Advanced tissue characterization in non-ischemic cardiomyopathies using contrast-enhanced cardiac magnetic resonance imaging

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ABSTRACT

يمكن استخدام التصوير بالرنين المغناطيسي للقلب والأوعية (CMR) للحصول على معلومات متكاملة عن كل من وظيفة القلب وخصائص الأنسجة المتقدمة. حيث بالإمكان باستخدام التقنيات ذات التباين المعزز الحصول على معلومات في غاية الأهمية من الناحية التشخيصية حول جدوى الأنسجة وكذلك حول تغيرات الالتهاب وأمراض التخزين وذلك من خلال إجراء فحص مدته 45 دقيقة. تجدر الإشارة أنه من شأن دمج المعلومات الوظيفية (SSFP) مع تقييم وذمة عضلة القلب وتقييم الإصابات القابلة للعلاج وتقييم الإصابات غير القابلة للعلاج (في حالات الاحتشاء والتليف الموضعي على سبيل المثال، باستخدام تقنيات الغادولينيوم الحديثة للتعزيز)، من شأنه أن يتيح لنا الحصول على معلومات تنبؤية ومحددة حول المرضى الذين يشكون من اعتلال عضلة القلب غير الإقفاري. يتيح لنا التصوير بالرنين المغناطيسي CMR ذو التباين المعزز تشخيص حالات اعتلال عضلة القلب غير الإقفاري بكامل الدقة والكشف عن الحالات الأولية والثانوية لاعتلال عضلة القلب وبالتالي يمكن استخدامه لتوجيه عملية العلاج ومن ثم الاستغناء في كثير من الحالات عن اللجوء إلى الإجراءات الجراحية.

Cardio-vascular magnetic resonance imaging (CMR) can be used to obtain integrated information on both cardiac function and on advanced tissue characteristics. Using contrast-enhanced techniques, highly diagnostic information on tissue viability, inflammatory changes, and on storage diseases can be obtained within a 45-minute examination. The combination of functional information (using steady-state free precession sequences cine techniques), assessment of myocardial edema (using T_2-based techniques), of reversible injury (for example in inflammatory diseases; using T_1-based techniques), and irreversible injury (for example in infarction and regional fibrosis, using late gadolinium enhancement techniques) allows disease-specific and prognostic information to be obtained in patients with non-ischemic cardiomyopathy. Contrast-enhanced CMR allows the accurate diagnosis of non-ischemic cardiomyopathies, identification of primary and secondary cardiomyopathies, and can be used to guide therapy, thus avoiding the need for invasive measures such as endomyocardial biopsy in many cases.

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Patients with cardio-myopathies (CM) require adequate imaging to allow a definitive diagnosis to optimally guide therapy. Using conventional imaging methods such as echocardiography, only information on ventricular size, function, and wall motion can be obtained, lacking detailed information on tissue changes and specific findings of different cardiomyopathies. Computed tomography (CT) adds to the non-invasive diagnosis of coronary artery disease by providing excellent and reliable non-invasive imaging of the coronary arteries, and allows assessing left ventricular (LV) function as well, but suffers from radiation, iodine-based contrast agents, and the lack of specific tissue information. Cardiac magnetic resonance imaging (CMR) has evolved into a reliable and accessible imaging modality and allows a comprehensive, completely non-invasive, and radiation-free examination of both cardiac function and tissue composition. Using a combined protocol, biventricular and atrial functional parameters can be obtained with excellent information on myocardial water content (edema imaging), myocardial reversible injury (using T_1-weighted early gadolinium enhancement) and irreversible injury (using T_1-weighted late gadolinium enhancement [LGE]).[1] Storage diseases such as, amyloidosis, cardiac hemochromatosis, or Fabry disease present with disease-specific imaging findings, and allow a non-invasive, highly reliable, and reproducible diagnosis and follow-up during treatment.

Application of advanced tissue characterization protocols can be also used in the diagnosis of acute myocardial inflammation (myocarditis) to assess cardiac changes during chemotherapy, and in the prognostic assessment of different cardiomyopathies to optimize medical management in these conditions. With the development of faster hardware and optimized software, CMR may be involved in a widely used routine imaging method to categorize cardiomyopathies, and to allow a specific diagnosis.[2] The purpose of this review is to give an overview of current CMR techniques in the non-invasive assessment of non-ischemic cardiomyopathies. Recent developments in image acquisition and image post-processing are discussed, typical cases are presented, and future outlooks are provided.

Principles of tissue characterization. Cardiac magnetic resonance imaging using LGE has been used initially only to assess myocardial viability in ischemic heart disease, but its use has expanded and now also covers the field of non-ischemic cardiomyopathies.[2,3] In contrast to an ischemia-related damage that always involves the sub-endocardial layers of the myocardium, and follows the distribution region of a coronary artery territory, fibrosis in non-ischemic damage, such as inflammation, typically involves the epicardial layers first, and does not usually follow coronary artery territories. The location of LGE within the myocardium (whether subendocardial, mid-myocardial, subepicardial, or transmural) together with the distribution region (following coronary artery territories versus widespread or diffuse) and the pattern (regional, patchy, or diffuse), allows a safe differentiation between ischemia-related and non-ischemic damages to the myocardium, and may even provide disease-specific information, thus improving the diagnostic yield of CMR.[4,5] Diagnosis and treatment in non-ischemic cardiomyopathies differ significantly from those in ischemic heart diseases and may be challenging. Although most initial presentations of patients are with a stable, non-critical course, the first clinical picture in myocarditis, especially in young male patients, may be dramatic and may involve cardiogenic shock, making a fast, reliable, and non-invasive diagnosis mandatory. Even when using a combination of all available clinical information (for example, history, physical findings and symptoms, ECG, seromarkers such as troponin T [TNT] and b-natriuretic peptide [BNP]), the diagnostic accuracy for inflammatory myocardial diseases such as myocarditis remains sub-optimal. Echocardiography is helpful to assess LV function, but cannot distinguish between acute and chronic myocardial injury. The sensitivity of seromarkers such as TNT is limited during the first hours after onset of acute myocardial injury. Endomyocardial biopsy, which could be considered the gold standard to assess tissue morphology, does not have a clinical role in the diagnosis of acute myocardial infarction, and is limited to patients with unexplained heart failure in most centers, given its invasive nature, risk of significant complications, sampling error, and lack of standardized histo-chemical protocols. Unlike other imaging modalities, such as nuclear cardiology techniques, CT and echocardiography, CMR uses a signal that directly reflects physical (magnetic) properties of the tissue under examination, thus, it does not depend on reflection, transmission, or radiation of signals. Using dedicated high-frequency pulse sequences, specific tissue characteristics can either be attenuated or selectively visualized, thus allowing a user-defined tissue signal is to be generated. Using this approach, fat or water can be suppressed, contrast inflow can be followed in any tissue and tissue composition can be assessed both visually and quantitatively. Although CMR is different from standard MRI techniques of other organs and requires a multi-disciplinary team of cardiologists, radiologists, technologists, and physicists, it is possible to scan nearly 100% of patients successfully, and without complications or side effects in less than 45 minutes for most clinical questions. This is often cheaper than using combined imaging approaches and may be even faster than the traditional methods; the patient's benefits from high diagnostic accuracy and a specific diagnosis to optimally treat their cardiomyopathy.

Ventricular morphology and function. Over the last decade, CMR has been widely accepted as the "gold standard" for the assessment of systolic function due to its high spatial and temporal resolution, excellent image quality, lack of geometric assumptions, and the ability to assess flow using phase contrast imaging (PC). The CMR-PC approach has been validated in vitro and in vivo and importantly, can be used to assess 3-dimensionally velocity. The morphological assessment of the left ventricle can be performed by either spin-echo (SE) T_1-weighted (black blood) or gradient-echo (GRE) (white-blood) sequences, both obtained during short periods of breath holding.[2] Using advanced hardware (1.5 T scanner, dedicated multi-element cardiac coils) and software [parallel imaging techniques, breath-hold sequences, and advanced cine-techniques such as steady-state free precession sequences (SSFP)], it is possible to obtain information on biventricular and biatrial size, mass, and function within a few minutes. Using multiple short axis or rotational long axis approaches, calculation of all relevant functional parameters is easy and does not require theoretical assumptions on ventricular size and shape.[2] Dedicated software allows fast evaluation with minimal inter-observer variability, thus providing more accurate assessment than most available imaging modalities. Patient's limitations only play a very limited role in CMR; successful imaging can

be carried out in nearly 100% of cases with excellent image quality. Valvular function can be assessed using a combination of cine imaging and flow-sensitive imaging; thus allowing direct quantification of both stenotic (planimetry or calculation of orifice area) and regurgitant valves (calculation of absolute and relative regurgitant fraction) without the need for invasive measurements in most cases. Although limited, diastolic functional information can be assessed following established echocardiographic parameters such as transmitral flow pattern and pulmonary vein flow pattern (**Figures 1a-d**).

Tissue edema. Increased myocardial water content (edema) leads to an alteration of the predominant magnetic properties of the affected tissue, because protons are more frequently bound to free water and thus have a longer transversal relaxation time or T_2-time. Using so-called T_2-weighted sequences, edematous areas will display as areas with higher signal intensity than remote myocardium. This has been shown to be diagnostic both in acute myocardial infarction and in acute myocarditis.[6,7] The distribution pattern of the edema often allows a classification of the damage into ischemia-related damages (usually affecting the subendocardium) and into non-ischemic damages (often starting at the subepicardial level and sparing the subendocardium). Direct comparison of the averaged and regional myocardial T_2 signal intensity values to that of remote skeletal muscle generates a T_2-ratio and allows diagnosing acute myocardial edema with a semi-quantitative approach. Recently, methods have been developed to map myocardial T_2 times, allowing a direct measurement of the myocardial T_2 values (**Figure 2a**).

Hyperemia. In any tissue, inflammation with preserved vasculature, and thus continuous blood supply, increased regional blood flow and volume can be found. In acute myocarditis, this is increasingly used as a diagnosed criterion by obtaining contrast-enhanced CMR images early after intravenous injection of gadolinium-based contrast agents to assess its initial vascular and brief interstitial steady state.[8] Normalization of myocardial contrast uptake to that of skeletal muscles compensates for influences of cardiac output, renal function, and signal post-processing, and is the most commonly used method to evaluate the "early enhancement" (EE) images. Increased contrast uptake in the EE images is indicative of reversible myocardial injury and can be used to non-invasively follow up

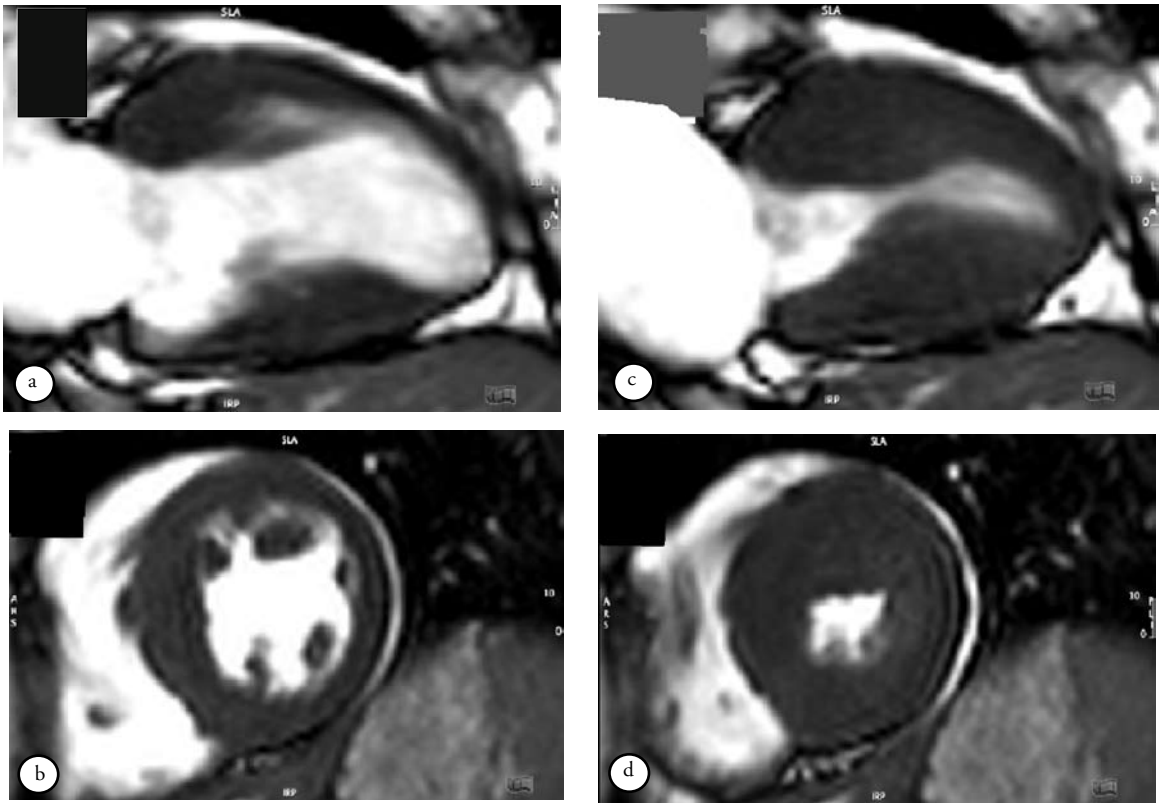

Figure 1 - An example of steady-state free precession sequences (SSFP) in **a**) 2-chamber view diastole, **b**) short axis orientation diastole, **c**) 2-chamber view systole, **d**) short axis orientation systole.

patients with suspected or diagnosed myocarditis. The regional distribution (endocardial versus epicardial sparing) again allows a classification into "ischemic" and "non-ischemic" damage[4,9-11] (**Figures 2b & 2c**).

Necrosis/fibrosis. Cardiovascular magnetic resonance using the LGE technique is used as a non-invasive tool for the assessment of myocardial viability. It has the advantage over other imaging techniques of directly visualizing fibrotic myocardium with high contrast and spatial resolution. This technique has proven prognostic value both in coronary artery disease and in non-ischemic cardiomyopathies.[5,12] Late gadolinium enhancement has been proven to represent chronic, irreversible myocardial damage in animal and human studies, and represents the current "gold-standard" for the non-invasive detection and quantification of scar tissue in the heart. Its superior spatial resolution allows detecting small, but relevant areas of fibrosis that may be missed by other imaging techniques, including nuclear techniques. It is best visualized using dedicated, T_1-weighted sequences with an individualized suppression pre-pulse to null the signal of healthy myocardium, typically 5-10 minutes after the intravenous administration of a gadolinium-based contrast agent.[13] For specific cardiomyopathies, including myocardial storage diseases, distinctive patterns of LGE distribution have been described. These patterns differ from ischemia-related scars and are usually easy to recognize. So-called mid-wall sign (mid-myocardial enhancement) is typically found in hypertrophic cardiomyopathy at the sites of RV insertion; small areas of sub-epicardial patchy enhancement can be seen with acute myocardial inflammatory changes, for example, in myocarditis. Using LGE techniques, CMR may be used as a non-invasive tool for easy differentiation between ischemic and non-ischemic myocardial damage, and may provide tools for the identification of disease-specific distribution of myocardial fibrosis. Furthermore, the presence and extent of LGE is associated with patients' risk for adverse events and an unfavorable outcome in, for example, dilated non-ischemic cardiomyopathies (**Figure 3a**).

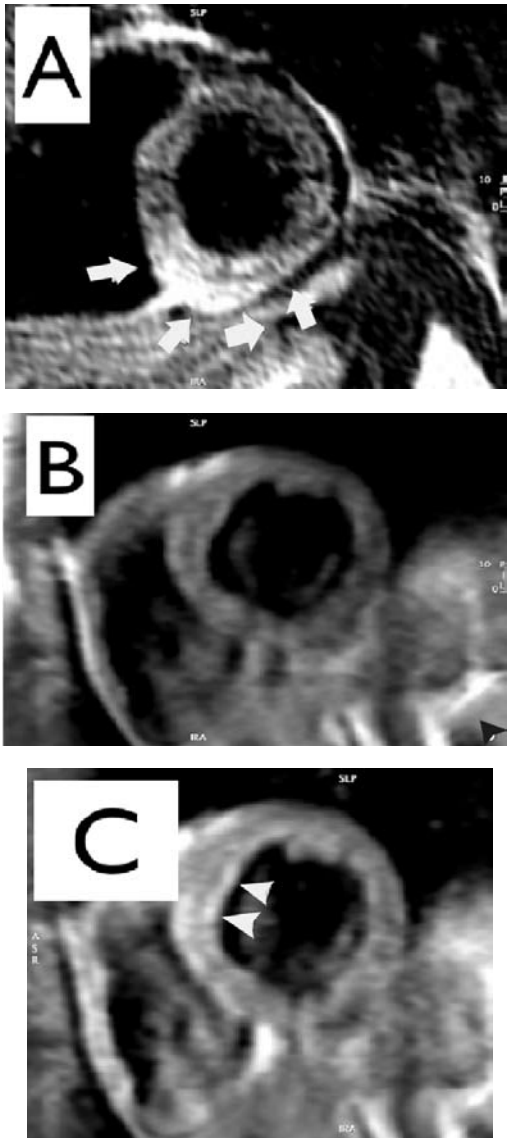

Figure 2 - Short axis images in acute infarction **a**) inferoseptal infarction, note increased signal intensity and wall thickening (arrowheads), **b**) pre-contrast T1 weighted image, **c**) post-contrast T1 weighted image, note subendocardial uptake (arrowheads).

Disease-specific findings. Myocarditis. Myocarditis is a common inflammatory cardiac disease. It appears to be a major cause of sudden death, and may progress to chronic dilated cardiomyopathy. From the clinical point of view, there are several challenges to the management of patients with myocarditis. Myocarditis is typically caused by viruses, toxic, or autoimmune mechanisms. Clinical diagnosis is often difficult due to unspecific or subtle symptoms, and the lack of other specific non-invasive diagnostic criteria. The ECG and serological markers have low sensitivity; endomyocardial biopsy is invasive and not appropriate unless patients suffer severe heart failure. The first challenge is to establish the diagnosis of myocarditis, which is usually based on clinical, pathological, or a combination of diagnostic criteria. The second challenge is to follow the disease activity to identify patients who may be at risk of chronic dilated cardiomyopathy development, which seems to be associated with ongoing myocardial inflammation and viral persistence. Cardiac magnetic resonance imaging has recently emerged as a non-invasive tool to diagnose myocarditis, as well as to follow its course in patients. Three features potentially associated with

acute myocardial inflammation may be visualized by CMR: 1) tissue edema, which may result in an elevated T_2 signal; 2) capillary leakage, which is assumed to be associated with an increased signal on T_1-weighted spin-echo images after gadolinium administration (elevated global relative enhancement); and 3) myocardial necrosis or scarring as indicated by the presence of LGE.[1,4,6,9,10,12] The CMR findings include characteristic findings of inflammation, regional or global wall motion abnormalities, pericardial effusion, and regional myocardial fibrosis. A recently published consensus[14] allows diagnosing an acute myocardial inflammation if 2 of 3 findings (regional or global edema; increased EE ratio; increased LGE) are present in the clinical setting of suspected myocarditis. The T_2-weighted images allow visualization of myocardial edema and, if present, pericardial effusion. Reversible myocardial damage can be seen by increased uptake of gadolinium-based contrast agents and semi-quantified in EE images after normalization to skeletal muscle. Irreversible injury in a non-ischemic distribution pattern can be seen on LGE images and most often affects the lateral segments, typically sparing the sub-endocardium (**Figures 3b & 3c**).

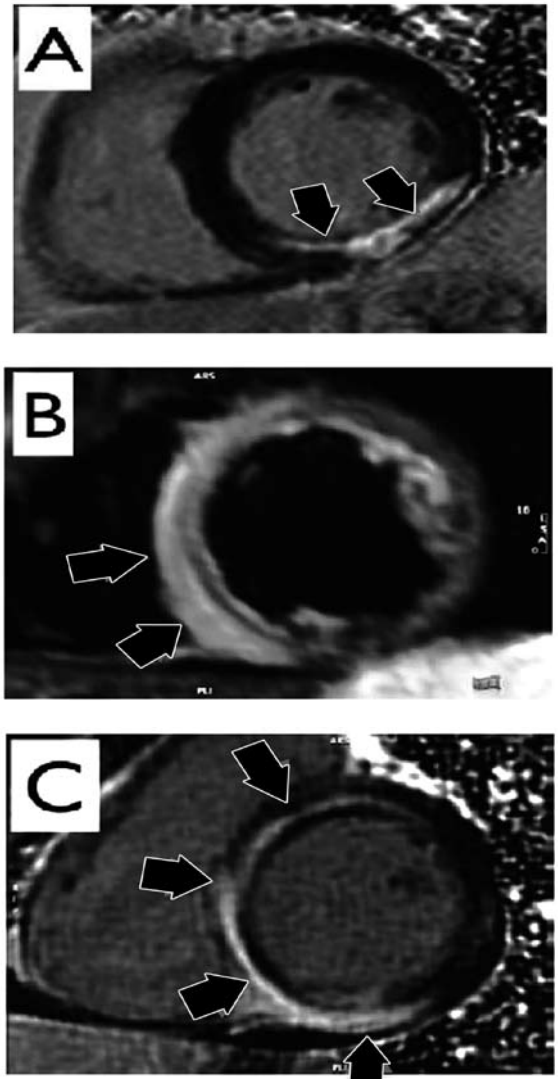

Figure 3 - Short axis images examples of cardiac fibrosis. **a**) late gadolinium enhancement in a chronic inferior infarction, **b**) post-contrast T1 weighted image showing epicardial uptake in the septum in a patient with acute myocarditis, **c**) late gadolinium enhancement in an acute fulminant myocarditis with non-ischemic distribution pattern.

Sarcoidosis. Sarcoidosis is a multi-systemic disease of unknown origin and may affect all organs. Cardiac involvement has a strong impact on the patient's prognosis, but is difficult to detect in vivo. This is reflected by the high rate of unexpected cardiac sarcoidosis in postmortem studies. In a study[15] of patients with necropsy proven cardiac sarcoidosis, it was established or suspected before death in only 45%, with cardiac involvement being fatal in 67%. Cardiac sarcoidosis is mostly identified by impaired systolic LV function, a feature of more advanced disease. The CMR findings in sarcoidosis may include regional wall motion abnormalities, and more severe cases may present with global LV dysfunction.[16,17] Early and late gadolinium images are expected to demonstrate myocardial inflammation and fibrosis, which is often transmural. As sarcoidosis is a systemic disease, normalization to skeletal muscle may produce false-negative results. Thus, absolute signal increase in the myocardium should also be assessed (**Figure 4a**).

Amyloidosis. In acquired and hereditary forms of amyloidosis, amyloid is stored extracellularly in potentially all organs including the heart and may be detected by imaging. Cardiac involvement mainly determines the prognosis, and previously required endomyocardial biopsy. Early detection of cardiac involvement would be desirable to optimize survival through aggressive treatments. In immunoglobulin light-chain and transthyretin-related amyloidosis, the presence of cardiac involvement is a major factor influencing both prognosis and treatment options. The CMR findings include impaired systolic function in later stages, restrictive physiology, and atrial dilatation. The wall thickness of both ventricles increases with storage of amyloid in the myocardium.[18] The T_2 images and EE ratio usually are normal, as there is no active inflammation with the storage of amyloid. Due to the dramatically increased distribution volume for extra-cellular contrast agents like gadolinium, "emptying" of the blood volume occurs soon after injection of contrast. Most patients show a diffuse uptake of gadolinium

with a characteristic bright subendocardial "ring" of enhancement.[18] Involvement of other organs in the storage process can be seen on scout images in many cases (**Figures 4b & 4c**).

Hemochromatosis. In both forms, acquired and hereditary, of hemochromatosis, there is a diffuse iron storage in organs, leading to reduced function. Again, cardiac involvement determines prognosis and is difficult to assess, as neither serum ferritin levels, nor liver iron content directly correlates to myocardial iron overload. The CMR can easily detect iron storage due to the significant T_2 and T_2* shortening effect of iron. This can be assessed visually (affected tissues are dark on all types of images) and can be quantitatively assessed by T_2* maps. Guidance of therapy by CMR T_2* values has been shown to effectively and dramatically improve overall prognosis and should be used whenever access to a CMR scanner is available[19-21] (**Figures 5a & 5b**).

Assessment of myocardial fibrosis in congenital heart disease. Late gadolinium enhancement can detect myocardial fibrosis in the left ventricle both in ischemic and non-ischemic cardiomyopathies and in the right ventricle in patients with pulmonary hypertension. This may contribute to a better understanding of the pathogenesis of right ventricular (RV) dysfunction, and the presence of arrhythmias in patients with congenital heart disease.[21] Late gadolinium enhancement imaging has been applied to patients with congenital heart disease, and is likely to make an important contribution to our understanding of the pathophysiology of RV dysfunction in repaired D-transposition of great arteries, congenitally corrected transposition of great arteries, repaired tetralogy of Fallot, and Eisenmenger syndrome.[22,23] In children, LGE imaging can detect fibrous tissue after outflow tract reconstruction,

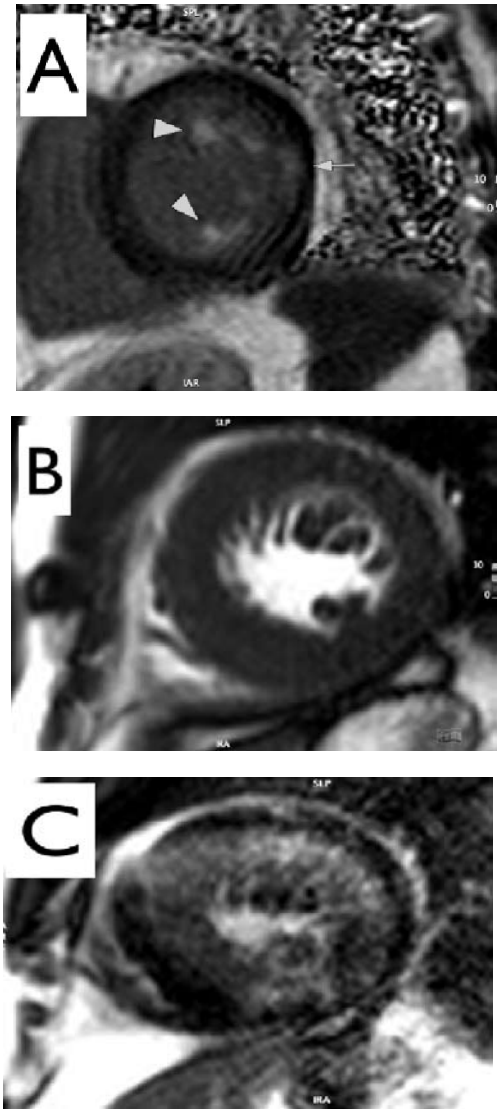

Figure 4 - An example of **a**) short axis late gadolinium enhancement image in a patient with cardiac sarcoidosis, note fibrosis of papillary muscles (arrowheads), b) diastolic short axis cine image in a patient with amyloidosis, note concentric severe hypertrophy. **c**) short axis late gadolinium enhancement image in a patient with amyloidosis, note diffuse extensive contrast uptake in a non-ischemic distribution pattern.

Figure 5 - Patient with cardiac hemochromatosis. **a**) coronal localizer, note low hepatic signal intensity. **b**)T2* map of the heart in short axis orientation, note reduced cardiac and hepatic signal intensity.

Mustard repair, and repair for transposition of great arteries.[22-24] The extent of LGE correlates well with ventricular dysfunction, poor exercise tolerance, arrhythmia, and neurohormonal activation.[25] Fibrosis at the attachment site of the right and left ventricle may be a result not of fibrosis, but rather of a diverse arrangement of the myocardial fibers in this area; RV patching causes the greatest amount of RV fibrosis and hence RV dilatation and/or dysfunction.[26] Hopefully, the role of CMR in the detection of fibrosis in patients with systemic right ventricle and Fontan repair, patients will contribute more to the understanding of the pathophysiology of heart failure in congenital heart disease, and will facilitate risk stratification for management of this high-risk.

In summary, advanced tissue characterization using contrast-enhanced CMR allows a fast integrated assessment of cardiac function, reversible and irreversible tissue injuries, and provides valuable prognostic information. Comprehensive imaging protocols can be implemented into routine imaging of patients with non-ischemic cardiomyopathies, and often allows a specific diagnosis. Treatment based on CMR findings can be used to effectively address specific aspects of each disease, thus improving overall patient prognosis.

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