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Role of Imaging Techniques for Diagnosis, Prognosis and Management of Heart Failure Patients: Cardiac Magnetic Resonance

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Abstract

Cardiac Magnetic Resonance (CMR) has evolved into a major tool for the diagnosis and assessment of prognosis of patients suffering from heart failure. Anatomical and structural imaging, functional assessment, T1 and T2 mapping tissue characterization and late gadolinium enhancement (LGE) have provided clinicians with tools to distinguish between non-ischemic and ischemic cardiomyopathies and to identify the etiology of non-ischemic cardiomyopathies. LGE is a useful tool to predict the likelihood of functional recovery after revascularization in patients with CAD and to guide the LV lead placement in those who qualify for cardiac resynchronization (CRT) therapy. In addition, the presence of LGE and its extent in myocardial tissue relates to overall cardiovascular outcomes. Emerging roles for cardiac imaging in Heart Failure with Preserved Ejection Fraction (HFpEF) are being studied and CMR continues to be among the most promising noninvasive imaging alternatives in the diagnosis of this disease.

Keywords

Cardiac magnetic resonance (CMR); Heart failure (HF); Heart failure with preserved ejection fraction (HFpEF); Heart failure with reduced ejection fraction (HFrEF); Left ventricular dysfunction (LV dysfunction); Cardiomyopathies; Infiltrative Cardiomyopathies; Late gadolinium enhancement (LGE); T1 mapping; T2 mapping; T2 weighted images; T2* imaging

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Conflict of Interest

Jorge A. Gonzalez declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent

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Introduction

Despite great advances in the treatment of cardiovascular disease, heart failure remains as one of the most common causes of death and hospital readmissions in United States, and the cost related with heart failure is near to 40 billion dollars per year.¹ Heart failure can be secondary to different etiologies, many of which are treatable and potentially reversible. Cardiac Magnetic Resonance (CMR) plays an integral role in the initial work-up of these conditions. (Figure 1). In the latest American College of Cardiology appropriate utilization guidelines for cardiovascular imaging in heart failure published in 2013; CMR is recommended as an appropriate imaging test in patients with newly suspected or diagnosed heart failure, also in those with heart failure associated with myocardial infarction (MI), in patients considered for revascularization and in those who meet criteria for ICD and CRT implantation.²

CMR Techniques used in Heart Failure Evaluation

A typical CMR study takes 45 minutes and scans are done with multiple 5 to 15 second breath holds. The first part of the protocol is typically an anatomic evaluation, including volume, mass and functional assessment using steady-state free precession imaging (SSFP). CMR is considered the gold standard for measurement of left ventricular (LV) and right ventricular (RV) volumes and function and, importantly, is highly reproducible when compared to other modalities.^{3, 4, 5} SSFP has become the standard technique for cardiac anatomic evaluation due to its higher contrast to noise ratio between the dark myocardium and bright blood pool and has replaced the older gradient echo sequence (GRE) routinely used until the end of the 1990's.⁶ Another part of the standard CMR protocol involves the use of gadolinium based contrast agents (GBCA) for evaluation of scar/fibrosis using late gadolinium enhancement (LGE). Inversion recovery pulse sequences are used with the inversion time set to null normal myocardium, therefore increasing the signal difference between normal and scarred/fibrotic segments. This allows the clinician to identify areas of fibrosis using CMR. LGE is quite reproducible. The clinical and histological changes occurring in the myocardium have been correlated and validated against histopathology.^{7, 8}

LGE can be used to differentiate between ischemic and non-ischemic cardiomyopathies and also among the non-ischemic pathologies by its distribution pattern. LGE aids in assessment of diagnosis and assessment of prognosis of patients with heart failure.⁹ Tissue characterization is another important tool used in CMR protocols. T1, T2, and T2* sequences can allow the imager to gain insight into the intrinsic characteristics of the myocardium.¹⁰ Native T1 corresponds to the longitudinal relaxation time (T1) of a given tissue prior to the use of any GBCA. The most often used sequence is the modified Look-Locker inversion recovery (MOLLI)¹¹ sequence and its shorter version called ShMOLLI.¹² The T1 value is dependent on the magnetic field strength in which the images are acquired: 1.5 Tesla (T) or 3 T. T1 is commonly prolonged with fibrosis, edema and infiltrative diseases and reduced in lipid, iron deposition and in acute infarction.

Gadolinium does not cross cell membranes and therefore accumulates entirely in the extracellular compartment. Thus, T1 values can be obtained pre and post-contrast to

calculate the extracellular volume (ECV). ECV is considered a marker of the extent of interstitial fibrosis in fibrotic diseases. Detecting changes in ECV may allow clinicians to quantify severity of disease, determine prognosis and more importantly establish an early diagnosis; potentially allowing clinicians to change the course of a disease.^{13, 14} T-weighted (W) images and more recently T2 mapping can identify myocardial edema and/or injury, differentiating between acute and chronic events.¹⁵ T2*-W sequences have been traditionally used for the diagnosis of iron overload conditions including hemochromatosis or in patients who received multiple transfusions due to hematological diseases like aplastic anemia, thalassemia and sickle cell anemia.

CMR Evaluation in Ischemic Cardiomyopathy

In the context of patients with coronary artery disease and heart failure, CMR can be used for different reasons including: 1) to rule out active ischemia and exclude ischemic heart disease as a possible reversible cause 2) to assess myocardial viability prior to revascularization 3) to assess prognosis 4) to plan cardiac resynchronization therapy (CRT) implantation with biventricular pacing or 5) to guide appropriate medical therapy. Stress CMR is performed routinely in many centers across Europe and the United States using adenosine or regadenoson infusion and is generally well tolerated. A negative study carries a good prognosis and is associated with very low risk of cardiovascular death and MI.¹⁶

The presence of LGE in a coronary distribution suggests CAD but the absence of it does not automatically rule out CAD because extensive areas of hibernating myocardium may have no evidence of enhancement. However, CMR has shown to be helpful on re-classifying patients with initial diagnosis of non-ischemic cardiomyopathy after coronary angiogram. Soriano et al¹⁷ prospectively enrolled 71 patients with heart failure and LV dysfunction with no prior history of MI and performed CMR with LGE and coronary angiography (CA) to compare the results. 81% of patients with obstructive CAD by CA and 9% of patients with non-obstructive CAD showed subendocardial and/or transmural enhancement consistent with prior infarction, suggesting a role for CMR in re-classifying patients as ischemic in the absence of obstructive CAD. McCrohon et al¹⁸ found in a cohort of 90 patients with heart failure and LV dysfunction, that even though the majority of patients had no evidence of LGE, a group of patients (13%) have LGE in coronary distributions suggestive of CAD, patients who would have ended up misclassified as non-ischemic otherwise. These cases most likely were due to coronary recanalization post-infarction or embolic infarction.

LGE provides supplemental prognostic value when compared to traditional risk factors. In the setting of acute myocardial infarction (MI), microvascular obstruction (MO), microvascular hemorrhage and tissue necrosis (infarct size) can be readily identified with CMR and they are associated with poor prognosis.^{19, 20} Additionally, CMR has a role in predicting late myocardial recovery and in identifying areas at risk after MI.^{21, 22} The excellent visualization of the myocardium allows an evaluation for LV thrombus, aneurysms and pseudoaneurysms.

In patients with chronic CAD, determination of myocardial viability is an important role for CMR. Kim et al²³ showed the ability of LGE to identify reversible and irreversible areas of myocardial injury prior to revascularization, which in turn is an important marker of likelihood of contractile recovery.²⁴ LGE and low-dose dobutamine (LDD) provide excellent accuracy in identifying segments that are targets for revascularization in patients with chronic CAD. LGE provides high sensitivity and negative predictive value (NPV) while LDD provides high specificity and positive predictive value (PPV).²⁵ Both techniques can be integrated into one protocol if needed; nevertheless, LGE has become the standard test ordered in clinical practice due to practical and time issues regarding the use of dobutamine.²⁶

CMR continues to evolve as a promising technique in guiding LV lead placement for CRT. Several studies have shown lower rates of CRT responders when the lead is placed in scarred myocardium on LGE.^{27, 28, 29, 30}

Predicting therapeutic response with beta-blockers of patients with heart failure and ischemia is possible with CMR. Bello et al³¹ demonstrated an inverse relationship between the scar extent at baseline and likelihood of contractile recovery 6 months later, therefore, predicting the recovery and remodeling of a myocardial segment based on LGE.

CMR Evaluation in Non-Ischemic Cardiomyopathy

CMR can help differentiate among the multiple etiologies of non-ischemic cardiomyopathy. Tissue characterization and LGE are the pillars of the diagnostic approach to patients with heart failure and provide additional prognostic information to the clinician in the early phase of the disease.³²

The presence and extent of LGE in non-ischemic cardiomyopathies can identify patients who are at risk of future heart failure re-admissions. These would allow hospitals and providers to target patients at risk and start aggressive monitoring protocols in the outpatient setting to those who exhibited significant evidence of LGE in an attempt to reduce repetitive heart failure hospital admissions, a major cost burden to society.³³

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease with prevalence of at least 1 in 500 patients in the general population, representing the most common genetic cause of heart disease and most frequent cause of sudden cardiac death (SCD) among young athletes.³⁴ CMR plays a key role in the diagnostic work-up of this disease. High resolution SSFP permits accurate assessment of wall thickness. It is particularly useful in those patients with difficult echocardiographic windows and unusual locations of hypertrophy such as the basal lateral wall and apex. T1 relaxation times are prolonged in patients with HCM and allow detection of underlying disease beyond the areas identified with LGE.^{35, 36} LGE can detect areas of fibrosis in patients with HCM. Traditional risk factors for SCD in patients with HCM such as family history of SCD, personal history of ventricular fibrillation (VF) or ventricular tachycardia (VT), frequent non-sustained VT on 24-ambulatory holter, LV wall thickness greater than 30 mm sometimes can be inconclusive in determining a patient's risk of SCD. Recent data suggest that the extent of LGE (>15% of the myocardial mass) can be added to the list and potentially play a major role in SCD stratification in this subset of

patients.³⁷ A recent meta-analysis³⁸ that included over a thousand individuals (n=1063) with HCM, showed that LGE was present in 60% of patients and highlighted the relationship between LGE and cardiovascular mortality in HCM. In addition, the presence of LGE showed a significant trend in predicting sudden death in these patients. To further evaluate this prospectively in a large scale, the National Institute of Health is currently funding a study to determine if these associations of LGE and other novel markers that include serum biomarkers of collagen metabolism will be able to predict SCD and other MACE in patients with HCM.³⁹

Myocarditis is caused by inflammation of the myocardium as a result of a viral infection; CMR plays an important role in diagnosis and prognosis of this disease. Some of the sequences used for the diagnosis are T2-W dark blood and T2-W bright blood, T1 and T2 mapping (which are now replacing the pure imaging sequences), and LGE.^{40, 41} The typical patient with myocarditis presents to the emergency room with chest pain, troponin elevation and non-obstructive CAD or with normal coronary arteries on invasive coronary angiography. The LGE patterns are classically described as mid-wall and/or subepicardial enhancement often in the basal inferolateral walls, findings that have been validated by histopathological studies.⁴² However, the LGE pattern not only constitutes a non-invasive diagnostic tool, but also can add prognostic information as well. Grun et al⁴³ showed that the presence of LGE is the best single predictor of all-cause mortality in a population of 222 patients with biopsy-proven viral myocarditis, independent of clinical symptoms at presentation.

Amyloidosis is an infiltrative systemic disease that produces classic LGE patterns as well. The amyloid protein increases the GBCA uptake in the myocardium and prolongs T1 relaxation time particularly as high as the blood pool T1 values. The LGE pattern and abnormal T1 values help in the diagnosis and prognosis of the disease based on the extent of the amyloid infiltration.⁴⁴ SSFP imaging can demonstrate biventricular hypertrophy and dysfunction and bi-atrial enlargement commonly found in patients with cardiac amyloidosis. Usually two kinds of amyloid infiltrate the myocardium. Immunoglobulin light-chain or AL, also known as primary systemic and transthyretin or ATTR, also known as senile. CMR can help in the diagnosis of both types and increasingly being used to discriminate between the two types of amyloid. Fontana et al⁴⁵ determined the native T1 values in 85 patients with ATTR amyloidosis, 79 patients with AL amyloidosis, 46 patients with HCM and 52 healthy volunteers. AL had the highest values for T1, followed by ATTR. Furthermore, ATTR was associated with more extensive LGE with a proportion close to 2-to-1 compared to AL. The investigators developed a diagnostic scoring system to help differentiate between the two amyloid conditions with 87% sensitivity and 96% specificity.

Sarcoidosis is a systemic multi-organ disease of unknown etiology that is characterized by granuloma formation. Cardiac sarcoid can be present in up to ¼ of patients with the disease and mortality in those who present with symptoms can be as high as 25%, an important target for early diagnosis and potential therapeutic intervention.⁴⁶ Sarcoidosis can be identified with CMR. Patients with cardiac sarcoid involvement commonly present with mid-wall or epicardial pattern of LGE that do not correspond to any coronary distribution. Nagai et al⁴⁷ detect LGE in 13% of patients with sarcoidosis in a cohort of 61

asymptomatic patients who carried the diagnosis of sarcoidosis but had not yet been diagnosed with cardiac sarcoid. Furthermore, Patel et al⁴⁸ showed an increased risk for ventricular tachyarrhythmia in a group of 52 asymptomatic individuals with biopsy proven extra-cardiac sarcoidosis and preserved LV function. These findings suggest that CMR can potentially be used in asymptomatic sarcoidosis patients without cardiac manifestation to potentially alter their disease progression by instating early and aggressive therapies. In addition, Greulich et al⁴⁹ studied 155 symptomatic patients with systemic sarcoidosis who underwent CMR to rule out cardiac involvement. LGE was found in 26% of patients and was found to be the best independent predictor of death and adverse events when compared to LV ejection fraction (EF), LV end-diastolic volume (LVEDV) and/or symptoms of heart failure. Figure 2 shows different examples of the use of CMR in patients with non-ischemic and ischemic cardiomyopathies.

Other Cardiomyopathies

CMR can be used in the diagnosis and prognosis determination by using T2* protocols allowing the quantification of cardiac iron levels. High iron levels are commonly seen in conditions like thalassemia due to frequent blood transfusions and in hemochromatosis. This technique enables use of therapies aiming at reducing the levels of Iron and therefore decreasing mortality rate in this subset of patients.⁵⁰

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrofatty infiltration of the right or both ventricles and presenting usually before the 4th decade of life with palpitations, syncope or SCD. Multiple criteria have been described⁵¹ because of the challenging task of imaging the right ventricle. However, CMR is a diagnostic tool that not only allows high resolution images of the RV and LV both, but allows the identification of LGE patterns seen in subset of patients with ARVC.⁵²

Takotsubo or stress cardiomyopathy is a reversible condition with a unique pattern of regional LV dysfunction which is typically apical but can include the mid ventricle or rarely the base alone. It is typically seen in later decades of life with female predominance and usually triggered by external stressors. Patients usually present with chest pain, heart failure, typical pattern of LV dysfunction, elevation of troponins and non-obstructive CAD. CMR has evolved as a useful technique to establish a definitive diagnosis and differentiate the disease from other forms of non-ischemic cardiomyopathies such as myocarditis. LGE usually is not found and T2-W images and/or T2 mapping suggests diffuse myocardial edema.⁵³

CMR is also helpful in the diagnosis of Chagas disease⁵⁴, LV non-compaction^{55, 56} and infiltrative disorders like Anderson-Fabry disease.⁵⁷ Maceira et al⁵⁸ found significant cardiac changes in a cohort of 94 asymptomatic individuals who were active cocaine abusers when compared to a group of healthy volunteers. LV end-systolic, LV mass index, RV end-systolic, LV and RV ejection fractions were all abnormal. These changes could represent early myocardial damage from the repetitive use of the sympathomimetic drug. 30% of patients had myocardial LGE and up to 71% of patients had abnormal findings in their CMR evaluation.

Habibi et al⁵⁹ found an important relationship between CMR-measured LA size and function in patients who participated in the MESA (Multi-Ethnic Study of Atherosclerosis) Study. In these patients LA changes preceded the development of heart failure. Neilan et al⁶⁰ were able to identify individuals at increased risk of future MACE after surviving a SCD episode and showed that CMR was able to reclassify a significant proportion of those patients and provide a correct diagnosis. Of the 137 patient that underwent CMR, 71% of them had LGE and over 75% had an arrhythmogenic substrate identified. 10% of patients had myocarditis, 2% were diagnosed with HCM, 2% were diagnosed with sarcoidosis and another 2% had ARVC.

More recently, the medical community is paying closer attention to patients with HFpEF (Heart Failure with Preserved Ejection Fraction) who account for up to 50% of cases of heart failure. CMR is currently being developed as a potential diagnostic tool, involving diastolic assessment, myocardial perfusion reserve analysis and quantification to help in the diagnosis of microvascular disease and T1 mapping characterization. The future looks promising for these techniques in this special subset of patients with heart failure.⁶¹

Conclusions

CMR has evolved over the last decade to become a key player in the diagnosis and prognosis of numerous types of cardiomyopathies encountered every day in clinical practice. CMR is the gold standard for measuring cardiac chamber size, volume, and function including the RV. The high quality images obtained by SSFP enable accurate wall motion analysis and anatomic/functional valve evaluation. T1 and T2 mapping for tissue characterization can identify the underlying etiology of heart failure. In addition, LGE provides a unique non-invasive assessment of scar/fibrosis within the myocardium that no other technique offers. A CMR-focused evaluation can aid in the early diagnosis of multiple cardiac conditions, potentially changing therapeutic steps along the way. The extent of LGE in different cardiac diseases continues to highlight the importance of fibrosis as a key independent risk factor associated with high MACE and poor response to medical and revascularization therapies. CMR will continue to play a key role in the diagnosis and prognosis of patients with heart failure in the years ahead.

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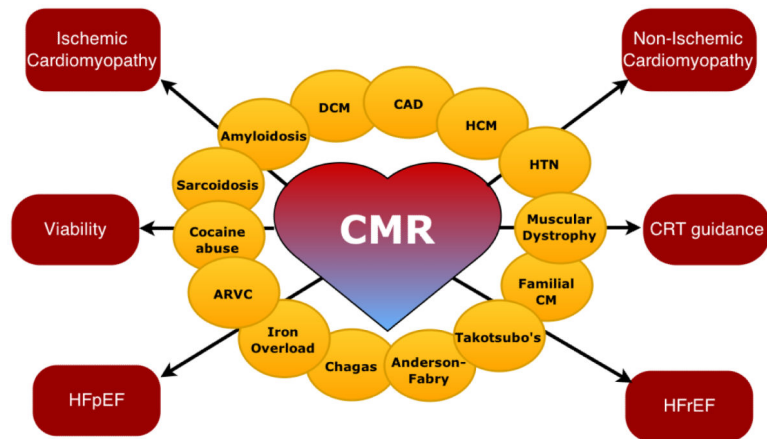


Figure 1. CMR Role in diagnosis and prognosis of different cardiac pathologies in patients presenting with congestive heart failure symptoms

DCM: Dilated cardiomyopathy, CAD: Coronary artery disease, HCM: Hypertrophic cardiomyopathy, HTN: Hypertension, ARVC: Arrhythmogenic right ventricular cardiomyopathy, HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, CRT: Cardiac resynchronization therapy, CM: Cardiomyopathy.

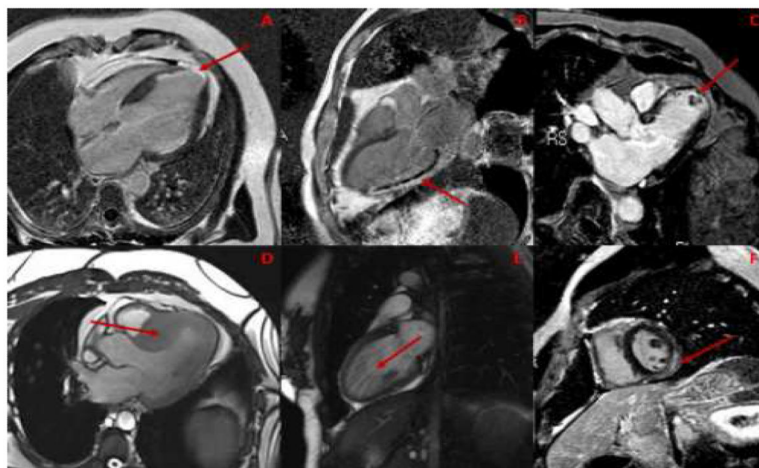


Figure 2. Clinical examples of the use of CMR in different cardiac pathologies
A: Evidence of transmural anteroapical LGE consistent with MI in a patient with chest pain. B: Extensive microvascular obstruction (MO) in patient with late-presenting STEMI. C: Transmural LGE and evidence of apical thrombus in patient with CAD and prior apical MI. D: Asymmetric septal hypertrophy in a patient with HCM. E: Case of non-compaction Cardiomyopathy. F: Mid-epicardial LGE in a 38 y/o male presenting with NSTEMI and no evidence of CAD on coronary angiography, consistent with myocarditis.