Heart – Invited Review

TITLE

Cardiac magnetic resonance imaging evaluation of myocardial disease

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WORD COUNT 3,177

KEY WORDS
Cardiovascular magnetic resonance; tissue characterisation; myocardial disease

ABSTRACT

Cardiovascular magnetic resonance (CMR) is a key imaging technique for cardiac phenotyping with a major clinical role. It can assess advanced aspects of cardiac structure and function, scar burden and other myocardial tissue characteristics but there is new information that can now be derived. This can fill many of the gaps in our knowledge with the potential to change thinking, disease classifications and definitions as well as patient care. Established techniques such as the late gadolinium enhancement technique are now embedded in clinical care. New techniques are coming through. Myocardial tissue characterization techniques, particularly myocardial mapping can precisely measure tissue magnetization - T1, T2, T2* and also the extracellular volume. These change in disease. Key biological pathways are now open for scrutiny including not just focal fibrosis (scar), but also diffuse fibrosis, inflammation, metabolism and infiltration. Other new areas to engage in where major insights are growing, include detailed assessments of myocardial mechanics and performance, spectroscopy and hyperpolarized CMR. In spite of the advances, challenges remain, particularly surrounding utilization, technical development to improve accuracy, reproducibility and deliverability, and the role of multidisciplinary research to understand the detailed pathological basis of the MR signal changes. Collectively, these new developments are galvanizing CMR uptake and having a major translational impact on healthcare globally and it is steadily becoming key imaging tool.

Introduction

The cardiovascular magnetic resonance community (CMR) aspires to deliver improvements in the diagnosis and management of patients with myocardial abnormalities and functional impairment as has been achieved for patients with acute coronary events. Myocardial damage is the end result of all cardiac disease, but there is increasing recognition that the myocardial response to a given insult or disease process is variable; stratifying and influencing that response may be key to improving the prognosis and management of cardiovascular disease. But there is a barrier: we classify myocardial disease by structure and function based on current technology – imaging (echocardiography, cardiovascular magnetic resonance, cardiac computerised tomography, nuclear tests) with the addition of just two blood biomarkers: Troponin and N-terminal pro b-type natriuretic peptide (NT-proBNP), representing myocyte damage and distress resulting in three broad groupings: genetic cardiomyopathy, systemic diseases (e.g. afterload, sarcoid, amyloidosis and many others) and adaptive (athleticism). On the basis of mainly their imaging phenotype, the genetic cardiomyopathies are typically sub-divided into five characteristic subtypes: arrhythmogenic cardiomyopathy (AC), hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy and left ventricular noncompaction (LVNC). We oversimplify what are in fact a set of complex heterogeneous diseases - a problem in current cardiology that the MOGE(S) classification system partly addresses.[1]

Myocardium is more than just structure and function (**Figure 1**). Proteomics can quantify in excess of 3,500 expressed LV myocardial proteins.[2] From years of data collected in the Mouse Genome Informatics database, developmental biologists project that ~9% of all genes in the mouse DNA (2,000 out of 23,000) will, if altered, induce some sort of a cardiac phenotype,[3] suggesting that, taking human cardiomyopathies alone, that there should be thousands of cardiomyopathies and not the five suggested by imaging. It is not that we need to split diseases up more, we just need a refined classification system that takes into account the complex biology of the myocardium - the pathways that determine outcome and are the targets of our current and future therapies.

In this article, we explore in myocardial disease the utility of one imaging modality, CMR. We will pay particular attention to the potential ability of this method to characterise myocardium and access underlying processes, either in isolation, or when combined with other imaging modalities.

CMR assessment of myocardial structure and function

Setting aside the above, cardiac size, wall thickness, morphology and function (mainly the ejection fraction) remain the first steps in myocardial assessment. The first 10 minutes of a CMR scan derives these using 4 long axis cines, a short axis cine stack and an aortic valve short axis view. This basic set of around 15 breath-held images is robust, high quality in perhaps 95% of all scans and conducted identically the world over according to a standardized acquisition protocol.[4] The key benefit is its dependability. Taking all-comers, the interpretation of CMR structure and function requires less skill than echocardiography. Blood-myocardial boundaries are cleanly delineated and consistent, translating into reduced measurement error and a better estimate of biological (rather than measurement) variability.

Better imaging of basic structure and function allows the creation of narrower normal reference ranges to better discriminate health and disease.[5] Overt classical phenotypes may be easy to recognise, defined by the non-overlapping point separating health and disease, but in the real world the vast majority of phenotypes show overlapping points so our discriminatory ability is defined by the resolution of our camera, here imaging. All acquired diseases start in health and transition overt disease. CMR has specific advantages for visualising the LV apex (apical HCM, LV thrombus), the lateral wall (circumflex territory, dystrophinopathies), the basal septum (early asymmetrical septal hypertrophy) and the right ventricle.

Advanced structure and function

Better imaging of basic structure and function extends the spectrum of detectable, more subtle phenotypes. A CMR example of an extended phenotype is apical HCM. CMR cleanly shows that normal myocardium tapers towards the apex. There is a CMR detectable variant of apical HCM missed by current definitions of LVH (>13 mm wall thickness – CMR measures thinner than echocardiography[6]) where this tapering is effaced – relative apical hypertrophy. This is

associated with a characteristic electrocardiographic change (deep T wave inversion) and a constellation of other findings[7,8] (>1 cm apical cavity obliteration, left atrial dilatation, apical microaneurysm and scar). CMR can supplement echocardiography in improving the identification of early disease features. The genetic cardiomyopathies may have abnormal fetal cardiomorphogenesis. HCM sarcomeric protein mutations produce pre-hypertrophic morphological and functional alterations of mitral valve, trabeculae, fibrosis and function (**Figure 2**). In subjects with a 50% pre-test probability, a CMR-only score predicts HCM sarcomere gene mutation carriage with 80% accuracy.[9] The phenotype also appears to have gene-specific features – lost once hypertrophy becomes established (*MYBPC3* mutation carriers have more crypts and less hypercontractility than others).

Late gadolinium enhancement imaging for scar identification

The single technique that stimulated the adoption of CMR into routine clinical practice was scar imaging. The late gadolinium enhancement (LGE) technique[10] was first used for visualising infarction. Here LGE transmurality was shown to be a powerful predictor of viability – the potential for functional recovery[11] and had sufficient resolution to permit microinfarct detection.[12] However, it was quickly realised that almost all cardiac diseases may be associated with focal myocardial scar and that the *early pattern* of scarring (**Figure 3**) identifies disease etiology (because later, diseases converge into a shared "burnt out" scar phenotype). Scar *extent* predicts risk – the risk being of heart failure and (with less predictive power) malignant arrhythmia. The LGE technique is robust, is now widely performed to a high standard and can be used as a surrogate endpoint in therapeutic studies (e.g. adjuvant treatment in acute infarction[13]).

Using conventional LGE techniques, some utilisations push the technique to its limits such as visualising the RV free wall, atrial scar visualisation[14] and "grey zone" visualisation in acute infarction. Here, although reliability becomes reduced and expert research scanning is required, important mechanistic insights can be made, that may change thinking and open new research avenues. There are however limitations. The biggest is that scar is not treatable – ideally the focus of LGE should be the non-scarred areas, particularly those with impairment and therefore the potential to improve with the right interventions (which may be time with respect to stunning, revascularization with hibernation, pacing with dyssynchrony, drugs, toxin removal, etc.). However, the technique does not inform on how non-scarred areas are adapting to the increased workload or whether they are at risk of generating new scar. Contrast is needed (relatively contraindicated if estimated glomerular filtration rate <30mls/m^2 and there have been observations of gadolinium deposition in patients receiving multiple doses[15]), and scar is hard to quantify (a voxel by LGE is either black or white, whereas fibrosis may be a continuum between 0 and 100%). The LGE technique also highlights focally increased myocardial extra-cellular water (focal fibrosis, focal oedema/inflammation and amyloidosis), meaning that the clinician has to infer the correct pathology from the wider clinical scenario. It also has only limited capability for differentiating active inflammation from inactive scar, and it does not detect or quantify diffuse fibrosis.

There are important developments in LGE imaging. The Phase Sensitive Inversion Recovery (PSIR) sequence removes the need for operators to accurately set the inversion time during scanning to null remote myocardium, increasing test robustness.[16] Imaging using motion correction averaging permits a substantial increase in resolution even with poor-breath holding by the subject, and the visualisation of new scar types. Other developments include advanced reconstruction algorithms using high performance computing, black blood imaging and superior performance in the presence of devices such as implantable defibrillators.[17]

Mapping: T1, T2, T2*

Recently, mapping has emerged as a powerful technique. T1, T2 and T2* are the fundamental tissue magnetic properties and they can be measured in a breath-hold with pixel-map displays, the values being color-coded (**Figure 4**). If T1 is measured before and after contrast, the myocardial extracellular volume (ECV) is mapped, representing the percentage of tissue that is extracellular water, a surrogate for the process holding water - fibrosis, amyloid or oedema. T1, T2, T2* and ECV change in disease, each being differentially sensitive to pathological process (**Table 1**). The technique potential is best considered in rare (infiltrations), common (oedema) and ubiquitous (diffuse fibrosis) disease processes. For a "feel" for the potential of mapping in

different pathological processes compared to health, transform the absolute difference into the maximum possible signal to noise (SNR) in standard deviation units (SD) in severe but not extreme disease (a measure of effect size). Provided minimal systematic bias by disease-tracking confounders like heart rate or anaemia, a SD change of 2 means the technique can detect between group differences for biological insights, >4 and it could determine choice of therapy in individuals, and >6, said therapy could be monitored during treatment. A measured value consists of combined biological and measurement variability. Considerable on-going work is reducing the measurement variability, so the above SD changes are increasing with technical development.

Infiltrations (iron, Fabry's, amyloid) are important because although rare, expensive therapies are available that need non-invasive targeting and/or development. Disease rarity impedes the research scale necessary to understand rare disease mechanisms, but persistence, if successful, may provide valuable wider insights into more complex commoner disease mechanisms. These diseases give very high mapping signal change. The only pathology that causes T2* to fall is iron overload (-7SD); T1 only falls in two currently known diseases, Fabry's (-6SD) and iron (-15SD). Amyloid native T1 elevation is marked (+8SD), but the ECV elevation in remote myocardium in amyloidosis (where the amyloid is causal of myopathy) is always above 45%, a level seemingly impossible in other diffuse diseases (although more needs to be known about global myocarditis). Mapping in these diseases has important benefits: it may offer superior reproducibility (T1 in iron[18]), earlier disease detection (T1 is low in 50% of Fabry's subjects without LVH[19]), or tracking change with therapy (amyloid[20]).

Oedema occurs in acute infarction and myocarditis but may be more ubiquitous in other diseases - if we could detect it. It is also a therapeutic target. Oedema can be intracellular as well as extracellular and whilst it increases native T1 and ECV, T2 appears specifically sensitive with high elevations. Oedema (by T1 or T2) can delineate the area at risk in acute infarction. Global inflammation by T2 can be found in acute heart failure[21] tracking histological inflammation, and in connective tissue diseases (e.g. systemic lupus, systemic sclerosis, rheumatoid arthritis[22]). Whilst there is increasing recognition of global myocarditis, LGE is likely to be seeing only "the tip of the iceberg".

Diffuse fibrosis is perhaps the key process missing from current clinical cardiology care. Think of the morbidity and mortality from liver or lung fibrosis - the heart is likely no different, but fibrosis is currently occult and difficult to quantify. T1 and ECV rise in fibrosis, with ECV appearing the better test (~ +3SD vs +4SD change). The ECV is shown to track fibrosis, and is a major therapeutic target. It is prognostic, and indeed outperforms ejection fraction[23] and BNP[24] in some cohorts, a result that, if generalizable, places the measured ECV as a fundamental myocardial property (**Figure 5**). A further insight is that the ECV and the intracellular volume, multiplied by myocardial mass, represent total cell volume and total matrix volume respectively - how these change in disease (e.g. LVH) is important. For example, in transthyretin-related (TTR) hereditary amyloidosis and light-chain amyloidosis, both have massive matrix increases – but TTR has more matrix *and* a higher cell volume suggesting compensatory hypertrophy may permit more tolerance of the amyloid burden.[25]

The mapping techniques are beginning to standardize: the first consensus statement has been published,[26] global quality control systems explored, commercial sequences available, mega-registries (e.g. Global CMR Registry, HCM Registry, UK Biobank) in progress, and a high volume of continued new insights in what is now the most active research area in CMR.

Advanced technologies

Other pathological processes are potentially tractable by CMR and earlier barriers to scanning are now surmountable.

^{31}Phosphorus MR spectroscopy measures myocardial energetics via phosphate bonds (adenosine triphosphate and phosphocreatine), derived from substrate oxidation, measurable by ^{13}Carbon spectroscopy. However, these nonproton species exist in concentrations several orders of magnitude lower than those of ^{1}Hydrogen nuclei of water, the usual CMR signal source, and whilst high field strength (7 Tesla) may help, it may not solve all the challenges. ^{1}Hydrogen spectroscopy from metabolites other than water is an evolving field but is still hard and measures only a few species (e.g. fatty acids). Hyperpolarized approaches,[27] currently pyruvate-based, are far more promising as the signal is 10,000 times higher – an area to watch.

Cardiac diffusion tensor imaging (cDTI) is being developed to study fibre orientation and microstructure for patient-specific models of cardiac function and potentially myocyte disarray – a known downstream consequence of sarcomeric gene mutations whose disease role is not fully elucidated. The heart is unlike the brain and the challenges of non-rigid cardiac deformation and respiratory motion are beginning to be met.[28]
Key patient cohorts (one in fifty patients over the age of 75) have historically been excluded from scanning due to pacemakers or defibrillators. MR-conditional devices are now mainstream; non-conditional device scanning is now protocolised in some centres and newer MR sequences have been designed to minimise device related image artefact.
Other rapidly advancing techniques include routine quantitative myocardial blood flow, 4D flow and positron emission tomography-CMR integration.[29] This technology is now available but key utilities have yet to be worked out. Underpinning many of the challenges above is the exploitation of increasing computing power permitting "more for less" – sparser sampling and more complex data reconstructions to accelerate imaging – not just 2 or 3 fold, but 10 fold.

Areas for improvement

There are however unresolved issues. CMR is not yet as widely available as echocardiography and has logistical issues: early disease may reveal itself during stress and the echocardiography lab is more conducive for this. Logistically, the patient is required to come to the CMR scanner whilst echocardiography has two additional choices: wheel the machine to the patient or simply take the machine out of your pocket and apply. Analysis of LV volumes is not well standardized. The ideal analysis tool would be fast, reproducible and include valve plane tracking, papillary muscles/trabeculae as myocardium and a segmentation method that was operator and disease independent. Currently, reference ranges need to be analysis-specific. Advanced myocardial mechanics assessed using CMR techniques, have yet to be shown to consistently aid clinical care.[30] CMR datasets are lower temporal resolution compared to echocardiography so short time interval events (like isovolumetric times important in diastology) and beat-to-beat variation are less well measured. CMR feature-tracking, a technique analogous to echocardiography speckle tracking, derives similar quantitative myocardial deformation parameters from standard cines, allowing quantitative assessment of complex ventricular mechanics such as strain, twist and untwist. However advanced CMR myocardial mechanics have yet to be shown to consistently aid clinical care[30] and this relatively young technology needs more intuitive, quick and standardized post-processing software to permit robust widespread clinical application.

Problem-driven approaches and future directions

Health and disease

Any technology with superior performance necessitates refinement of disease definitions (think troponin over creatine kinase for the definition of myocardial infarction) and typically a widening of the recognized disease spectrum. Earlier disease detection is needed both because our imperfect therapies work best if applied earlier, and for the institution of population-level screening programmes, such as for competitive sports. However, single time-point imaging, is limited, especially when confounders such as 'physiological' variation, sport or common confounders like obesity or hypertension are present. The advantage of CMR is structure/function plus tissue characterisation, and this is useful for serial screening of cardiotoxic effects of chemotherapy, and monitoring for active myocardial inflammation in rheumatological disorders, but the risks of gadolinium deposition with repeat scanning require further study[15] and some of the earliest functional disease changes may be better detected by echocardiography.
Advanced analytics and atlas-based approaches may help. This is well established in some fields such as neurology where anatomical and functional data can be synthesised to provide computer-based decision-making tools for diagnosis and management. By developing a range of ethnic and disease-specific atlases, our ability to distinguish health from early disease phenotypes may improve.[31,32]

Scale

Only recently has CMR become a high volume, widely available tool such that it could be used in large clinical trials or cohort studies. It is now recognised that CMR adds value for trials –

both in terms of power to detect change (smaller sample sizes) and the advantages of tissue characterisation to aid mechanistic understanding or as a surrogate endpoint. Efforts are being made to increase scan and analysis efficiency (working towards free breathing acquisitions with complete machine learning-based analytical approaches) to improve workflows. Together these efforts have seen CMR incorporated into prospective biobanking cohort studies including UK BIOBANK (100 000 subjects), the Multi-Ethnic Study of Atherosclerosis (MESA), and others. There is also acceptance of the exponential value of collaboration – data from multiple single cohort studies and registries are being formally amalgamated to increase our understanding of specific disorders (e.g. HCM Registry, Global CMR Registry). However, not all is well–CMR is still underutilised in some key jurisdictions. In the USA for example in 2013, 12,033 Medicare-billed clinical CMR scans were performed, with the maximum number of scan reports by any single operator being 260, and the average number being 36. UK estimates of CMR need (1,200 per million population) suggest a US target of 380,000 scans a year – 30 fold more – a large gap.[33] Without this closing, the key observations, research scale, disease redefinitions and guideline incorporations needed to better patient care may stall.

Opportunity for stratified management of cardiac conditions

The disease of our time in cardiology is heart failure whose prevalence, morbidity and associated costs are reaching epidemic proportions. The past 15 years of research has brought relatively scant success in developing new therapies. Much of this lack of progress is related to the 'one size fits all' approach to study recruitment in drug trials, which remains based on simple criteria like an ejection fraction range or a dilated, hypertrophic or restrictive phenotype. CMR tissue characterisation of underlying pathophysiology (inflammation, interstitial fibrosis, myocyte hypertrophy, and even fibre disarray) could change this and help provide superior categorisation linked to the therapeutic target. Combining CMR data with genetic information may also help, particularly in cardiomyopathies, however marked individual patient heterogeneity suggests that gene expression is grossly modified by a range of environmental and epigenetic factors. Integrating CMR phenotyping data with molecular and cellular pathophysiological signals, including plasma biomarker profiling and markers of upstream regulatory processes such as microRNAs, should better stratify heart failure and identify new druggable targets. Myocardial fibrosis is a key emerging target for pharmacological intervention in heart failure where CMR, using ECV quantification, would clearly be useful. Closer collaboration between the pharmaceutical industry and CMR research units may therefore be required to translate the potential benefits of novel therapies into clinical benefit for patients with heart failure.

Conclusion

CMR is coming of age for myocardial disease. Some opportunities and issues surrounding the potential utility of CMR are outlined including technical developments, utility, practical clinical challenges, delivery, quality control, clinical trial use, and standardization. Importantly, CMR can bring better measurement of key myocardial processes into clinical play, changing the way we think about diseases, their categorisation and their care, but there are large gaps. Nevertheless, the future is full of opportunities.

Funding

G.C. is supported by the National Institute for Health Research Rare Diseases Translational Research Collaboration (NIHR RD-TRC), by the European Society of Cardiology (ESC, EACVI) and by NIHR University College London Hospitals Biomedical Research Centre. J.C.M. and C.M. are directly and indirectly supported by the University College London Hospitals NIHR Biomedical Research Centre and Biomedical Research Unit at Barts Hospital, respectively.

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TABLES

Table 1. The spectrum of myocardial biology revealed to date by myocardial tissue mapping technologies.

Leading Biological Process	Characteristic Disease	T1 Mapping Signal	T2 Mapping Signal	T2* Mapping Signal	ECV Signal	Main References[§]
FIBROSIS						
Focal	Myocardial infarction, no hemorrhage[~]	↑	↑		↑	Verhaert et al. 2011; Ugander et al. 2012
Diffuse: Primary cardiac disease	Aortic stenosis	—	↓		—	Bull et al. 2013; Jabbour et al. 2011; Liberato et al 2015; Singh et al. 2015
	Systolic heart failure	↑	↑[±]		↑	Iles et al. 2008; Bohnen et al 2014; Su et al. 2014
	Diastolic heart failure	↑			↑	Su et al. 2014
	Hypertrophic cardiomyopathy	↑	—		↑	Ho et al. 2013; Ismail et al. 2014
	Non-ischaemic dilated cardiomyopathy	↑	↑		↑	Puntmann et al. 2013; Nishii et al. 2014
	Congenital heart disease				↑	Plymen et al. 2013
Diffuse: Extracardiac disease with cardiac manifestations	Diabetes	↑			↑	Wong et al. 2013
	Hypertensive heart disease	↑			—	Treibel et al. 2015
	Obesity				↑	Shah et al. 2013
	Mitochondrial cardiomyopathy	↑	↑		↑	Lee et al. 2014
	Rheumatoid arthritis	↑			↑	Ntusi et al. 2015
	Systemic sclerosis	↑	↑[‖]		↑	Ntusi et al. 2014; Barison et al. 2015
	Systemic lupus erythematosus	↑	↑		↑	Puntmann et al. 2013; Zhang et al 2015
OEDEMA	Acute myocarditis	↑	↑		↑	Ferreira et al. 2013; Hinojar et al. 2014
	Takotsubo cardiomyopathy	↑	↑			Thavendiranathan et al. 2012; Garg et al. 2015
	Anti-synthetase syndrome	↑	↑		↑	Sado et al. 2016
	Active systemic capillary leak syndrome	↑			↑	Etel et al. 2015
	Acute cardiac allograft rejection	—/↑	—/↑		—	Usman et al. 2012; Vermes et al. 2014; Miller et al. 2014; Greenway et al. 2015
INFILTRATION						
Glycosphyngolipid	Anderson-Fabry disease	↓	↑^	—	—	Messalli et al. 2012; Thompson et al. 2013; Sado et al. 2014
Iron	Thalassaemia major	↓		↓	↑	He et al. 2009; Hanneman et al. 2015
	Sickle Cell Disease	↓		↓		Alam et al. 2015
	Hereditary haemochromatosis	↓		↓		Alam et al. 2015
	Myocardial infarction, with hemorrhage	↓	↓	↓		Verhaert et al. 2011; Pedersen et al. 2012; Kali et al. 2013
Amyloid	AL amyloid	↑			↑	Banypersad et al. 2015
	TTR amyloidosis	↑			↑	Fontana et al. 2015
Toxins	Uraemia in chronic kidney disease	↑			↑	Edwards et al. 2014
	Cobalt		↑[+]			Samar et al. 2015
	Anthracycline	↑	—		↑	Tham et al. 2013

— No significant change; ↑ Significant increase; ↓ Significant decrease; ▭ Unreported to date.

[§] Reference list is non-exhaustive - several other references may exist that are not listed here.

[~] Signal change refers to area of infarct myocardium and not remote.

[#] If myocardial haemorrhage accompanies acute infarction.

± In acute heart failure.

[‖] Quantitative assessment of T2-weighted black blood images.

^ Quantitative assessment of T2-weighted black blood images pre- and post-treatment.

+ Visual assessment of T2-weighted black blood images only.

FIGURES

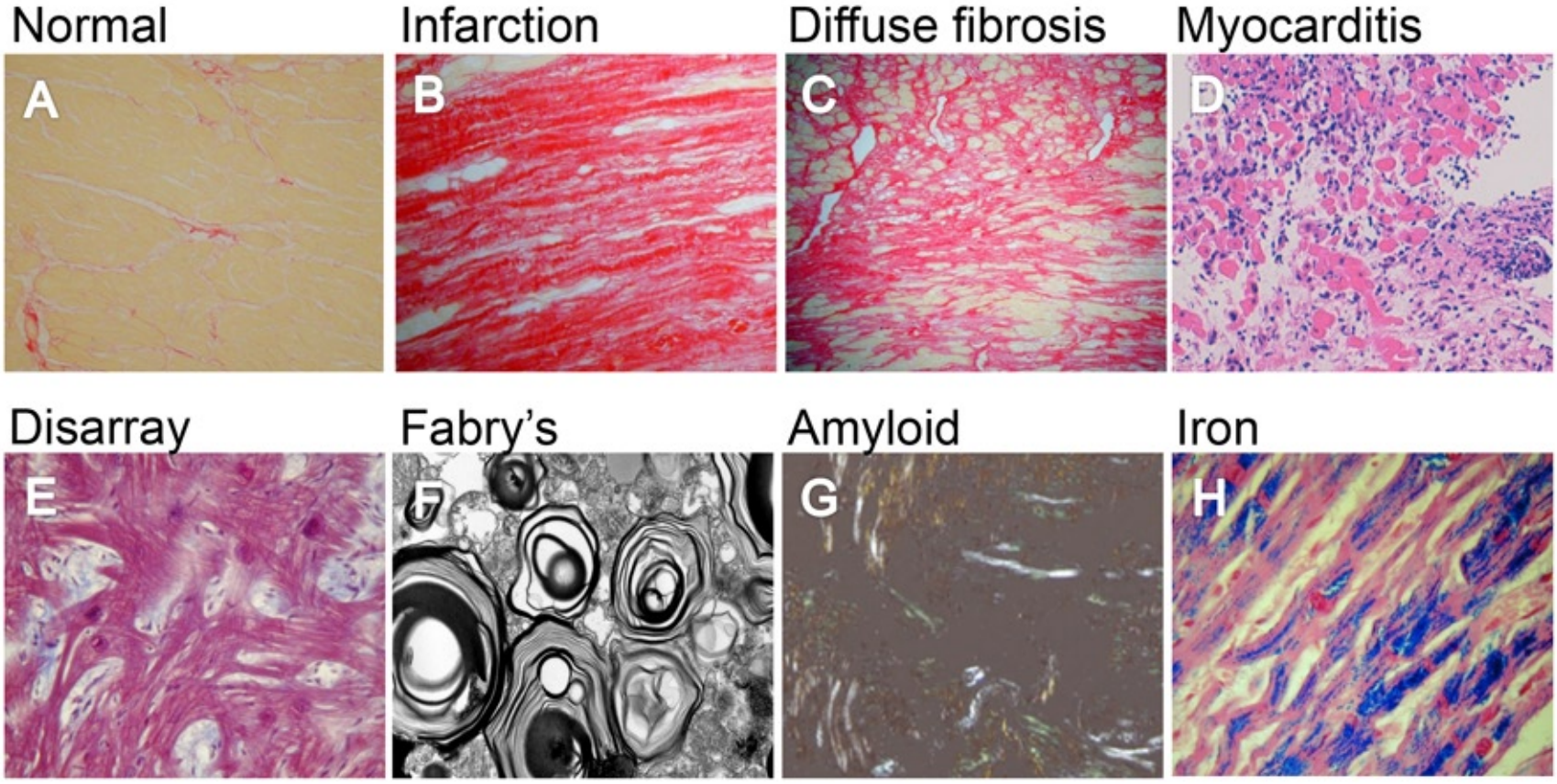
Figure 1. Myocardial biology by histology.
Using various microscopes (light, scanning electron, cross-polarized), and various stains (picro sirius, Masson's, Prussian blue, Congo red), histology reveals active myocardial processes. Similarly CMR using different sequences can point to all eight of these processes which, if robust, could contribute to clinical care in cardiology. CMR = cardiovascular magnetic resonance.

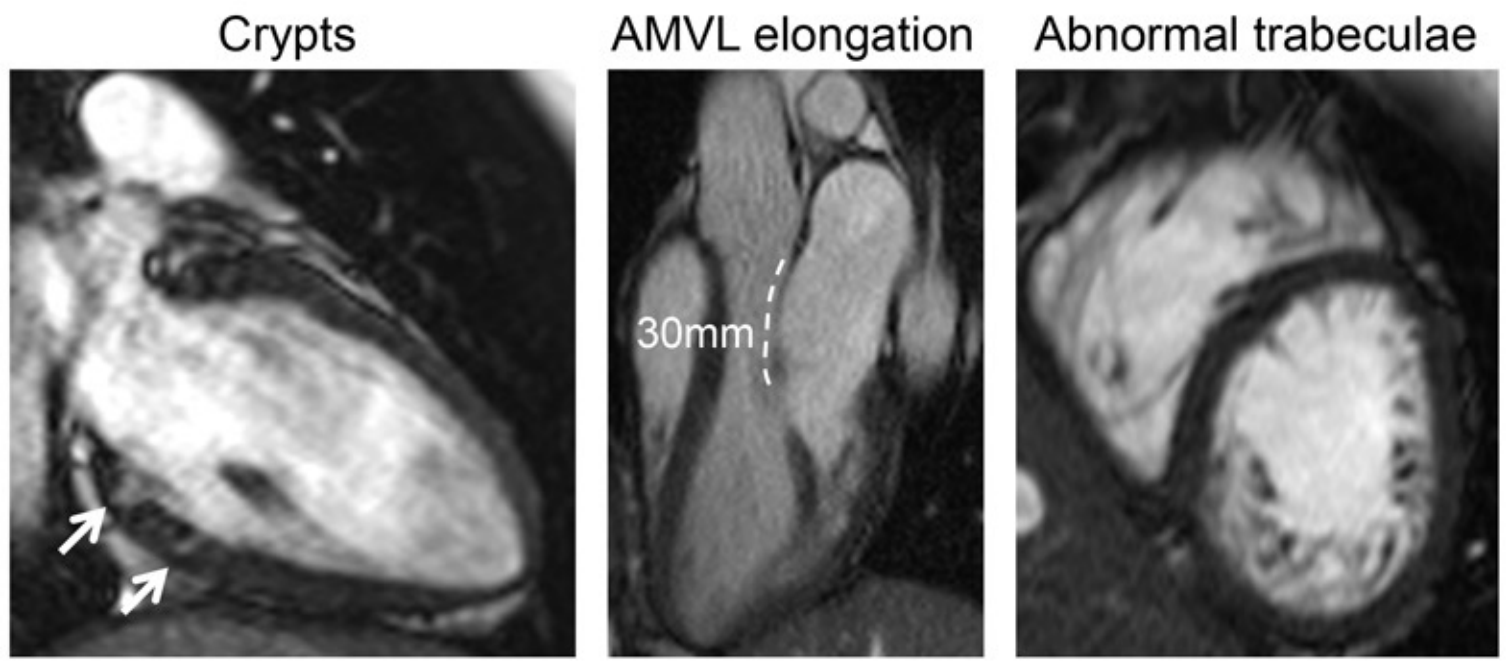
Figure 2. Advanced morphological features in subclinical hypertrophic cardiomyopathy.
Patients with subclinical HCM (before developing overt left ventricular hypertrophy), already exhibit subtle architectural cardiac abnormalities detectable by CMR. These include but are not limited to: the presence of multiple myocardial crypts (**A**), abnormal elongation of the AMVL (**B**) and increased left ventricular apical trabecular complexity (**C**). AMVL = anterior mitral valve leaflet; HCM = hypertrophic cardiomyopathy.

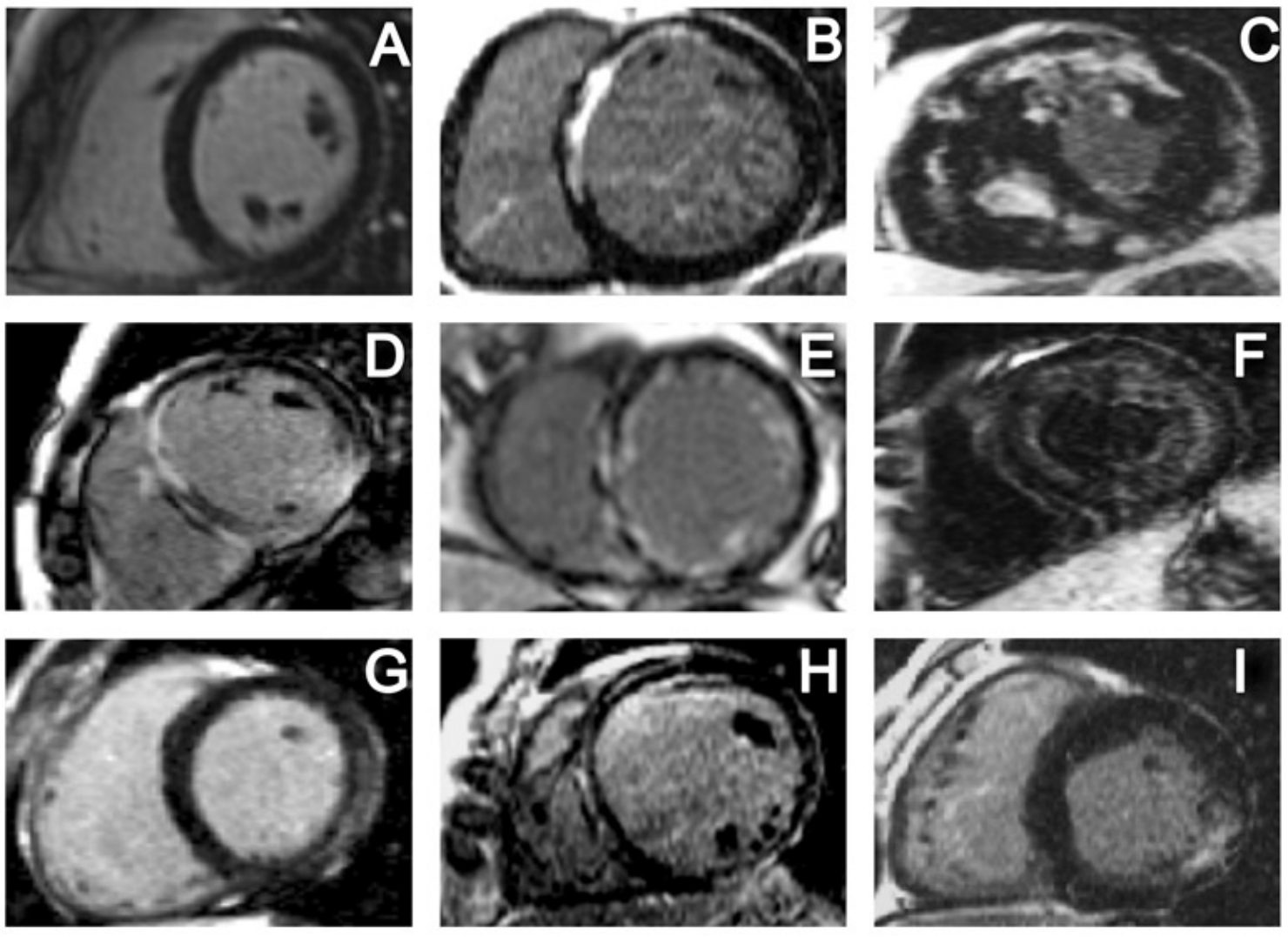
Figure 3. Characteristic scar patterns in health and disease.
Scar imaging patterns by CMR **A**. Healthy volunteer (no scar). **B**. Myocardial infarction (subendocardial, territorial). **C**. HCM (here advanced, progressive disease). **D**. Cardiac sarcoid (mixed pattern of characteristic scarring with bright sometimes epicardial, sometimes endocardial scar). **E**. Eosinophilic (thin layer of circumferential endomyocardial scar). **F**. Cardiac amyloidosis (subendocardial diffuse and global LGE). **G**. Myocarditis (subepicardial LGE especially laterally). **H**. Dilated cardiomyopathy (midwall scarring). **I**. Fabry's (hypertrophy with focal inferolateral LGE). LGE = late gadolinium enhancement. Other abbreviation as in Figure 2.

Figure 4. Native myocardial T1 maps in health and disease.
Native T1 maps by ShMOLLI in short axis. **A**. Healthy volunteer: the myocardium appears homogeneously green. **B**. HCM: there is asymmetric septal hypertrophy with modest patchy high T1 (red). **C**. Fabry's: the myocardium has a lower T1 value (blue speckling) due to intracellular lipid accumulation, except in the inferolateral wall, which is red due to fibrosis. **D**. Severe iron overload: the myocardium appears blue with very low T1 from iron. **E** and **F**. AL and TTR cardiac amyloidosis respectively: the myocardium is thickened and has a higher T1 value (red) with AL having more T1 elevation but less hypertrophy. AL amyloid = light-chain amyloidosis; ShMOLLI = shortened modified Look-Locker inversion recovery sequence; TTR = transthyretin-related (TTR) hereditary amyloidosis. Other abbreviation as in Figure 2.

Figure 5. Extracellular volume mapping and its prognostic value.
A. Short-axis MOLLI colour map and matching LGE (**C**) in HCM showing high native T1 values. In **C** there are 2 foci of LGE at the right ventricular insertion points, with matching regions of abnormal post-contrast T1 values (**B**) and high ECV (**D**). The ECV map was reconstructed using haematocrit, native and post-contrast T1 values. **E.** Prognostic value of tertiles of CMR-ECV represented by this Kaplan-Meier plot for event-free survival. In a consecutive cohort of all-comers referred for CMR (n = 473) and followed-up for 13.3±9.0 months, higher CMR-ECV was associated with an increased event rate (log-rank test P = 0.013). Figure **5E** is an adaptation of the illustration by Kammerlander et al.[24] reproduced with the permission of *JACC Imaging*. CMR-ECV = extracellular volume as determined by cardiovascular magnetic resonance imaging T1 mapping; MOLLI = modified Look-Locker inversion recovery sequence. Other abbreviations as in Figures 2 and 3.


Normal
Infarction
Diffuse fibrosis
Myocarditis
A
B
C
D
Disarray
Fabry's
Amyloid
Iron
E
F
G
H


Crypts
AMVL elongation
Abnormal trabeculae
30mm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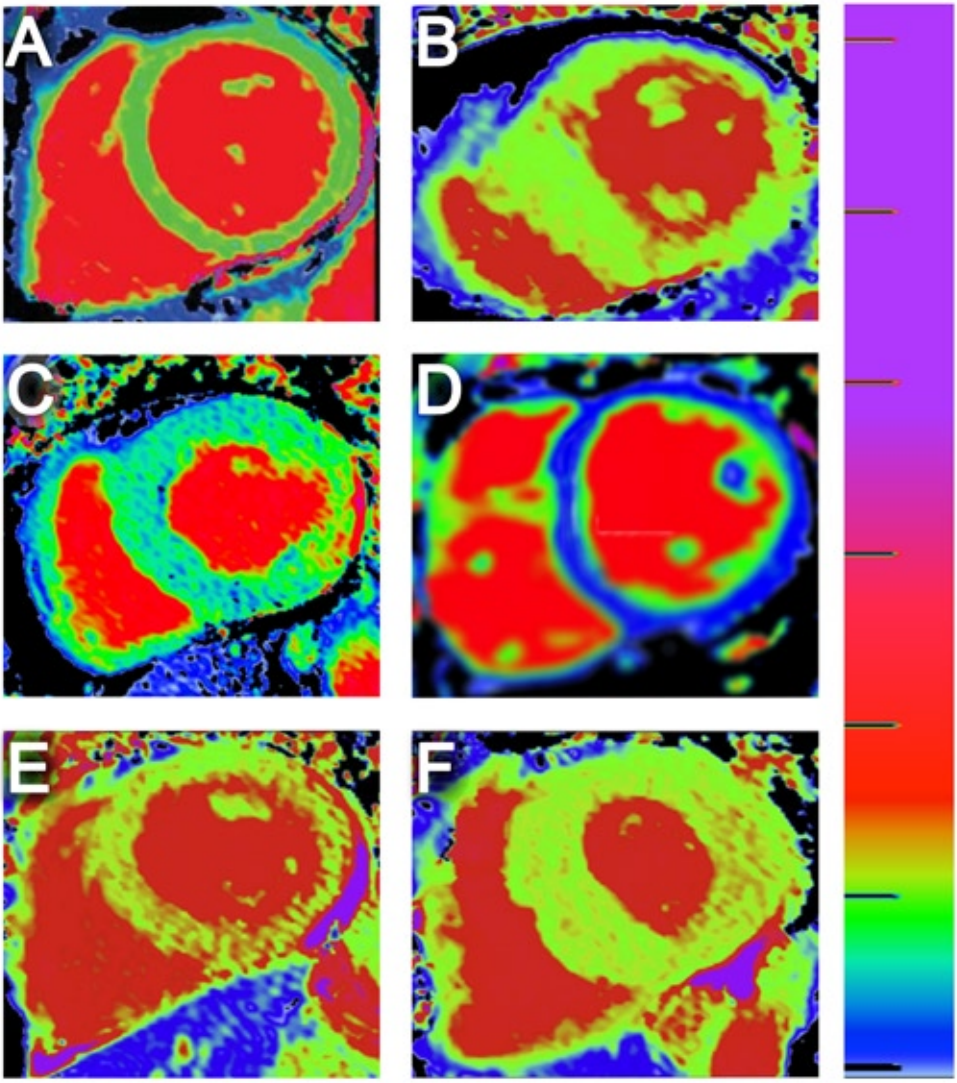
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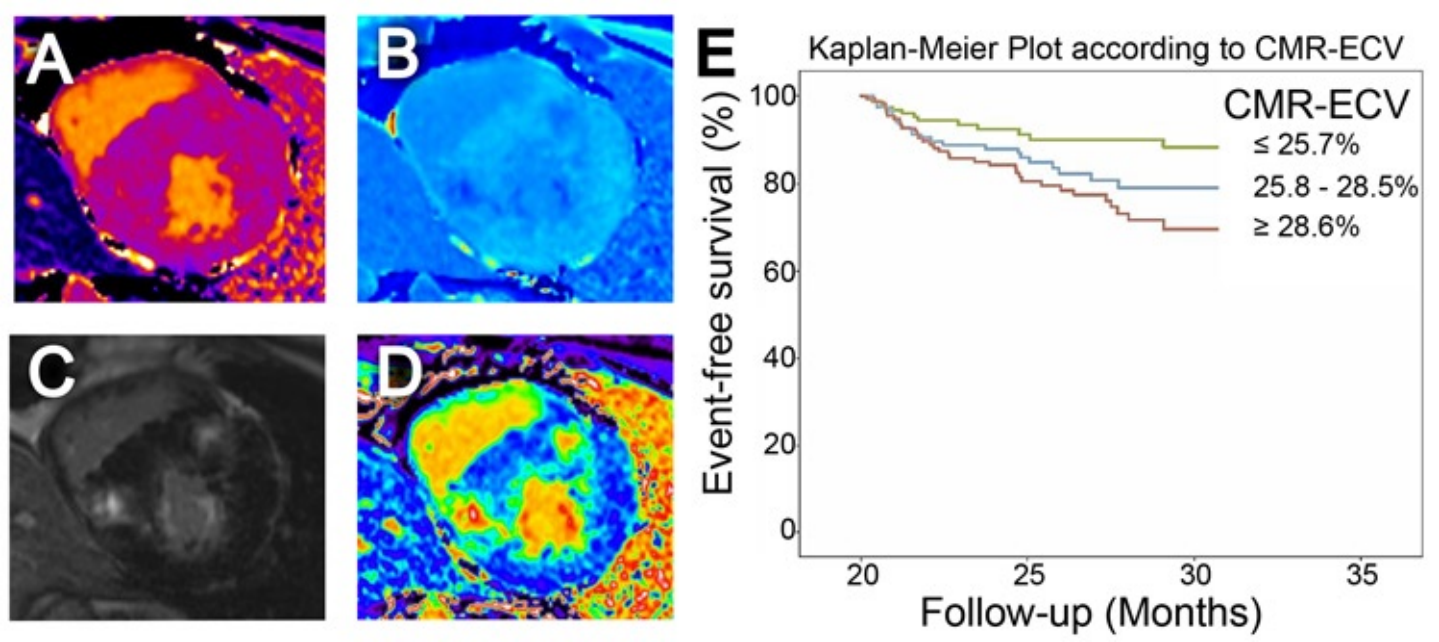
A
B
C
D
E
Kaplan-Meier Plot according to CMR-ECV
CMR-ECV
≤ 25.7%
25.8 - 28.5%
≥ 28.6%
Event-free survival (%)
100
80
60
40
20
0
20
25
30
35
Follow-up (Months)