

Title: Quantitative Cardiac MRI**Abstract:**

Cardiac MRI has become an indispensable imaging modality in the investigation of patients with suspected heart disease. It has emerged as the gold standard test for cardiac function, volumes and mass and allows non-invasive tissue characterization and the assessment of myocardial perfusion. Quantitative MRI already has a key role in the development and incorporation of machine learning in clinical imaging, potentially offering major improvements in both workflow efficiency and diagnostic accuracy. As the clinical applications of a wide range of quantitative cardiac MRI techniques are being explored and validated, we are expanding our capabilities for earlier detection, monitoring and risk stratification of disease, potentially guiding personalized management decisions in various cardiac disease models. In this article we review established and emerging quantitative techniques, their clinical applications, highlight novel advances and appraise their clinical diagnostic potential.

Keywords: quantitative, mapping, perfusion, machine learning, tissue characterization

Introduction

Cardiac Magnetic Resonance Imaging (MRI) is now indispensable for many common clinical scenarios arising during the care of cardiac patients. Not only it is established as the gold standard test for cardiac function, myocardial volumes and mass (1), but is also the imaging modality of choice for myocardial tissue characterization. In recent years, a series of technical developments have transformed diagnostic capabilities by introducing new quantitative evaluation methods for these and other areas such as perfusion, 4D flow and myocardial mechanics. Combined with an expansion of cardiac MRI services and the wider availability of new imaging sequences, quantitative cardiac MRI enhances our understanding of cardiac pathology, exploring the link between biology and clinical manifestation of cardiac disease. Here, we review established and emerging quantitative techniques, their clinical applications, highlight novel advances and appraise their clinical diagnostic potential.

Quantitative evaluation of cardiac volumes and function

Cardiac MRI as the gold standard in cardiac segmentation

Quantitative segmentation of the cardiac chambers is a key step in the assessment of cardiovascular (CV) disease. The measurement of ventricular volumes, mass and systolic function allows identification and grading of pathologies, prognostic assessment and the monitoring of changes under therapy. For example, myocardial wall thickness in hypertrophic cardiomyopathy (HCM) and the ejection fraction (EF) in heart failure act as key parameters for defibrillator or resynchronisation therapy (2,3). However, different imaging modalities yield different results (4). With the use of cutpoints for clinical decisions (e.g. above or below 35% ejection fraction, 15mm or

30mm wall thickness), can have major reclassification implications resulting in widely different clinical decisions (5). Two- and three- dimensional (2D and 3D) transthoracic echocardiography (TTE) and MRI delineate contours with high precision in phantoms (*ex-vivo*) (6) but both TTE methods measure lower ventricular dimensions *in-vivo* compared with MRI (7). There is a technical limitation of echocardiography to distinguish trabeculae (and low blood flow yielding low contrast) from compacted myocardium. The more flow independent image quality of steady state free precession (SSFP) cardiac MRI allows better endocardial definition and a more three-dimensional approach with fewer geometric assumptions, making it the gold standard for measuring ventricular volumes and ejection fraction (8). The issue of “normal range” of trabeculations has been a matter of debate, with different criteria used between various imaging modalities (9). How trabeculae, and for that matter papillary muscles are considered (part of the LV blood pool or part of LV mass) alters LV mass and volumes but also derived parameters eg EF (12). There is no uniformly accepted convention as to how these should be measured and analyzed. The most important thing to do is to ensure the per-patient analysis is the same as that used to derive reference ranges. As papillary muscles can hypertrophy in some diseases (Fabry, hypertrophic cardiomyopathy), for accuracy reasons (papillary muscles are made of muscle, not blood), we prefer to treat them and trabeculae as myocardium not blood. There is some concern however that this reduces measurement precision.

Clinically it is just as important to reliably detect change over time - measurement precision (repeatability), in terms of initiating and monitoring treatment. Similarly, from a research perspective, test precision determines trial sizes and power calculations for

sample size estimations. Precision is also particularly important as there is no easily applied gold standard for volumes and mass in human ventricular measurement, but precision can be measured (through test: retest; coefficient of variation) (Table 1). Ventricular segmentation with cardiac MRI - our most accurate and precise method for cardiac structure evaluation - also has variability. The complex geometry of the heart as well as the anatomical and imaging variability pose a challenge. Contouring is tedious, costly and even with quality control and training investment, variability persists. Measured chamber size values vary with pulse sequence (SSFP vs spoiled gradient echo (13)), 2D or 3D acquisition and analysis method (14). The latter includes software platform, mathematic formulae (e.g. Simpson's rule), contour detection method (e.g. fully manual or semi-automated contour delineation), measurements made in long-axis or short-axis views, treatment of long axis function, whether papillary muscles/trabeculae are counted as muscle or blood pool, and reader experience. Attempts to minimise variability through standardisation of have only been partial (15).

Novel means of segmentation in Cardiac MRI

Manual delineation of ventricular contours even by experienced MRI readers has intraobserver and interobserver variation (20) as well as interscan variability, reducing precision. Semi-automatic or fully automatic segmentation can remove some of this variability. These methods can be: (A) image-driven if they identify voxels belonging to the blood pool, myocardium or appendage by assessing the difference in signal intensity or (B) model-driven if they are based on strong prior knowledge, like that from cardiac atlases or statistical shape models, and are trained in manually

annotated data (18). There are several types of image-driven techniques, but thresholding, region-growing, clustering and voxel classification are the most widely used. The choice of one method over the other is not straightforward and depends on a number of factors, including constraints of the protocol and the specificities of the disease being studied. A comparison of these different methods is difficult as the ground-truth is also difficult to define. Model-driven fully automated segmentation tools based on artificial intelligence (AI) might be particularly useful (Figure 1). Convolutional neural network (CNN) approaches to ventricular segmentation started with a 2015 Kaggle competition, where 1000 datasets were provided. The open source code was subsequently repurposed by many (19) (20). The larger and the more diverse the dataset is (different diseases, magnets, pulse sequences, image quality), the more generalizable the model becomes. The latest approaches are moving on from comparison with clinician contours (e.g. using Dice scores) to similarly diverse test: retest datasets for precision. Best current results suggest non-inferiority to expert human performance (21). Such approaches if rolled-out to global healthcare systems could completely remove intra- and inter-observer variability, standardize global practice and save time. There are however challenges in the future: training datasets will need to reflect global practice and all diseases and evolve over time as techniques change. In addition, they permit robust linkage of normal reference ranges to current analysis methods (as the normal range can be re-computed for each model improvement), and lower the barriers to using more representative population reference ranges. Furthermore, should models become super-human (i.e. improved measurement precision) then new biology may become detectable in existing studies

with reanalysis, improve prognostic power as new studies would need fewer patients to detect an effect, and interval scanning will have smaller detectable differences.

Going beyond ejection fraction

Global systolic function measurements like EF can be insensitive to early cardiac diseases. Regional myocardial dysfunction may occur before global impairment so deformation imaging detects early contractile dysfunction (22). Systolic myocardial deformation occurs longitudinally (basal-apical shortening), circumferentially (shortening along the circular perimeter) and radially (thickening of the myocardium towards the centre of the cavity) and is measured as strain, a measure of the degree of deformation of a segment. Different diseases affect these differently, either globally or regionally – for example, ischaemia is mainly subendocardial and if coronary artery disease related, territorial; amyloid is apex sparing; Fabry, dystrophinopathies and others affects the basal inferolateral wall first.

Tissue Doppler imaging and Speckle Tracking have been widely used in echocardiography for measuring strain, but these are heavily dependent on operator and technical aspects (e.g. frame rate, acquisition angle) (23). Cardiac MRI strain imaging uses either specific pulse sequences during acquisition (tagging, phase velocity mapping, displacement encoding with stimulated echoes [DENSE], strain-encoding) or post-processing analysis of standard cine images (23) such as Feature Tracking (FT) (Figure 2) (24). Although DENSE provides images with good spatial resolution, clinical experience is limited. Tagging is a more validated tool for myocardial deformation assessment and has better reproducibility than FT, but its

interpretation can be affected by spatial resolution and tag fading through the cardiac cycle. FT has the advantages of not requiring additional time in the scanner for image acquisition, as it can use most conventionally acquired SSFP cines with minimal annotation and processing time. However, FT remains dependent on image quality and does not account for through-plane motion (23). Overall the adoption barriers are lower for FT than other techniques for myocardial deformation to guide clinical care.

The clinical applications of myocardial deformation imaging are numerous. Strain analysis can identify segments that will recover after an acute myocardial infarct (25) and can detect small contractility changes during dobutamine stress testing (26). Patients with hypertrophic cardiomyopathy have abnormal strain in hypertrophied segments regardless of late gadolinium enhancement (27). Strain can also detect cardiotoxicity in patients undergoing chemotherapy before left ventricular (LV) EF impairment (28) and early cardiac involvement in rare diseases (29) (Figure 2).

Nonetheless, standardization is needed. Different vendors, pulse sequences and software account for the difficulty in attaining normal ranges for strain in cardiac MRI (24). Similar to LVEF, manual contouring variability must be considered, but AI might also be able to minimize these. It is worth highlighting that unlike speckle-tracking echocardiography, where the use of strain has been shown to have prognostic implications in multiple cardiac pathologies (30), similar data on the prognostic utility of feature tracking with CMR are currently lacking.

Quantitative tissue characterization using parametric mapping techniques

Our ability to evaluate myocardial tissue by exploiting the magnetic properties of various myocardial structures has had a major impact in clinical cardiology. Late gadolinium enhancement (LGE) techniques using post-contrast T1-weighted sequences have been used to evaluate focal myocardial processes such as fibrosis, and have been extensively used in ischemic and non-ischemic heart disease (31). Similarly, T2-weighted sequences enabled evaluation of edema and inflammation (32). Both of these techniques are limited by the qualitative nature of the assessment enabled as both rely on the relative difference in the relaxation properties of the diseased versus the distal “healthy” myocardium. Cardiac MRI parametric mapping techniques allow the spatial visualization of quantitative changes in the myocardium based on changes in myocardial T1, T2, T2* and extra-cellular volume (ECV) (33), enabling evaluation of diffuse changes within the myocardium.

T1 mapping and its clinical applications

T1 mapping involves the acquisition of a series of co-registered images at different times of T1 recovery, allowing the pixel-wise illustration of an absolute T1 relaxation time through the generation of a color-encoded map (34). The use of T1 mapping as an imaging biomarker for tissue characterization is based on the principle that changes in longitudinal relaxation time (T1) reflect changes in the water content as well as the local molecular environment (35), therefore quantitative evaluation of T1 relaxation allows identification of various pathophysiological processes affecting the myocardium (36) (Figure 3).

Since the original description of T1 relaxation measurements by Look and Locker in 1970 (37), a number of methods have been described and clinically used, including the Modified Look-Locker Inversion recovery (MOLLI) pulse sequence (38), Shortened MOdified Look-Locker Inversion recovery (ShMOLLI) (39), saturation recovery single-shot acquisition (SASHA) sequence (40) and saturation pulse prepared heart-rate-independent inversion recovery (SAPPHIRE) (41). Among these, MOLLI appears to be the most widely validated and commonly used sequence (Table 2). Despite similar reproducibility in vivo measurements between T1 mapping sequences, it appears that inversion-recovery (IR) based techniques (MOLLI, ShMOLLI) have more clinical potential as inversion recovery permits greater sampling of a recovery curve and therefore greater separation of T1 species than saturation recovery (SR); and the heart rate variability independence of SR can be accounted for in IR approaches during reconstruction. SR approaches are more magnetization transfer insensitive than IR so are technically more accurate compared to a slow spin echo T1 ground truth, but it is not clear whether this is clinically important as the primary purpose of mapping is to differentiate health from disease rather than accurately measure T1 (42,43) .

T1 mapping can be used for both native (pre-contrast) and post-contrast T1 relaxation measurements. Native T1 mapping can provide quantification of the composite signal from both the cellular (including myocytes) and extracellular space with pathological effect size being reflected by greatest T1 shortening to greatest lengthening: iron (shortest), fat, athletic training, normal, fibrosis, amyloid, edema (longest) (36). T1 mapping as a potential imaging biomarker is therefore useful, particularly for the rare

diseases. It adds value to LGE and may differentiate some conditions with similar imaging phenotypes and allow earlier disease detection (44) with prognostic implications (Table 2)

Post contrast T1 relaxation reflects changes in the extracellular space, but also renal clearance, hematocrit and total body contrast volume of distribution so calculation of extracellular volume fraction (ECV) is preferable. Unlike native T1, ECV represents a physiological parameter, is less sequence and field strength dependent. It is a measurement of the free water, myocardial water between cells (myocardial and red blood cells). This may reflect fibrosis in some circumstances, and has been correlated with histological estimates of collagen volume fraction in some diseases (47), but may reflect amyloid or extracellular edema in other circumstances. Small changes can also be seen with myocardial capillary vasodilatation, or potentially capillary rarefaction (48). A synthetic ECV can also be calculated by estimating the hematocrit from blood T1 - the more anemic, the longer blood T1 becomes -, providing an immediate method of ECV derivation and display as a map (49). For most patients, increase in ECV predominantly reflects changes in collagen volume fraction, a final common pathway in many disorders with prognostic impact (50), potentially incremental to LGE (51). Despite its well established diagnostic and prognostic capacity (63), LGE misses diffuse disease and correlates less well with collagen in the presence of diffuse fibrosis (54).

T2 mapping and its clinical applications

T2 mapping is an additional promising technique for tissue characterization. The main biological determinant of T2 relaxation is the amount and macromolecular state of water and T2 is found to reflect mainly myocardial edema. If there is also myocyte death (troponin release, a blood biomarker), this is likely to reflect myocardial inflammation – a pathophysiological process that may be responsive to specific treatments (Table 3). Two types of mapping sequences are often used for T2 mapping, including a single-shot turbo spin-echo (TSE) sequence with multiple echoes and bright-blood T2-preparation pulse-based sequences (55). Newer sequences enabling acquisition of dark blood myocardial T2 maps, potentially allowing improved definition of the blood-myocardium border have recently been reported (56).

T2 mapping has been extensively studied in the diagnosis and risk stratification of patients with myocarditis. It not only improves diagnostic accuracy, but also predicts outcomes (57,58) with higher T2 values predicting major cardiovascular events and hospitalization. T2 mapping is also being explored in other inflammatory diseases including acute cardiac allograft rejection (57), sarcoidosis (59), systemic lupus erythematosus (60) and acute infarction, with the potential of reducing the need for invasive cardiac biopsy in some scenarios. Elevated T2 mapping values compared to healthy controls have also been demonstrated in subsets of dilated cardiomyopathy (58) and aortic stenosis (61,62), potentially enabling disease sub-stratification (63). The combination of T2 and T1 mapping offers incremental information in some diseases, including patients with cancer-treatment related cardio-toxicity, differentiating between early and later cardio-toxicity by attempting to differentiate chronic interstitial fibrosis from edema (64).

Quantification of T2* relaxation time and its clinical application

In clinical medicine, T2* had an immediate impact in clinical processes and patient outcomes in the management of iron-overload cardiomyopathies. T2* relaxation is the decay of transverse magnetization in the presence of static magnetic field inhomogeneity and is particularly sensitive to the presence of iron. Calculation of myocardial T2* involves the acquisition of serial images of a mid-ventricular short axis view at increasing echo times (TE), allowing the formation of an exponential decay curve of signal intensity vs TE ($y = Ke^{-TE/T2^*}$ where K represents a constant, and y represents the image signal intensity) (78). Quantification of tissue iron overload with T2* was shown to strongly correlate with liver (67) and reasonably with myocardial iron (68) from histology data. Cardiac T2* below 10ms is associated with the risk of developing heart failure and arrhythmias (69) in patients with thalassemia major - a condition which represents a clear human model of tissue iron overload. The introduction of T2* tied to therapeutic escalation resulted in an impressive reduction (>60%) in UK deaths from thalassemia (70). The ability for serial quantitative assessment of tissue iron overload has allowed T2* to serve as an outcome measure in trials evaluating different iron chelator therapies (71) and to become the standard of care in chronically transfused patients, allowing targeted intensification of treatment before the development of heart failure (Figure 5). R2* maps (1/T2*) are potentially more user friendly as R2* linearly correlates with iron burden and the maps extenuate abnormality, for example Figure 5, where blue is normal (<50Hz) and any pixels >50Hz are green / yellow / red highlighting iron burden.

Quantitative perfusion cardiac MRI

Revascularisation only improves symptoms if a stenosis is causing ischemia. Performing percutaneous coronary intervention (PCI) on non-flow limiting lesions worsens outcomes (72) and revascularizing myocardium with higher ischemic burdens is more beneficial (73). Non-invasive ischemia testing is therefore the gateway to invasive angiography. Cardiac MRI with stress perfusion has high sensitivity and specificity for the detection of flow limiting coronary artery disease (86) and uses non-ionizing radiation. However, there are disadvantages. It is subjective and operator dependent. Windowing the images can result in different interpretation of ischemia. There is also the theoretical possibility of missing “balanced” ischemia due to triple vessel disease. Quantitative perfusion therefore may have advantages. This is shown by the PET literature where patients with reduced perfusion reserve or stress flow on quantification have worse outcomes whether they have occlusive coronary artery disease or other conditions such as dilated cardiomyopathy and hypertrophic cardiomyopathy (78).

Semi-quantitative approaches to perfusion cardiac MRI have been performed, all involving measuring the signal intensity (SI) in the myocardium during the first pass of a gadolinium based contrast agent. Examples include the contrast enhancement ratio (CER), the myocardial to LV upslope index and the upslope integral ratio. The contrast enhancement ratio requires the baseline and the peak SI in the area of interest. By using the formula $(SI_{\text{peak}} - SI_{\text{baseline}}) / SI_{\text{baseline}}$, perfusion can be compared semi-quantitatively in different areas of the myocardium. The CER can be accurate for the detection of CAD against truth standards of PET and invasive angiography in expert centres (78). The myocardial to LV upslope index is calculated by dividing the initial upslope of the myocardial SI-time curve by the initial upslope of the LV SI-time curve

in the regions of interest. The upslope integral ratio is the area under the curve of the myocardial SI-time curve following baseline adjustment. The main problem of semi-quantitative methods is firstly that microsphere studies show they underestimate higher flow rates (79) with the CER and myocardial to LV upslope index becoming non-linear above $\sim 1\text{ml/g/min}$ flow or $\sim 3\text{ml/g/min}$ for the upslope integral ratio and secondly, they require extensive, expert operator post-processing limiting clinical adoption.

Fully quantitative techniques have been developed. Absolute quantification requires the measurement of both the arterial input function (AIF, highly concentrated gadolinium) and myocardial signal changes (lower gadolinium concentration) but accurate simultaneous measurement in these two domains requires too much compromise(80). Two main approaches overcome this: the “dual bolus” and “dual sequence” techniques. Once the AIF is accurately measured there is a deconvolution step in which the measured contrast concentration in the myocardium can be converted to an absolute MBF (81). Both the dual bolus and dual sequence techniques have shown good correlation with absolute MBF measured using microspheres (82).

The dual bolus approach involves the administration of initial low dose contrast (for AIF measurement) then usual higher dose (for myocardial response). This is clinically cumbersome. The dual sequence approach uses an additional low resolution gradient echo sequence acquired immediately after the R wave optimised for the AIF followed by a long recovery delay, higher resolution gradient echo or balanced SSFP readout to measure the myocardial signal (83). This approach is more straightforward but

requires onerous post-processing (eg manually tracing 50 stress and rest measurements on 3 LV slices), impeding clinical adoption.

Automation of these is now possible (84). One solution is “Perfusion Mapping” (85), a dual sequence approach with inline analysis through the Gadgetron framework (86). In brief, AIF images are acquired with a dual sequence approach ($T2^*$ loss minimized by using a short readout, wide bandwidth and short duration RF pulse with 2 echoes to permit $T2^*$ decay correction). Following latest generation respiratory motion correction (MOCO), the blood pool is automatically segmented using machine learning to extract the AIF and signal converted to gadolinium concentration using Bloch simulation. For myocardial imaging (3 slices, parallel imaging, high resolution), MOCO, coil normalisation and conversion of signal to Gd concentration is performed. These images are then used to calculate absolute MBF for each voxel of tissue using a model (here the blood tissue exchange (BTEX) model) by solving partial differential equations (87). Advantages of the approach is that a single bolus of contrast is required, the sequence is free-breathing and quantitative perfusion maps are outputted inline alongside the raw perfusion images with no user input required, increasing the likelihood of clinical adoption. Technical validation has been performed against PET and coronary angiography, including invasive in-vivo direct flow measurement (88–91). However, currently this sequence is only available in around 40 centres (as of February 2019). Other approaches to pixel-wise perfusion quantification have been proposed with initial promising results (92).

An alternative to first pass perfusion is myocardial arterial spin labeling (ASL) where a radiofrequency pulse to arterial blood modifies its longitudinal magnetization, “labeling”

it (93). This blood flows into the myocardium, and if two sets of images, one with and one without the ASL are taken and subtracted, myocardial blood flow can be derived – without gadolinium and with relatively simple modelling. ASL is used in brain imaging (94) but cardiac and respiratory motion and reduced SNR require more work to permit effective clinical deployment in cardiac MRI. A variety of different approaches are being explored (95)(96), but scans are still long. There remain issues with heart rate variability and validation is in the domain of correlation with other technical methods rather than patient related outcomes (97).

Conclusion

Quantitative cardiac MRI is rapidly evolving within cardiac imaging, and is shaping the way we understand and diagnose cardiac disease. It represents a prime example of how new technological developments can have a direct impact on our understanding of pathophysiology of disease, translating to changes in clinical practice and patient outcomes. Quantitative MRI has a key role in the development and incorporation of machine learning in clinical imaging, potentially offering major improvements in both workflow efficiency and diagnostic accuracy with new biomarkers becoming clinically available. Finally, as the clinical applications of these techniques are explored and validated, it is likely that quantitative cardiac MRI techniques will serve as non-invasive imaging tools capable of earlier detection, monitoring and risk stratification of disease, potentially guiding personalized management decisions in various cardiac disease models.

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Tables:

Table 1. Minimal detectable changes (MDC)* - a precision measurement - of left ventricular parameters using cardiovascular magnetic resonance (CMR) compared to 2D and 3D echocardiography.

Minimal detectable changes in left ventricular parameters				
Immediate rescan interval			One- year rescan interval	
Modality	CMR	2D Echo	CMR	3D Echo
Study	<i>Grothues et al (98)</i>	<i>Grothues et al (98)</i>	<i>Moody et al (99)</i>	<i>Thavendiranathan et al (100)</i>
Study date	2002	2002	2015	2013
Sample size	60	60	42	56
Population	Heart failure LVH Healthy volunteers	Heart failure LVH Healthy volunteers	Healthy volunteers	Cardio-oncology (normal EF)
EF (%)	4	12	5.8	6.0
Mass (g)**	15	49	5.9	-
EDV (mls)	13	26	12.7	34.8
ESV (mls)	11	27	7.2	13.9
SV (mls)	10	26	-	14

*MDCs are calculated for immediate rescan interval from data published by Grothues et al from the formula published by Moody et al. It is important to note that the method to calculate MDCs can result in different absolute values. Here, the method used by Thavendiranathan et al typically results in slightly lower MDCs compared to Moody et al. **The difference between the MDC for LV Mass with an immediate rescan interval than a one-year scan interval may be attributable to improvements in scan acquisition and epicardial border delineation. (EF – ejection fraction, EDV – end diastolic volume, ESV – end systolic volume, SV – stroke volume)

Table 2. Recent studies evaluating the role of T1 mapping and ECV in various cardiac disease models

Authors,	Year of publication	Disease/ Pathology being investigated	Number of patients/ controls	Field Strength (T)	T1 mapping sequence	Outcome/Conclusion
Kowallick et al, (101)	2018	Atrial fibrillation (AF)	43 patients 22 controls	3	MOLLI	Higher native myocardial T1 values in patients with AF, reduced 3-months post AF ablation
Luetkens et al, (102)	2018	Atrial fibrillation (AF)	61 patients	1.5	MOLLI	Atrial T1 value predictor of poor outcomes post ablation
Roller et al, (103)	2018	Chronic thromboembolic pulmonary hypertension	21 patients	1.5	MOLLI	Native T1 mapping indicative of reverse myocardial tissue remodeling after balloon pulmonary angioplasty
Chen et al, (104)	2018	Dilated cardiomyopathy (DCM)	46 patients	3	MOLLI	Post-contrast T1 calculated ECV was a strong predictor of adverse cardiovascular events in patients with severe DCM
Pradella et al, (105)	2018	Mitral valve prolapse (MVP)	34 patients	1.5	MOLLI	Higher native T1-values, lower post-contrast T1-values and increased ECV-values in patients with MVP
Tagaki et al, (106)	2018	Chemotherapy - radiotherapy induced cardiotoxicity	14 patients	3	MOLLI	T1 mapping detects early changes post therapy in cancer patients
Karur et al, (107)	2018	Anderson-Fabry disease (AFD), Hypertrophic cardiomyopathy (HCM)	30 - HCM 30 - AFD	3	MOLLI	T1 mapping can provide independent and incremental diagnostic value in differentiating the two conditions
Sade et al, (108)	2018	Acute cellular rejection in cardiac transplant recipients	38 patients	1.5	MOLLI	T1 mapping can serve to guide endomyocardial biopsy (EMB) in patients with suspected allograft rejection
Muehlberg et al, (109)	2018	Anthracycline-based chemotherapy	30 patients	1.5	MOLLI	Early decrease of T1 times can predict the development of subsequent cardio-toxicity
Inui et al, (110)	2018	Dilated Cardiomyopathy (DCM)	33 patients	3	MOLLI	ECV can predict improvements in LVEF in patients with DCM
Martinez-Naharro et al, (111)	2018	Transthyretin Amyloidosis (ATTR)	271 patients	1.5	MOLLI	Native T1 mapping and ECV are good diagnostic techniques for cardiac ATTR that are associated with prognosis
Araujo-Filho et al, (112)	2018	Left ventricular non-compaction cardiomyopathy (LVNC)	36 patients 18 controls	1.5	MOLLI	Patients with LVNC showed increased ECV and native T1 compared with controls

Yanagisawa et al, (113)	2018	DCM	25 patients 15 controls	1.5	MOLLI	T1 mapping can be used for assessment of myocardial fibrosis associated with DCM
Torlasco et al, (114)	2018	Iron overload/ Thalassaemia	138 patients 32 controls	1.5	MOLLI	T1 mapping is complementary to T2* in detecting cardiac iron overload
Puntmann et al, (115)	2018	Coronary artery disease	665 patients	1.5/3	MOLLI	T1 is an important predictor of outcome in CAD patients, over and above the traditional risk stratifiers
Yu et al, (116)	2018	Dermatomyositis (DM) Polymyositis (PM)	25 patients 25 controls	1.5	MOLLI	T1 mapping detects subclinical myocardial involvement in PM/DM patients
Lin et al, (117)	2018	Light chain amyloidosis (AL)	82 patients 20 controls	3	MOLLI	ECV (post-contrast T1) independently prognostic for mortality in AL amyloidosis
Reinstadler et al, (118)	2018	ST elevation MI (STEMI)	255 patients	1.5	MOLLI	Increased remote zone native T1 values were associated with worse clinical outcomes post STEMI.
Lee et al, (119)	2018	Aortic stenosis	127 patients 33 controls	3	MOLLI	T1 value on noncontrast T1 mapping CMR is a novel, independent predictor of adverse outcome in patients with significant AS.
Vita et al, (51)	2018	Dilated Cardiomyopathy (DCM)	240 patients	3	cine Look-Locker	ECV offers improved prognostication in patients with DCM compared to LGE or native T1 mapping.
Nakamori et al, (120)	2018	Dilated Cardiomyopathy (DCM)	36 patients	3	MOLLI	Diffuse myocardial fibrosis in DCM may be reliably assessed by native T1 mapping
Cui et al, (121)	2018	End-stage ischaemic and dilated cardiomyopathy	22 patients	1.5	MOLLI	ECV derived from cardiac MRI correlated well with histological collagen volume fraction in patients undergoing transplant due to ischaemic or dilated cardiomyopathy.
Jellis et al, (122)	2018	RV function	102 patients	1.5	Inversion recovery Look-Locker	Post-contrast T1 mapping provides incremental information regarding global RV function and structure
Guo et al, (123)	2018	Systemic Lupus Erythematosus (SLE)	110 patients 50 controls	3	MOLLI	Native myocardial T1 values and ECV, rather than current clinical rheumatic and cardiac indices, could serve as early detection markers of myocardial injury in patients with SLE
Mordi et al, (124)	2018	Hypertensive heart disease and Heart failure with preserved ejection fraction (HFpEF)	84 patients 28 controls	3	MOLLI	ECV is the strongest imaging diagnostic marker for independently differentiating between hypertensive heart disease and HFpEF.
AF - atrial fibrillation; DCM - dilated cardiomyopathy; MVP - mitral valve prolapse; AFD - Anderson-Fabry disease; hypertrophic cardiomyopathy - HCM; ATTR - transthyretin amyloidosis; DM - Dermatomyositis ; PM - Polymyositis; AL - light chain amyloidosis; STEMI - ST elevation myocardial infarction; AS - Aortic stenosis; LVNC - Left ventricular non-compaction cardiomyopathy; SLE- Systemic Lupus Erythematosus; HFpEF - Heart failure with preserved ejection fraction; ECV - extracellular volume fraction; RV - right ventricle; CAD - coronary artery disease; LGE - late gadolinium enhancement; EBM - endomyocardial biopsy						

Table 3. Recent studies evaluating the role of T2 in cardiac disease

Authors	Year	Disease/ Pathology being investigated	Number of patients/ controls	Field Strength (T)	T2 mapping sequence	Outcome/Conclusion
Vermes et al (57)	2018	Acute rejection in cardiac transplant patients	20 patients	1.5	T2-prepared bSSFP sequence	A combined CMR approach using T2 mapping and ECV quantification could potentially decrease the number of routine endomyocardial biopsies performed to diagnose acute rejection
Spieker et al (58)	2018	Dilated cardiomyopathy (DCM)	70 patients 62 controls	1.5	Gradient Spin Echo (GraSE)	Myocardial T2 relaxation times may help to non-invasively detect myocardial inflammation
Winau et al (60)	2018	Systemic Lupus Erythematosus (SLE)	92 patients	3	Gradient and spin echo (GraSE) sequence/Fast low angle shot (FLASH) sequence	CMR with T2 mapping reveals myocardial oedema as the strongest predictor of hs-TropT release
Fehrmann et al (61)	2018	Aortic stenosis (AS)	72 patients 27 controls	3	Gradient Spin Echo (GraSE)	Mean myocardial T2 was significantly elevated in AS patients pointing towards a potential role of oedematous/inflammatory processes in the pathophysiology of myocardial remodelling associated with AS
Kvernby et al (62)	2018	Aortic stenosis (AS)	15 patients	3	Gradient Spin Echo (GraSE)	T1 and T2 relaxation times related to diffuse myocardial fibrosis in aortic stenosis
Haslbauer et al (64)	2018	Cardio-toxicity from cancer related treatment	115 patients 57 controls	3	T2- Gradient Spin Echo (GraSE) T2-FLASH	T1 and T2 mapping can demonstrate distinct biosignatures of early and late myocardial cardio-toxicity.
Ridouani et al (125)	2018	Cardiac amyloidosis	44 patients 40 controls	1.5	bSSFP sequence with an adiabatic T2 preparation	Myocardial native T2 significantly is increased in cardiac amyloidosis, with greater increase seen in AL patients in comparison to ATTR patients
Kotecha et al (126)	2018	Light-chain (AL) and Transthyretin (ATTR) Amyloidosis	286 patients 30 controls	1.5	T2-prepared SSFP sequence	T2 is higher in untreated AL amyloidosis compared with treated AL and ATTR amyloidosis, and is a predictor of prognosis in AL amyloidosis
Wang et al (127)	2018	Pulmonary Hypertension (PHT) and severe aortic stenosis (AS)	18 -patients with PHT 19- patients with AS	1.5	T2-prepared SSFP sequence	T2 values correlated with structural and functional remodeling in both diseases.
Gastl et al (128)	2018	Aortic stenosis (AS)	43 patients	1.5	Gradient Spin Echo (GraSE)	T2 mapping can be used to characterize myocardial hypertrophy due to severe AS and to monitor myocardial adaptations after transcatheter aortic valve replacement.
Tessa et al (129)	2018	Non-ST elevation myocardial infarction (NSTEMI)	47 patients	1.5	T2-prepared sequence TrueFISP	T1 and T2 mapping detect myocardial edema without significant stenosis at CA and vice versa

bSSFP - balanced steady state free precession; GraSE - Gradient Spin Echo DCM - dilated cardiomyopathy; PHT - pulmonary hypertension; hypertrophic cardiomyopathy - HCM; ATTR - transthyretin amyloidosis; AL - light chain amyloidosis; NSTEMI - non-ST elevation myocardial infarction; AS - Aortic stenosis; SLE- Systemic Lupus Erythematosus; HFpEF - Heart failure with preserved ejection fraction; ECV - extracellular volume fraction; hs -Trop T - high sensitivity troponin T.

Figure Legends:

Figure 1. Illustration of AI-derived left ventricular endocardial segmentation in end-systolic short-axis images (2D steady-state free precession acquisition). Endocardial contours are shown in red. Source: J.A. and J.M, data to be published.

Figure 2. Cardiac MRI feature tracking in a patient with Fabry disease. Endocardial and epicardial borders are drawn on short-axis and long-axis. (A) and (B) show short-axis radial strain in end-diastole (ED) and end-systole (ES), respectively. The bullseye 16-segment model (American Heart Association) is derived (C). A graph of radial myocardial strain throughout the cardiac cycle is shown (D). Circumferential (E, F, G and H) and longitudinal strain (I, J, K and L) analyses are also shown. Of note, peak longitudinal strain (J and K) was reduced in the mid inferolateral, lateral and anterior segments – despite the absence of hypertrophy or scar – suggesting early disease detection. All analyses were performed in CVI42 software (Circle Cardiovascular Imaging, Calgary, Canada).

Figure 3. Articles related to T1 mapping using CMR. Search performed on Pubmed on the 4th of February 2019. (T1 and MAPPING) AND ("heart"[MeSH Terms] OR "heart" OR "cardiac"). Titles and abstracts were reviewed to ensure relevance to cardiac magnetic resonance imaging and T1 mapping. *Includes both original research and review articles.

Figure 4. T1, T2 and ECV (left to right) maps for (top to bottom) (A) a healthy control, (B) patient with myocarditis, (C) patient with Fabry disease and (D) a patient with amyloid. The color look up tables of the parametric maps allow visual interpretation. The healthy control shows normal T1 (990ms), T2 (48ms) and ECV (26%). In myocarditis (B) the basal lateral wall has high T1 (1200ms), T2 (61ms) and ECV (50%). In Fabry (C) the lateral wall is similar (T1 1220ms, T2 62ms and ECV 55%), but there is remote T1 lowering (820ms) and hypertrophy. In amyloid (D) there is mild LVH and globally elevated T1 (1130ms) which is particularly high in the lateral wall (1230ms) in this case, T2 is mildly elevated in the lateral wall (55ms) and global ECV is high (44%) – a value beyond that possible in global diffuse fibrosis.

Figure 5: T1, T2* and R2* (relaxation rate) maps (left to right) in a patient with severe cardiac iron overload (B) and in a healthy control (A). In cardiac overload the T1 mapping value (650ms) and T2* (9.8ms) are low, whereas the relaxation rate (R2*) is elevated (99Hz).

Figure 6. Basal, mid and apical slices for a patient with severe right coronary artery disease. There are standard perfusion images (A&B) and quantitative perfusion maps (C&D). Vasodilator stress perfusion (A&C) and rest perfusion (B&D). On the perfusion maps, the myocardial blood flow in the area of hypoperfusion is 0.65ml/g/min compared to 2.95ml/g/min in the remote myocardium. Rest myocardial blood flow is 1.00ml/g/min.

Figure 7. Quantitative perfusion maps for a patient with apical hypertrophic cardiomyopathy. The vasodilator stress maps (A) demonstrate hypoperfusion in the hypertrophied apex and basal anteroseptum. Remote myocardium has a myocardial blood flow (MBF) of 1.71ml/g/min, hypoperfused myocardium has an MBF of 0.46ml/g/min. Rest shows homogenous flow with an MBF 1.08ml/g/min. Therefore flow has fallen at peak stress.