Late Gadolinium Enhanced (LGE) Cardiovascular Magnetic Resonance (CMR) imaging has a unique ability to characterize diverse mechanisms of non-ischemic myocardial injury. The pattern and extent of LGE findings have been studied across a wide range of cardiomyopathy states. To date, these collective findings provide strong justification for the use of LGE-CMR in the evaluation and prognostication of patients with Dilated, Hypertrophic, Restrictive and Inflammatory cardiomyopathies. This review article summarizes relevant studies in the field and highlights the clinical role of LGE-CMR in contemporary practice.

Keywords: Cardiomyopathy, Fibrosis, Late gadolinium enhancement, Magnetic resonance imaging, Prognosis

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gadolinium, the registration of these images allows for voxel-based estimation of the extra-cellular volume (ECV) fraction (11). This may be particularly valuable for patients with non-ischemic cardiomyopathy where fibrosis may be both regional and diffuse, the latter being challenging to characterize with conventional LGE techniques. This promises to expand the capacity of gadolinium-based CMR imaging to identify and prognosticate patients with cardiomyopathy.

The following review highlights studies identifying the prognostic value of LGE in a variety of non-ischemic cardiomyopathies. For ischemic cardiomyopathy, similar reviews can be found elsewhere (12, 13).

**Interpreting LGE-CMR: Visual versus quantitative techniques**

It is prudent to first recognize variability by which LGE imaging has been studied by various investigators over the years, and how addressing this through standardized reporting is of priority for wide-spread clinical application as a prognostic tool. Two ways of evaluating LGE images exist; i) visual scoring with description of distribution pattern, and ii) signal-threshold based quantification using computer-assisted algorithms. While a combination of these approaches appears optimal, the latter has been challenging to introduce into routine clinical workflow. Visual scoring can be performed using a sub-segmental model (14) with good agreement with signal-threshold based techniques for total fibrosis burden.

The pattern of fibrosis is an important and signature feature associated with specific non-ischemic cardiomyopathy states. Fig. 1 illustrates the 6 typical patterns of LGE that should be identified with routine clinical reporting (15).

Fig. 1 Schematic of typical late gadolinium enhancement (LGE) patterns in various cardiomyopathy states. (a) Ischemic cardiomyopathy: patient with transmural inferoseptal LGE and nontransmural lateral wall LGE. (b) Dilated cardiomyopathy: patient with midwall “striae” LGE throughout the interventricular septum. (c) Hypertrophic cardiomyopathy: patchy midwall LGE within the hypertrophied septal wall segments. (d) Viral myocarditis: epicardial-based LGE in the anteroapical and inferolateral walls. (e) Sarcoidosis: dense epicardial-based LGE of the anteroapical and inferior walls. This case also shows right ventricular involvement. (f) Amyloidosis: diffuse, global, subendocardial to epicardial LGE involving both the left and the right ventricle. Figure from John Stirrat, James A. White The Prognostic Role of Late Gadolinium Enhancement Magnetic Resonance Imaging in Patients With Cardiomyopathy. Canadian Journal of Cardiology, Volume 29, Issue 3, 2013, 329-336 http://dx.doi.org/10.1016/j.cjca.2012.11.033
diomyopathy (17), whereas >3SD has been identified to best represent fibrosis in Non-Ischemic Dilated Cardiomyopathy (NIDCM) (18) and Hypertrophic Cardiomyopathy (HCM) (16). The second most commonly employed quantification technique is Full Width at Half Maximum (FWHM) (19) (Fig. 2) and is suitable for the identification of dense replacement fibrosis. This technique references the peak signal of visually identified fibrosis and applies a threshold at 50% of this peak signal. The summed extent of fibrosis is typically expressed as a % of Left Ventricular (LV) mass.

Studies evaluating the prognostic value of LGE in various non-ischemic cardiomyopathy have used a combination of these described visual and/or quantitative techniques. Careful attention must therefore be paid to specific techniques used and the comfort and experience of the clinician in reproducing such analyses.

**Non-ischemic dilated cardiomyopathy (NIDCM)**

Significant interest has emerged surrounding the improved risk stratification of patients with NIDCM. Indeed, the recently reported DANISH trial highlighted a poor discriminative power of left ventricular ejection fraction (LVEF) criteria alone to appropriately select patients likely to benefit from primary prevention Implantable Cardioverter Defibrillator (ICD) (20). Numerous studies have now identified a 30-40% prevalence of non-ischemic fibrosis, typically described as a mid-wall septal “striae” pattern, on LGE-CMR in this referral population (5, 21). While the pathophysiology of this phenomenon remains uncertain, the presence of any LGE (22) or specifically a septal striae pattern of LGE (5, 21, 23) has been associated with elevated rates of adverse cardiac outcomes in this population.

A recent meta-analysis, including 2,948 NIDCM patients from 29 studies, showed that the presence of any LGE was
strongly associated with arrhythmic endpoints (sustained ventricular arrhythmia, appropriate implantable cardioverter-defibrillator therapy or sudden cardiac arrest) with an odds ratio of 4.3 (24). This association remained significant for studies with a mean LVEF >35% (odds ratio 5.2), indicating LGE to be a superior risk stratifier of arrhythmic risk over LV function in this population.

Towards standardizing the reporting of this important finding and reducing reliance on expert opinion, recent efforts have focused on establishing objective criteria for mid-wall septal fibrosis (18). Using an STRM based approach, non-expert analysis was able to stratify NIDCM patients into high versus low risk (22% versus 3% annualized risk, Hazard Ratio (HR)=8.7) of cardiac mortality or appropriate ICD therapy using a septal fibrosis cut-off of 3% by LV mass. The use of such criteria is important for non-expert sites as subtle, physiologic signal changes of the basal septum are not uncommon and may reduce the specificity of this finding (25).

**Hypertrophic cardiomyopathy (HCM)**

Given high prevalence of HCM in the general population, estimated at 1 in 500, and an estimated 0.5 to 1% annual risk of arrhythmic event (26), substantial efforts have and continue to be made in establishing risk prediction models for this population. While existing guidelines provide little emphasis on imaging markers beyond LV wall thickness (27), interval evidence provided by LGE-CMR has provoked emerging recommendations that LGE imaging should now be considered a first-line risk prediction tool in this population (28). The presence or extent of LGE seen in HCM does not appear to show strong association with underlying genotype (29). When present, it is most typically of a mid-wall patchy distribution in hypertrophied segments (Fig. 1), which may be of septal, apical or diffuse phenotype.

Numerous studies have identified that the presence of LGE is a significant predictor of ventricular arrhythmias (30), Sudden Cardiac Arrest (SCA) (31), and all-cause/cardiac mortality (32) in this population. A recent meta-analysis including 2,993 HCM patients from 5 studies confirmed the presence of any LGE to be associated with an elevated risk of SCA (OR 3.41), cardiovascular mortality (OR 2.93) and a trend for heart failure death (OR 2.21) (33).

Given that LGE is highly prevalent in HCM, occurring in approximately two-thirds of patients (32, 34-36), challenges exist for its use as a binary variable in driving clinical decision making. Accordingly, several studies have focused on the prognostic role of LGE quantification in this cohort (35, 37). The largest of these, published by Chan et al., included 1,293 HCM patients followed for a median of 3.3 years for SCA or appropriate ICD therapy. Using expert manual threshold adjustment, %LGE was a significant predictor of the primary outcome (adjusted HR of 1.46/10% LV mass) (38). A LGE burden ≥15% was associated with a HR of 2.14 and an estimated 5-year event rate of 6.3%. Accordingly, this threshold has now become a potentially important stratifier of risk in this population. When combined with a second publication by Ismail et al. also reporting adjusted risk for quantitative LGE extent (35), meta-analysis showed LGE extent to be a strong independent predictor of SCA (adjusted HR 1.36/10% LGE) (33).

Given an expanded focus on LGE extent (rather than binary presence) for risk stratification in this population, standardization for the reporting of LGE extent is of immediate priority. Sub-segmental visual scoring is a validated option (14). However, should signal threshold-based approaches be sought, a recent study critically examining all techniques identified the STRM > 3SD approach to most accurately reflect expert, manually adjusted thresholds for total LGE burden (16).

**Cardiac sarcoidosis**

The presence of granulomatous myocardial fibrosis in sarcoidosis is readily identified by LGE imaging, and may be found in 19-26% patients with systemic disease (7, 39). The typical pattern of LGE identified in this population is that of dense, sub-epicardial fibrosis in the basal to mid anteroseptal and/or inferoseptal segments, however, a wide variety of LGE distribution has also been reported. The presence of LGE in this population has been associated with Sudden Cardiac Death (SCD) or ventricular arrhythmia (40), death or VT (41, 42), and death, aborted SCD or appropriate ICD therapy (43). Event hazards associated with LGE in this population have been reported to be as high as 31.6 (43).

A recent meta-analysis, inclusive of 760 patients with known or suspected cardiac sarcoidosis (95% with extracardiac sarcoidosis, 22% with known cardiac sarcoidosis), showed the presence of LGE to be associated with significantly elevated risk for all-cause mortality (OR 3.06), as well as the composite outcome of ventricular arrhythmia, ICD shock or SCD (OR 10.74). The annual event rate for the composite outcome was 11.9% in those with LGE versus 1.1% among those without LGE (44).

It is important to recognize the potentially synergistic value of Positron Emission Tomography (PET) in this population. While LGE imaging identifies accrued fibrosis burden, a recognized nidus for arrhythmia, Fluoro-deoxyglucose (FDG) PET imaging may provide incremental value for the identification of disease activity (45). In a recent study by Blankstein et al., the presence of regional FDG uptake identified increased risk of death or ventricular tachycardia beyond that of perfusion abnormalities alone, the latter being a surrogate marker of myocardial scar (46). Another recent study by Ohira et al. including two groups of patients with
cardiac sarcoidosis; one group with chronic mild conduction system disease (CSD) and the other with new-onset atrioventricular (AV) block. This showed that, while CMR can adequately detect cardiac involvement in patients with chronic mild CSD, FDG PET may be valuable for detecting cardiac involvement in patients with new onset AV Block and a negative CMR (47). The potential of combined LGE/FDG imaging to be of clinical value in this population through the recent availability of hybrid PET-MRI hardware is of particular interest (48).

**Cardiac amyloidosis**

Cardiac involvement in systemic amyloidosis is common among patients with immunoglobulin light-chain amyloidosis (AL or “primary”) and transthyretin (ATTR) type amyloidosis, the latter having both wild type and mutant sub-types. It is well recognized that a primary driver of mortality among these conditions is the presence of cardiac involvement, commonly leading to rapid clinical deterioration and high 1-year mortality (49). For the detection of cardiac involvement, LGE-CMR has emerged as a robust and prognostically relevant imaging test in patients with known or suspected cardiac amyloidosis with numerous studies describing presence of a diffuse, sub-endocardial based pattern of LGE in patients with confirmed cardiac involvement (8, 50). Following small sentinel studies (51, 52), several larger cohort studies have gone on to demonstrate reliable associations between this pattern of LGE and elevated mortality (53, 54). The most recent study by Boynton et al. including 76 histological proven AL amyloidosis showed that diffuse pattern of LGE is associated with all-cause mortality in univariable analysis (HR 2.93) and multivariable analysis (HR 2.43) (54). In a recent meta-analysis, inclusive of 425 patients with known or suspected cardiac amyloidosis from 7 studies (mean follow up of 25 months), LGE positive patients had a 5-fold increased risk of mortality versus those without this finding (55). This meta-analysis included both AL and ATTR amyloidosis.

It is important to recognize challenges surrounding conventional LGE imaging among patients with amyloidosis owing to diffuse myocardial involvement (potentially eliminating visual reference tissue) and rapid clearance of gadolinium from the circulation related to high systemic amyloid burden (51). To assist in this diagnosis several approaches have been validated, including rapid visual T1 assessment using a T1 scout sequence where the relative T1 of blood and myocardium can be compared (56), phase-correction of LGE images (57), and quantitative T1 mapping techniques (58), as shown in Fig. 3. Preliminary data suggests the potential of T1 mapping without contrast administration to identify patients with biopsy-proven systemic amyloidosis (AL) with 1.5T T1 values using a ShMOLLI sequence >1,044 ms being predictive of all-cause mortality with a HR of 5.39 (59). This may be particularly valuable for patients with associated renal dysfunction.

**Conclusions**

LGE imaging has achieved a level clinical maturity that supports its routine use among patients with all forms of non-ischemic cardiomyopathy. Meta-analyses have now been published summarizing strong prognostic utility in patients with NIDCM, HCM, sarcoidosis, and amyloidosis, supporting the consistent findings of numerous contributory studies. This work provided a foundation for larger, prospective cohort studies currently underway that will further clarify the role of LGE in these populations, such as the NIH-funded Hypertrophic Cardiomyopathy Registry (NCT-01915615) soon to
complete international site enrolment (60). Along with anticipated consideration of these contemporary studies in societal guidelines, a more expanded and consistent role for LGE imaging in the management of patients with non-ischemic cardiomyopathies is expected.

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