptomatic CVD; therefore, strain imaging may represent an effective tool for detection of subclinical CVD and identification of RA patients at increased risk for developing HF.[37]

However, STE also has important limitations. The quality of the 2D image is an important factor and satisfactory recordings are not obtained for all patients. Poor speckle tracking can lead to false-positive results, which is a major concern. Although progress is being made, for the present, accurate

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strain is limited by frame rate and heart rate. With variable heart rates, the bulls-eye recording may not be generated. There is also a major technical issue. To date, only one manufacturer is producing reliable strain data that are similar in multiple laboratories and are responsible for the vast majority of strain data in the literature. Efforts are being made by all manufacturers to correct this problem, which needs to be properly addressed before STE can become a commonly used component of routine echocardiography.[38]

Comparison data of STE with the current gold standard CMR in the evaluation of different pathologies are rather scarce. However, STE, even if properly performed and interpreted, can only identify an early myocardial abnormality; it can document neither the pathophysiologic background nor the disease acuity of the detected lesion. Therefore, it cannot offer the potential of individualized treatment according to a lesion's pathophysiology.

Radionuclide/Computed Tomography (CT) Assessment

Multigated Acquisition of the Cardiac Blood Pool or Equilibrium Radionuclide Angiocardiography. Multigated acquisition (MUGA) of the cardiac blood pool is an established imaging modality for evaluation of LV function; however, the high availability of echocardiography contributed to significantly reduce use of MUGA, although MUGA's high reproducibility is of great value for the diagnosis and follow-up of HF.[39]

Single-photon Emission CT and Single-photon Emission CT/CT. This modality has been extensively used to assess myocardial perfusion as well as ventricular function in ischemic heart disease. Thallium-201 chloride was the first pharmaceutical clinically used for imaging myocardial perfusion.[40] However, because of its relatively long half-life and low-energy radiographic emission, it is not the ideal agent for imaging, due to the relatively high radiation dose with lower image quality compared with technetium agents.[41] Technetium-based agents for assessing myocardial perfusion have been well established.[42] They have the convenience of production by local radiopharmacies from cold kits and they present no or minimal redistribution, so that images can be obtained many hours later without loss of diagnostic accuracy. This makes the planning of imaging easier and, if the images are unsatisfactory, rescanning can be performed. Finally, gating the study enables measurement of LV volumes, EF, and diastolic function. In conjunction with CT, anatomic information from hybrid imaging can be used to plan the implantation of various intracardiac devices.[43-46]

Positron Emission Tomography (PET) and PET/CT. There is increasing evidence for use of PET and PET/CT in a clinical setting for the assessment of myocardial perfusion, function, and viability. Cardiac PET perfusion imaging has an overall sensitivity of 92% and a specificity of 85% for the detection of CAD.[47] Sampson and colleagues[48] have also demonstrated similar results for cardiac PET/CT perfusion with rubidium-82, showing a sensitivity of 93%, a specificity of 83%, and a normalcy rate of 100%. The integrated PET/CT cameras allow anatomic as well as functional imaging of the coronary arteries to detect CAD. Coronary calcium scoring and CT coronary angiography can be performed in one setting, in combination with PET myocardial perfusion imaging.

Cardiac Catheterization

Cardiac catheterization provides information about the anatomy and function of coronary arteries, ventricle, intracardiac and lung pressures, vascular resistance, valve area, aorta, and pulmonary arteries. Furthermore, it allows the performance of diagnostic and therapeutic procedures (coronary angiography and angioplasty). CAD is the underlying cause in approximately two thirds of patients with HF who are admitted to a cardiology department, and is also a serious problem in RA patients. Recent studies suggest that there is less often a history of prior myocardial infarction (MI) in patients with HF, although CAD is often evident on angiography.[49-51] Therefore, clinicians should proceed directly to coronary angiography in patients with HF to exclude CAD.[52]

Although cardiac catheterization is the "holy grail" of cardiology, it requires radiation and pitfalls are not unusual, including emboli, adverse effects of contrast agents, arrhythmias, and catheter trauma. Major complication rate, including death, MI, stroke, ventricular fibrillation, vascular problems, and bleeding, is 1.7% to 2.6%.[53]

Why Currently Used Imaging Techniques Are Not Enough for HF Evaluation in RA

Despite the growing body of research on CVD, the exact etiologic mechanisms involved in the increased risk and worse outcomes of HF in RA remain unclear. Myocardial disease resulting from either the rheumatic disease itself or antirheumatic treatment,[54] pericardial and/or valvular disease,[55] as well as a higher prevalence of unrecognized or subclinical CAD[56] have been proposed as potential

explanations. The direct association between various disease activity markers with HF[57] and the evidence of a signature aberrant immune responsiveness in severe myocardial dysfunction[58] suggests a key pathogenetic role for systemic inflammation and immune dysregulation. To lend more support to the former, a recent histopathologic study showed that staining for citrullination was higher in the myocardial interstitium of RA patients compared with rheumatic and nonrheumatic disease control groups, a finding that further links autoimmunity with myocardial dysfunction and HF in RA.[59]

The phenotype of HF in RA differs from that in control subjects without RA, and RA patients are less likely to be obese or hypertensive, or have history of ischemic heart disease.[60] Additionally, they also present with a different constellation of clinical signs, which makes the clinical evaluation complex, because symptoms such as ankle swelling and reduced functional capacity can be misinterpreted as signs of RA rather than progressing HF. Studies that used echocardiograms found that even asymptomatic patients with RA are more likely to have diastolic abnormalities with well-preserved left ventricular ejection fraction (LVEF) compared with control subjects without RA,[61-64] suggesting that mechanisms of developing HF are different in this population. Considering that no controlled studies have clearly demonstrated an independent relation of RA to systolic dysfunction, the high incidence of HF in RA patients can be attributed to structural changes of the left ventricle affecting the diastolic properties of the heart.[65] LV myocardial deformation including, at first glance, fundamentally contradictory findings such as hypertrophy,[66] reduced LV mass,[67] and concentric remodeling[68] have been reported in RA, resulting in relaxation abnormalities during LV filling and larger left atrial dimensions. The discrepancies in the direction of changes of LV mass may represent sequential alterations from hypertrophy to wasting associated with the systemic features of the disease.[69] Taken altogether, these findings reflect an influence of the chronic inflammatory milieu on regional and global myocardial remodeling, as cumulative inflammation is considered an important contributor to the development of HF by inducing cardiac fibrosis and attenuating myocardial contractility.[70] It is worth noting that similar characteristics of subclinical diastolic dysfunction with increased left atrial volume[71] and relaxation abnormalities with preservation of LVEF have been described in patients with scleroderma and systemic lupus erythematosus,[72,73] indicating that underlying mechanisms of myocardial involvement in systemic rheumatic diseases share common pathogenic pathways potentially governed by autoimmunity and chronic inflammation. The presence of isolated diastolic dysfunction, which is associated with increased mortality in the general population,[74] may also have a significant input on increased and premature CV deaths in RA patients.

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Experimental data suggest that proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1, which are overexpressed in RA, contribute to the aforementioned deleterious effects on the myocardium.[75,76] The association of IL-6 with diastolic dysfunction in RA[61] further emphasizes the impact of abnormal immune response on the myocardium, reinforcing the hypothesis that chronic exposure of cardiac tissue to inflammatory mediators leads to adverse ventricular remodeling. This is in harmony with the observation that methotrexate reduces the risk of development of HF,[57] and is in agreement with other reports that suggest that antirheumatic therapy improves CV risk profile.[77,78] However, the effect of TNF-α antagonists on HF in patients with RA remains an issue of debate,[79] and a number of investigations in this field have yielded inconclusive results.[80-82] On the other hand, small case series have demonstrated improvement in myocardial performance and normalization of LV morphology assessed by echocardiography after treatment with TNF-α inhibitors.[83,84] Thus, definite conclusions will require extended observations and large controlled studies, and as long as this question remains unanswered, biologic agents are generally contraindicated in patients with functional class III-IV HF.

In summary, the background of heart involvement in RA is complex, and encompasses different pathophysiologic mechanisms not fully understood to date. The unfavorable prognosis of HF mandates the early detection of subtle cardiac injury and the identification

of high-risk patients at a preclinical stage. Despite the application of European League Against Rheumatism recommendations,[85] a substantial proportion of RA patients with high CV risk remain unrecognized and recent thoughts suggest the enhancement of CV risk stratification and management with approaches such as carotid ultrasonography and multidetector tomography coronary artery calcification scores.[86] Taking into account the limitations and the weaknesses of traditional risk scores to estimate CV risk in patients with RA,[87] the implementation of a flexible, nonradiating, and highly reproducible noninvasive diagnostic tool to assess cardiac disease in asymptomatic patients may potentially limit long-term morbidity and mortality in this population. Unfortunately, currently used diagnostic techniques have serious limitations. Conventional echocardiography, although inexpensive and highly available, can detect myocardial lesions only if they are severe enough to induce detectable flow or wall motion changes. Only novel, load-independent techniques such as tissue Doppler imaging[88] and STE[28] have been able to capture subclinical impairment of myocardial function, but their reproducibility still remains under evaluation. Additionally, echocardiography is not capable of performing tissue characterization and, therefore, cannot capture early inflammatory phenomena occurring in the myocardium of RA patients. Furthermore, it is an operator-dependent technique with poor reproducibility, an important drawback for accurate follow-up studies. Nuclear assessment, although it offers reproducible measurements of cardiac function, is also unable to detect small myocardial lesions (subendocardial myocardial infarction and scar due to myocarditis or vasculitis), typically found in RA, due to low spatial resolution, and—last but not least—it is a radiating technique, inappropriate for serial evaluation. Finally, although radiographic coronary angiography provides valuable information for intracardiac pressures and coronary artery anatomy and function, it remains an invasive, radiating technique that cannot be routinely used for HF follow-up in RA.

The Emerging Role of CMR

CMR images are derived from signals produced by protons (hydrogen nuclei), which are present in abundance in the human body, and consist mainly of water. The relaxation of the net vector of protons is attributable to two distinct but simultaneous processes, referred to as the longitudinal (T1) and the transverse (T2) relaxation times, which can give important information about human tissues. Basic pulse sequences used in CMR are gradient-echo, which can form a cine loop, and spin-echo, which is more useful for anatomic imaging. Late gadolinium-enhanced (LGE) images, taken 15 minutes after the use of the paramagnetic contrast agent gadolinium, allow the detection of myocardial fibrotic tissue (scar), which appears as a bright area in a background of nulled, black myocardium ("bright is dead").[89]

CMR measures ventricular volumes, EF, and myocardial mass of both ventricles noninvasively and without contrast agent, and provides three-dimensional (3D) images of the heart, which is also feasible with 3D echocardiography. CMR EF, volumes, and mass are more accurate and reproducible than other imaging techniques; however, there is a good correlation between CMR and these techniques.[90] However, recent data comparing the EF measurements, performed by echocardiography, nuclear techniques, and CMR, proved that EF measurements by various techniques are not interchangeable. The conclusions and recommendations of research studies in HF should, therefore, be interpreted in the context of locally available techniques. In addition, there are wide variances in volumes and EF between techniques, which are most often marked in comparisons using echocardiography. This suggests that CMR is the preferred technique for volume and EF estimation in HF patients because of its 3D approach for nonsymmetric ventricles and superior image quality.[91]

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Echocardiography is still the everyday bedside tool for ventricular function evaluation, but CMR is ideal for serial evaluation of HF in RA due to its high reproducibility. In a direct comparison of CMR versus echocardiography for reproducibility, it was shown that for an 80% power and a *P* value of .05, the sample size required is 505 patients for validation using 2D echocardiography, but only 14 patients when using CMR.[92]

Recent data about RA evaluation using CMR support that the progression to HF in RA may occur through reduced myocardial mass rather than hypertrophy.[66] Finally, the high spatial resolution of CMR allows the early detection of important pathophysiologic phenomena that can potentially contribute to the development of HF

in RA, such as myocardial inflammation (edema-fibrosis imaging), and myocardial perfusion defects (stress perfusion-fibrosis imaging), due to both macrovascular disease (CAD) and microvascular disease (vasculitis).

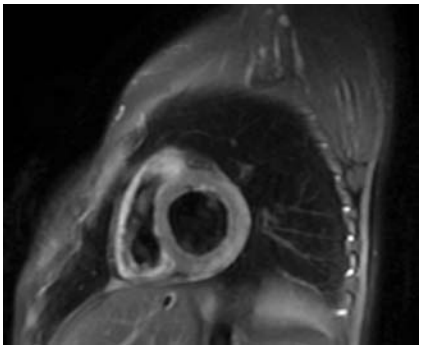
Myocardial Inflammation

CMR is the ideal technique for the evaluation of inflammation involving the heart. Myocarditis very often has a subclinical course, which cannot be easily detected with standard inflammatory indices evaluated in the blood (eg, erythrocyte sedimentation rate, C-reactive protein) and can lead, under certain conditions, to dilated cardiomyopathy[93]; additionally, in early stages, it can also remain undetected by the commonly used imaging techniques, because they are unable to distinguish slight tissue structure changes (eg, edema, cell infiltration), which can occur without associated changes in LVEF—the most often detected parameter by echocardiography. According to current experience, in myocardial inflammation due to infectious causes (ie, viral myocarditis), a decrease in LVEF was not evident during the course of the disease, whereas an increase in cardiac troponin was found in only 20% of cases.[93] Myocardial biopsy is an invasive procedure, its diagnostic value is limited due to a number of reasons (eg, sampling error, variation in observer expertise)[92] and according to ACC/AHA guidelines should be reserved only for patients with unexplained new-onset HF < 2 weeks in duration, associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise, and therefore cannot be used as a screening or follow-up tool.[94]

CMR contributes to the diagnosis of myocarditis using three types of images: T2-weighted (T2-W) images, early T1-weighted (T1-W) images taken 1 minute, and delayed enhanced images (LGE) taken 15 minutes after the injection of a contrast agent.[93]

T2-W is an indicator of tissue water content, which is increased in inflammation or necrosis and also represents an index of lesion acuity. The presence of positive T2-W images in RA patients is indicative of myocardial edema during the acute phase of myocardial inflammation (Figure 1) and can be identified simultaneously or early before the appearance of LGE lesions.[29,31] However, it is not possible to differentiate between necrosis and inflammation only by T2-W images. To enhance the detection of pathology on CMR, images after early and delayed gadolinium injection should be obtained. Higher levels of early myocardial enhancement after gadolinium administration are due to increased membrane permeability or capillary blood flow. Contrast agent deposition in the delayed images (LGE) identifies the presence of fibrosis and it is patchy, subepicardial, or intramural, not following the distribution of coronary arteries (Figure 2). A combined CMR approach using T2-W, early enhancement, and LGE has a sensitivity of 76%, a specificity of 95.5%, and a diagnostic accuracy of 85% for the detection of myocardial inflammation.[93]

Figure 1. Positive T2-weighted imaging (edema imaging) in the lateral wall of the left ventricle during acute myocarditis due to rheumatoid arthritis.



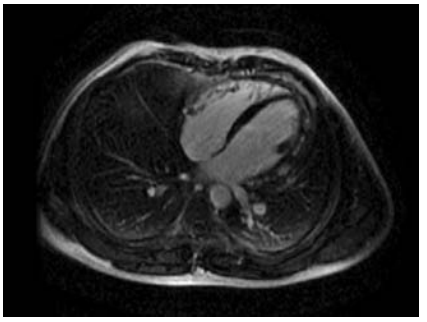


Figure 2. Patchy myocardial fibrosis in the left ventricle lateral wall during myocarditis due to rheumatoid arthritis.

2D echocardiography has a limited role in the diagnosis of acute myocarditis due to the lack of specific diagnostic criteria. The application of new echocardiographic modalities has increased its diagnostic value; however, their contribution to diagnosis of acute myocarditis is still under investigation.[95] Additionally, the nuclear technique using antimyosin antibodies, has high specificity but suffers from very low sensitivity and is not currently in use.[96] Until now, CMR has been successfully used for the evaluation of myocardial inflammation in RA,[19,97-103] and has also documented that myocarditis may precede RA relapse.[97]

Myocardial Ischemia

In contrast to echocardiography that detects ischemia through wall motion abnormalities either after dobutamine injection or after exercise, CMR can detect is-chemia in two different ways. One is the observation of wall motion abnormalities (abnormal wall motion and wall thickening) using the stress factor dobutamine (similar to stress echocardiography, but without the limitation of an acoustic window). Compared with stress echocardiography, stress CMR using dobutamine has better sensitivity (86% vs 74%) and specificity

(86% vs 70%)[104-106]; however, it is time consuming and therefore is mainly used for research protocols.

Observation of myocardial perfusion by the first pass of a bolus of a T1-shortening contrast agent (first-pass gadolinium), injected into a peripheral vein,[107-109] represents the most commonly used perfusion assessment in CMR practice. Data acquired during intravenous vasodilator stress (most commonly adenosine) delineate the underperfused regions associated with myocardial ischemia. The spatial resolution of CMR myocardial perfusion imaging of 2 to 3 mm is greatly superior to other imaging modalities, such as nuclear techniques, so that subendocardial ischemia can be more reliably identified.[109,110] Recent developments led to further improvements in spatial resolution to approximately 1 mm in the imaging plane.[110-112] The interpretation of CMR myocardial perfusion studies in clinical practice is most commonly visual, but quantitative approaches are also available[113-117] and have been validated against radiographic angiography and PET.[109,113] The Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease (MR-IMPACT) study[118] of 234 patients reported improved detection of coronary stenosis by CMR compared with single-photon emission CT (SPECT) in the first multicenter, multivendor comparison. Recently, the Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography for Diagnosis of Coronary Heart Disease (CE-MARC) trial,[119] the largest, prospective, real-world evaluation of CMR, has established CMR's high diagnostic accuracy in coronary heart disease and superiority over SPECT and recommended that it should be adopted more widely for CAD investigation.

Evaluation of myocardial perfusion using CMR revealed that myocardial perfusion defects were frequent in patients with RA and no known cardiac disease.

Evaluation of myocardial perfusion using CMR revealed that myocardial perfusion defects were frequent in patients with RA and no known cardiac disease. These abnormal findings were associated with higher RA disease activity, suggesting a role for inflammation in the pathogenesis of myocardial involvement in RA.[99]

Myocardial Viability (Fibrosis Detection): Clinical Significance of LGE Imaging

CMR is the most reliable imaging technique to detect and quantify scar or fibrotic tissue due to irreversible myocardial damage (viability study). Following acute ischemic injury, the myocardial distribution volume of gadolinium is increased, due to sarcolemmal rupture and abnormal wash-out kinetics. Both acute and old infarctions retain contrast agent and, therefore, appear bright.[120] The preferred imaging time for scar detection is between 10 and 20 minutes after contrast agent administration when the differences among scar, normal myocardium, and blood pool are maximal. This method is referred to in the literature as LGE CMR, and is the gold standard for the in vivo assessment of myocardial scar, because it can detect infarction in as little as 1 cm^3 of tissue—substantially less than other in vivo techniques. LGE has shown excellent agreement with histology in animal and human studies.[121] It is also important to notice that CMR can detect subendocardial MI missed by SPECT or PET.[122,123] The extent of scar visible on CMR predicts the potential for functional recovery after revascularization.[121] In patients with LVEF $>$ 30%, significant scarring ($>$ 5% LV) identifies a high-risk cohort similar in risk to those with LVEF $\leq$ 30%. Conversely, in patients with LVEF $\leq$ 30%, minimal or no scarring identifies a low-risk cohort similar to those with LVEF $>$ 30%.[124]

Recently, the CMR pattern in an RA population presenting with HF was described by Mavrogeni and colleagues.[125] In these patients, LGE did not show only the pattern found in ischemic heart disease (subendocardial or transmural LGE, following the distribution of coronary arteries; Figure 3), but also intramyocardial or subepicardial lesions not following the distribution of coronary arteries, mimicking viral myocarditis, or diffuse subendocardial fibrosis (Figure 4), due to diffuse subendocardial vasculitis. All this information, missed by currently used techniques, became available by CMR, clarifying the multiple aspects of HF pathophysiology in RA. Potential mechanisms of HF in RA that could be identified by CMR are presented in Table 1.

The extent of scar visible on CMR predicts the potential for functional recovery after revascularization.

Conclusions

Although great progress has been achieved in the epidemiology of HF in RA, many aspects of the pathophysiologic background are still missing, due to limitations of currently used techniques. CMR,

TABLE 1

Potential Mechanisms of Heart Failure in Rheumatoid Arthritis That Can Be Identified by Cardiac Magnetic Resonance

Cardiac Disease During RA	Left Ventricular Function	Positive T2 Imaging	Positive LGE	LGE With CA Distribution
Myocarditis	Normal or abnormal	Yes in acute phase	Patchy subepicardial/or intramural in acute or chronic phase	No
DSV	Normal or abnormal	Yes in acute phase	Diffuse subendocardial	No
MI	Normal or abnormal	Yes in acute phase	Segmental subendocardial or transmural	Yes
Stress perfusion defects in CAD	Normal or abnormal	No	Segmental subendocardial or transmural perfusion defects with or without LGE	Yes
Stress perfusion defects in DSV	Normal or abnormal	Yes/no depending on acuity	Diffuse subendocardial perfusion defects with or without LGE	No

CA, coronary artery; CAD, coronary artery disease; DSV, diffuse subendocardial vasculitis; LGE, late gadolinium-enhanced images; MI, myocardial infarction; RA, rheumatoid arthritis.

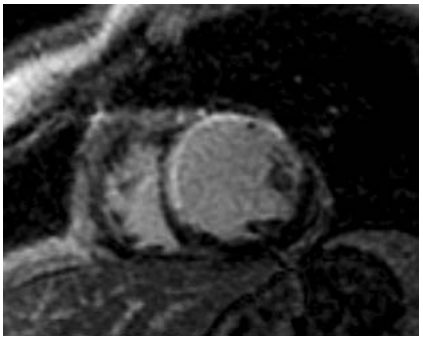


Figure 3. Transmural anterior myocardial infarction in a rheumatoid arthritis patient with left anterior descending artery occlusion.

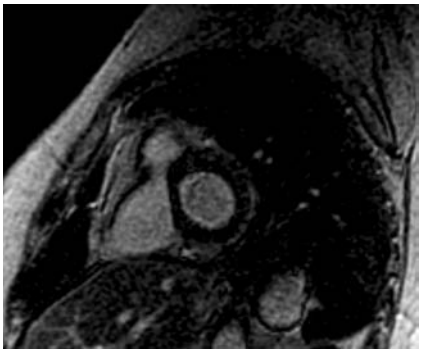


Figure 4. Diffuse subendocardial fibrosis due to diffuse subendocardial vasculitis in a patient with rheumatoid arthritis.

a technique that can capture early—noninvasively and without radiation—the slight myocardial changes of patients with RA, seems to be currently the most accurate diagnostic tool for their assessment. However, multicenter studies are needed to establish the clinical implications of CMR in the evaluation and management of HF in RA patients. ■

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MAIN POINTS

- Cardiovascular disease is the main cause of premature morbidity and mortality in rheumatoid arthritis (RA).
- The prevalence of heart failure in RA still remains twofold higher than that in the general population.
- Currently used imaging techniques for heart failure (HF) evaluation are not capable of detecting disease acuity and the different patterns of HF pathophysiology seen in RA patients.
- Cardiac magnetic resonance can capture early, noninvasively, and without radiation the slight myocardial changes that are missed by other imaging techniques; it can also detect disease acuity and offer excellent reproducibility for follow-up studies.

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