CMR endpoints selection in myocardial infarction experimental and clinical trials: from pathophysiology to outcomes.

JACC Scientific Expert Panel.

SUPPLEMENTAL MATERIAL

INDEX:

Methodology for appointing the Scientific Expert Panel, identification of topics and selection of statements/recommendations.

Organizers of the meeting (BI and VF) appointed a scientific committee (CB, DH, IE, JS, RF-J, CK) to discuss the appropriateness of the meeting, clinical needs, topics to be discussed, and more importantly identification of experts in the field to cover all aspects relevant to the goal of the meeting. The appointment of international experts was decided by general agreement between the scientific committee. Once the panel of experts was appointed, and the topics to be discussed decided, JACC editorial was notified to get preliminary approval of the group of experts and topic for a *JACC Expert Panel submission* (under the understanding that the paper needed to undergo a full external peer review processed handled by independent editors).
Open discussions took place in the meeting and summary of key points circulated. Verbal agreements were taken during the meeting and then ratified accepting the table of statements/recommendations. Areas of controversy were solved by agreeing on inclusive text under the intention of delivering clear and useful recommendations. Some statements were controversial and corresponding statements/recommendation not unanimously supported. Only if majority of experts agreed with the statement/recommendation, this was included in tables. When a statement/recommendation was supported by a majority but no all experts, this is noted by an asterisk at the end of the statement/recommendation (i.e. asterisk denotes controversy among the expert panel). Statements/recommendations without the support of a majority of experts were not included in tables.

Relevance of animal models to human pathophysiology

Studies in animal models underpin our current understanding of the pathophysiology of myocardial I/R,(1,2) and informed the concept of I/R injury(3) and post-MI remodeling.(4,5) Animal models provide mechanistic and translational information along a continuous spectrum: at one end of this spectrum are models providing molecular and cellular data necessary to identify mechanisms of injury and targets for cardioprotection; at the other end are those models providing data on safety, efficacy and optimal study protocols to be applied in clinical studies.
As reperfusion is the essential element of the treatment of STEMI patients, preclinical models of acute MI consist in general in a transient coronary occlusion. CMR has become a very useful tool for experimental I/R studies to be able to track even subtle myocardial changes and heart function across time in a translational manner.

Small animal models.
The most widely used small animals in myocardial I/R studies are rodents (mostly mice, but also rats). They are easy to keep and handle, relatively inexpensive, easy to genetically manipulate (mice), have a short life span, and can be imaged with a wide variety of techniques, including CMR. Important limitations of small animal models of I/R are their size. Additional limitations are the differences between species in cardiovascular anatomy and physiology, heart rate (around 600 bpm in mice), aspects of arrhythmogenesis, and response to I/R across strains from the same species.(6,7) Also, from the CMR perspective, sequences developed in small animals (usually at high field (7.0 and 9.4 Tesla (T) magnets) are different from those applied in clinically available magnets (1.5 or 3T).

Large animal models

Large animal models provide important mechanistic and translational information beyond that provided by small animal models. Their main advantages derive from their anatomical and physiological characteristics, which are much more similar to humans than rodents. Pigs are the most widely used animals in pre-clinical studies of MI. Although the initial and fundamental studies on myocardial I/R were conducted in dogs,(1,2) the use of this species has been declining during the last two decades. Dogs and pigs have different physiological traits of which the most relevant to I/R studies is native collateral circulation, which is large and variable in dogs, and virtually absent in healthy pigs.(8-10) Collateral flow is a main determinant of the relationship between duration of coronary occlusion and infarct size. In addition, reperfusion-mediated myocardial salvage declines much more rapidly in pigs than in dogs.(11,12) Healthy humans have poor native collaterals (similar to the case of pigs), but older patients with underlying coronary artery disease may have developed important collateral networks (similar to the case of dogs)(13) and reperfusion-mediated myocardial salvage may decline even slower (12). Although other species have occasionally been used in coronary occlusion experiments, their use does not appear justified at present. An important reason is the need to reduce the variability to a minimum between laboratories, which means reducing the number of models. In some cases there are also serious ethical problems (primates).

General aspects of the design of preclinical studies

Before potential cardioprotective therapies are entered into pilot clinical trials, it is appropriate to perform experimental studies in large animal models. The execution of pilot clinical studies based on small animal studies alone is high-risk and thus not recommended.(14) Large animal studies should be performed according to a pre-specified protocol and sample size based on the primary outcome, in an intention-to-treat basis with an *a priori* protocol dictating exclusion criteria.(7,15) Whilst following a specific design as here indicated allows to maximize the chances for positive translation into humans, still related inherent uncertainty remains due to the following issues. Preclinical studies on myocardial I/R are generally performed in juvenile healthy animals and in most cases only one gender is used.(7) Another limitation is the lack of coronary artery disease and comorbidities. Finally, there is evidence that some medications routinely administered to patients with STEMI may modulate myocardial injury secondary to I/R, the clearest case being antiplatelet agents.(16) Up-to-date recommendations on preclinical studies on myocardial I/R can be found elsewhere.(15)
A promising approach to improve quality of preclinical evidence in order to make translation faster and safer is the implementation of networks formed by different laboratories using the same models and highly standardized procedures with centralized facilities and core labs to perform large, adequately powered multicenter preclinical trials.(17) Experimental research is expensive and continuous funding through grants and other funding schemes is needed to sustain the workflow.

LGE methodology

LGE imaging principles

As indicated in the main document, LGE most typically involves acquisition of inversion recovery imaging 10-20 minutes after administration of intravenous gadolinium-based contrast agents. The sequence is designed to exploit the image contrast between infarcted and viable tissue because of the marked T1-shortening effect of the contrast that accumulates in the infarct but is (nearly) absent in non-infarcted myocardium after a few minutes. An inversion pre-pulse is delivered that inverts longitudinal magnetization of the tissue. This longitudinal magnetization tends to return to the baseline equilibrium at a rate proportional to the T1; thus, recovery occurs much more rapidly in the infarcted myocardium. The sequence is designed to time acquisition at the time where longitudinal magnetization of non-infarcted has recovered by approximately 50% and appears black, whereas magnetization of infarcted tissue has recovered substantially and appears white.

The sequences, contrast dose and timing of acquisition are highly standardized, extensively validated, widely available, and extremely reproducible, making it suitable for widespread use in single- or multi-center studies.

Post-processing of LGE images

LGE images should be analyzed by observers who have been trained with software that is designed for infarct sizing. The latter should be confirmed on both the axial and long axis acquisitions. The epicardial and endocardial borders of the ventricle can be delineated by manual, semi- or fully automated methods. The papillary muscles, trabeculae and blood pool should be excluded from these contours. The apical short axis slice may be excluded to rule out partial volume effects.

Quantifying infarct size

The gadolinium enhanced myocardial mass (grams) can be quantified using computer assisted planimetry which may be user-defined (i.e. manual) or fully automated.
Delineation of the infarct territory involves identifying the border of the bright infarct zone from the lower signal intensity of neighboring unaffected tissue and the remote zone. Now we are presenting the main approaches used for this task.

Manual delineation

The manual approach involves the observer drawing a border around the bright infarct zone to separate it from neighboring unaffected tissue. This approach is subjective but it minimizes the potential for errors introduced by an algorithm.
It is important to note that all “automatic” methods of quantifying LGE first requires “subjective” manual delineation of endocardial and epicardial borders.

Thresholding of signal intensity

The hyperintense zone on LGE can be segmented using different thresholds for SD signal intensity vs. the mean signal intensity in the remote zone. Many studies have used disparate thresholds, ranging from 2SD to 6 SD. It is important to highlight that there are limitations of using any single signal intensity threshold for determining infarct size. myocardium.myocardiumWith very high resolution (e.g. ex-vivo 3D imaging) partial volume effects, in which there are admixtures of both viable and nonviable myocardium, are significantly reduced and thus low signal intensity thresholds might be appropriate. Using currently in-vivo protocols, most frequently used thresholds for delineating the hyperintense zone are >5 SD or >6 SD difference in signal intensity vs. the mean signal intensity of a region of interest (ROI) in the remote zone. ROIs should be identified and confirmed by the user, rather than by a fully automated approach. The size of the remote zone ROI should be sufficiently large be representative and in general, 2.0 cm^2 is taken as representative.

Full Width at Half Maximum

The FWHM technique invokes half the maximal signal within the scar as the threshold for boundary delineation and attempts to take care of partial volume effects.(18,19) A ROI should be identified in the infarct zone and hyperenhancement is calculated as pixels where signal intensity is greater than 50% of the automatically determined maximum signal intensity in the infarct zone. The FWHM method is unaffected by ROI size as it selects the threshold based on the single pixel with highest signal intensity.

Otsu's Automatic Threshold (OAT)

The OAT method automatically identifies hyperenhanced areas and has minimal user dependence. The OAT method involves automatic calculation of the signal intensity threshold for each slice by dividing the signal intensity histogram in each slice into 2 groups (enhanced, normal) based on the signal intensity threshold giving the least variance (lowest sum of variances) and thus most homogeneity of signal intensities within each group. Endo- and epicardial contours are user-defined, as is also manual correction of noise artefact. OAT does not involve ROIs and so is user-independent compared with other approaches.

EWA

The EWA method (Expectation maximization, Weighted intensity, A priori information) make use of an intensity threshold by Expectation Maximization (EM) and a weighted summation to account for partial volume effects.

Comparative diagnostic performance of methods to quantify LGE

The use of 2SD is a reasonable way to detect if there is myocardial damage, but the detection of some damage is not the same as the determination that 100% of the tissue is dead. In general, if LGE image intensity is between 2-to-4 or 2-to-5SD, it is likely that the myocardium represents an admixture of both alive and dead myocardium. Therefore, the use of a 2D threshold approach can lead to an over-estimation of infarct size. x5SDs and x6SDs are less affected by partial volume effect between dead and alive tissue.(19,20) The FWHM approach has good reproducibility. McAlindon et

al(21) measured infarct size repeatedly in 40 patients with recent STEMI. They found that the manual and FWHM methods were associated with the lowest inter- and intra-observer variability for infarct size, with similar findings for inter-scan variability. Vermes et al(22) found no differences between the OAT and the 5-SD threshold methods. Khan et al(23) assessed infarct size in 10 STEMI patients repeatedly at 1.5T and 3.0T. They found that the FWHM method was accurate and reproducible, whereas the threshold approach (5SD) and OAT methods over-estimated infarct size at both field strengths. Engblom et al. compared all these methods and EWA against expert delineations. (24) Interestingly enough, thresholding between 2-8 SD and FWHM provided similar results with respect to predicting functional outcome after coronary revascularization.(25) Klem et al. evaluated the reproducibility of 3 core laboratories for the measurement of infarct size using a variety of methods.(26) Unlike prior investigations, this study included the step of manually tracing the endocardial and epicardial borders of LV myocardium which is a requirement for all methods. Interestingly, even automated techniques with no user interaction for infarct borders resulted in significant within-patient variability given the need to subjectively trace endocardial/epicardial contours. Manual planimetry and visual scoring had similar reproducibility to automated techniques.

CMR sequences for edema imaging

T2-weighted pulse sequences

Dark-blood T2W-CMR methods are widely used for clinical and research purposes.(27-34) Blood signal is suppressed applying a pair of non-selective and slice-selective inversion pulses and timing the acquisition read-out when blood longitudinal magnetization is nulled. Dark blood T2W short tau inversion recovery (STIR) pulse sequences apply an additional third inversion pulse to null the fat signal. In addition, fat suppression STIR pulse sequences merge T2 with proton density effectively increasing the sensitivity of the method to edema compared with pure T2 weighted sequences.(27) Strategies to optimize image quality include surface coil intensity correction through prescan normalization and slice-related shimming to reduce bright rim artefacts. In STIR, signal loss in the inferior wall may occur due to movement artefacts in combination with the effects of the dark blood inversion pulse. Optimized timing of the turbo spin echo (TSE) factor can limit artefacts from cardiac motion, however this is harder to optimize at higher heart rates, especially with variation in R-R intervals. Timing optimization maneuvers may complicate the examination. Motion tracking can further improve image quality. Dark blood T2W-CMR is prone to bright artefact from slow moving blood at the LV wall, particularly at the LV apex.(35,36) The artefact causes subendocardial bright rim artefacts which can be particularly problematic when associated with a regional wall motion abnormality in a post-MI patient. More recently, bright blood T2W-CMR techniques have emerged as potential alternatives to dark blood T2W-CMR. Building on previous work of Shea et al,(37) Kellman *et al* (35) developed a bright blood T_2-prepared single-shot steady state free precession (T_2-prepared SSFP) method which involves surface coil intensity normalization, parallel imaging techniques and motion-corrected averaging. T_2-prepared SSFP can provide a uniform proton density field map and can be used for T_2–mapping to measure absolute values of T_2 relaxation (ms) in the heart. Aletras *et al* (38) developed another bright blood T2W method, ACUT$_2$E (Acquisition for Cardiac Unified T2 Edema) which is a hybrid of TSE and SSFP.(35) This hybrid method, which does not involve a T_2 preparation, has a

SSFP readout gated during diastole. TSE-SSFP creates a coherent train of T2W spin echoes.(38) The bright blood ACUT$_2$E TSE-SSFP method has higher SNR and contrast-to-noise (CNR) compared with T_2-prepared SSFP.(38) Coil sensitivity corrections with the ACUT$_2$E method may be imperfect because of non-uniform proton density field map. Furthermore, neither ACUT$_2$E nor STIR can be used for T_2mapping and like STIR, ACUT$_2$E is dependent on subjective image interpretation.

T2-mapping

In breath-hold parametric T2-mapping, the signal intensity within a single pixel of the image reflects the proton relaxation time in milliseconds for the tissue. T2-mapping has been validated against pathology for myocardial water content quantification in experimental MI models.(39,40) The acquisition may involve either balanced SSFP(40,41) or spoiled gradient echo (GRE) sequence with an initial T2 spin echo preparation module ,(42) or a hybrid spin echo excitation with segmented echo planar readout (GraSE).(39) T2 relaxation time (ms) should be determined from at least 3 images acquired with different echo times (e.g. 0, 25 and 50 ms) plotting an exponential decay curve using a 2- or 3-parameter fitting model.(43) The parametric map is a product of pixel-wise fitting for a T2 decay curve derived from of a series images with different spin-echo TE, either by T2 preparation or refocusing pulses. Saturation pulse acquisition may help to remove T1 recovery bias.

Pixel-mapping should involve motion correction(44) and free-breathing methods capable of generating 3D T2 maps are emerging.(45,46) T2-mapping has associations of myocardial T2 (ms) with age and sex and field strength.(47,48) The clinical applications of T2-mapping in post-MI patients are discussed in main document.

T1 mapping

The longitudinal relaxation time (native T1, ms) represents the capability of a proton to release energy to its surroundings i.e. the lattice (normally to the molecule that contains the proton) after excitation.
There are several T1-mapping methods available or in development. T1-mapping involves fitting a T1 curve (normally inversion recovery) to each pixel in a series of images with different degrees of T1 recovery using a two- or three-parameter fit.(43) Native T1 values are also influenced by age, sex and CMR field strength.(49)

T1 assessment is sensitive to motion artefacts and imperfect breath holding, which may reduce image quality.(43) The most commonly used methods are Modified Look-Locker inversion recovery (MOLLI),(50) and short-MOLLI (shMOLLI).(51) The MOLLI method has high precision but accuracy may be impaired by heart rate, magnetization transfer variation and technical factors e.g. miscalibrated flip angles. The shortened version of MOLLI (ShMOLLI) shortens breath hold time and is less heart rate dependent.(51) Newer methods aimed at improving accuracy such as SASHA are under investigation.(52) A detailed review of T1-mapping methods is beyond the scope of this review and can be found elsewhere.(43)

Data on comparison of sequences for imaging edema

In patients with known or suspected acute MI, bright blood T2W CMR has higher diagnostic accuracy than dark blood T2W CMR with less impact of coil sensitivity variations.(53) This problem mainly affects detection of acute myocardial injury in the basal and mid inferior as well as posterior left ventricular walls. Dark blood T2W-STIR may have reduced diagnostic accuracy for non-anterior MI compared to anterior MI, leading to underestimation of the extent of edema.(35,36)
Ferreira *et al*(54) found that T1 maps had a higher diagnostic performance for detecting acute myocardial edema as compared to T2W CMR with either dark blood STIR or bright blood $ACUT_2E$. Native T1 increases with fibrosis and edema. A potential drawback of T1 mapping for imaging myocardial edema is the confounding effect of concomitant myocardial fibrosis (scar) secondary to previous, chronic MI.(50) In a multicenter study comparing contrast-enhanced cine-SSFP with T2W-STIR in 215 patients both methods provided similar estimates for the extent of myocardial edema however, cine imaging provided higher quality images overall.(55) In an experimental model of MI, the extent of edema was similar when depicted by early gadolinium enhancement, T1- and T2-maps.(56)
A comparative study using repeatedly 4 different edema sequences (T2W-CMR, $ACUT_2E$ TSE-SSFP, T2 mapping, early gadolinium enhancement) showed higher intra- and inter-observer agreement and greater test-retest reproducibility in the quantification of edema using T2 mapping.(57)

Edema post-processing methods.

The precision and accuracy of myocardial edema imaging are influenced by patient characteristics, such as the presence and extent of MVO and technical factors, such as image acquisition and display. A computer display of a digital CMR image should have light-dark settings. The level setting corresponds to the dark-bright setting of the display. The setting for the window width reflects the range of pixel values to be incorporated into the display, and therefore determines image contrast. For standardized imaging assessments between and within subjects, the window-level settings of the displayed image should in general not be altered. If manual adjustments are necessary, then the approach should be standardized.(58)

Same thresholding approaches presented for LGE apply for edema post-processing (see previous section).

T1- and T2 maps may have artefacts relating to susceptibility effects or cardio-respiratory motion. The color map can be assessed against the raw (grey-scale) images. Artefacts should be excluded from quantitative analyses.

Edema-based CMR methodologies for retrospective AAR size estimate

In the main document it has been presented the current uncertainty about the validity of edema-based CMR for retrospective AAR quantification. In order to provide a historical perspective, we now present the different CMR methodologies proposed for this purpose.

T2W-CMR

Classical (pathology-based) studies have demonstrated that after I/R there is an intense edematous reaction confined to the AAR.(59-61) Areas of increased water content display a prolongation of T2 relaxation times. Based on these premises, García-Dorado et al proposed that ex-vivo CMR could identify post-MI edematous regions confined to the AAR.(62) A decade later, Aletras et al. were the first to publish an in-vivo CMR study testing the association between edema region as depicted on CMR and actual AAR.(63)

A number of experimental and clinical studies have compared T2W imaging of myocardial edema with different AAR standards such as Evan's blue,(64) coronary angiography jeopardy scores,(65) single photon emission computer tomography (SPECT),(66) infarct-endocardial surface area,(65,67) CE-SSFP,(55,68,69) and T1-mapping.(70,71)

Against this positive studies, some studies have questioned the use of T2W-imaging to delineate the AAR following I/R. Kim et al proposed that increased T2 signal was confined to areas of infarction and did not delineate the AAR in the canine reperfused MI model and in patients.(31) Using a porcine reperfused MI model, Mewton et al proposed that post reperfusion T2W-imaging significantly overestimated the AAR when compared to perfusion defect during index coronary occlusion.(72)

T2-mapping

T2-mapping has also been proposed as a method to differentiate salvaged from infarcted myocardium within the AAR in a canine model of reperfused MI with higher T2 values within the infarct zone when compared to the salvaged myocardium, a difference which increased from 4 to 48 hours post-MI, suggesting differential edema dynamics in salvaged and infarcted myocardium.(73) These results are consistent with the pathology evidence showing that larger amounts of edema occur in the actual infarcted than in salvaged myocardium.(59-61)

T1 mapping

Native T1 mapping has been shown to delineate regions with increased water content, assumed to correspond to the AAR in both experimental and clinical studies. The principle behind this observation is that edema results in prolonged T1 relaxation times.(74,75) Although the correlation between increased water content and T1 relaxation times prolongation has been demonstrated in other organs different from the heart,(74,76) the physical principle is expected to apply to heart as well. In 2012, Ugander et al first proposed that native T1-mapping could delineate the AAR in a canine reperfused MI model when compared to T2-mapping and microspheres.(70) In the same year, Dall'Armellina et al suggested that native T1-mapping (ShMOLLI) delineated the same region as T2W-imaging in STEMI and NSTEMI patients.(77) Subsequent studies have tested native T1-mapping (MOLLI) to delineate the AAR as compared with different standards such as SPECT,(78) T2-mapping,(71,79) microspheres, and CT perfusion.(80)

Contrast-enhanced methods

Administration of contrast-media before CE-SSFP imaging provides enhanced tissue characterization through T1 shortening.(55,81-83) In this case, the hyperintense signal is a function of T2 and T1 effects. The method is appealing because additional scans for imaging edema may be avoided, thus shortening the duration of the CMR exam. This method for AAR quantification has been tested against myocardial perfusion scintigraphy in experimental models(82) and post-MI patients.(55,69,81,83) The explanation for the hyperintense signal on non-contrast SSFP and CE-SSFP images is complex, and include relaxation effects (increase in T2/T1 ratio, as well as proton density, within the AAR compared to the remote myocardium), as well as the alteration in thermal equilibrium (including magnetization transfer).(84) The extent of CE-SSFP abnormalities is stable from 3-30 minutes after contrast injection.(55,82)

Early gadolinium enhancement (EGE) imaging during a very short time window at 2-3 minutes after contrast media administration has been proposed to delineate the AAR as compared with a microspheres standard in an experimental model of MI.(56) The explanation for the hyperenhancement on EGE images in the AAR is not clear.

Gadolinium is an extracellular contrast which is distributed in areas of increased ECV and its wash out is slower than from regions without increased ECV. Post-MI extracellular edema results in increased ECV, which can be visualized and quantified by CMR.(85,86) ECV mapping has been recently proposed as a method to delineate the AAR by means of the area of increased intercellular space, in both experimental and clinical studies. Using the porcine reperfused MI model, Jablonowski et al suggested that CMR overestimated MI size when compared with TTC staining acutely (6 hours reperfusion) but not at 7 days, and found that this difference at 6 hours was due to higher ECV in salvage myocardium within the AAR, and this difference disappeared at 7 days most likely due to resolution of myocardial edema within the salvage myocardium within the AAR.(87) In STEMI patients, Hammer-Hansen et al also proposed an overestimation of MI size when imaging too soon after contrast injections with higher ECV values within the salvaged myocardium when compared to remote myocardium.(88)

Other CMR methodologies for AAR depiction not based on edema.

Given the uncertainty of edema extension as an accurate surrogate for AAR (see main document), the possibility of having surrogates for AAR not relying on edema formation would be of great value. As described elsewhere in this document, there are several techniques with proven value for this matter but they have important limitations precluding its applicability in clinical trials (e.g. ex-vivo measures (dyes, microspheres), computed tomography (radiation, need to obtain imaging before reperfusion) or SPECT (radiation, low resolution). In addition given that the best imaging surrogate for infarct size is LGE CMR, the ideal tool should be a CMR one.

The endocardial extent of infarction on LGE images (termed Infarct-endocardial surface length (ESL) in a single slice or area (ESA) if calculated from a stack of slices) has been suggested to delineate the AAR following STEMI. It is based on the wavefront theory of necrosis progression, in which infarction develops subendocardially and extends

transmurally with time. In 2007, Ortiz-Perez et al were the first to propose that Infarct-ESA on LGE images could delineate the AAR, when compared to the BARI and APPROACH coronary angiography jeopardy scores in reperfused STEMI patients.(89) A study proposed that Infarct-ESA delineated the AAR in STEMI correlated with T2W-imaging and angiography jeopardy score.(90) However, several subsequent clinical studies have suggested that Infarct-ESA on LGE images significantly underestimates the AAR when compared to T2W-imaging questioning its use as a method for delineating AAR in STEMI patients.(65,67,91,92)
The advantages of Infarct-ESA on LGE imaging for delineating the AAR include: it does not require an additional CMR sequence, it is performed at the same exact time-point, and it offers full LV coverage. However, the disadvantages include questions over its accuracy for quantifying the AAR, the reduction in LGE over the first week following STEMI, it not being measurable in early reperfused STEMI patients with minimal or absent LGE as in aborted infarction where the AAR cannot be determined with ESA.(67)

Overall, contrast-based methods for AAR quantification have not been extensively validated and the mechanisms by which they delineate AAR is not completely understood. For these reasons they should be taken with the same caution as other edema based methods.

Intervendor differences in LGE, non-parametric edema imaging and mapping methodologies

LGE and T2/T1 mapping are the recommended techniques for outcome evaluation (see main text). Still non-parametric edema imaging is still being used extensively.

LGE is a highly reproducible technique from imaging acquisition point of view and the reproducibility is modulated by the analysis technique as discussed in this supplement.

The particular MRI platform used for acquiring non-parametric edema images and the specific protocol parameters are important. Nordlund et al have shown that, in a multi-vendor, multi-center comparison, the commonly used T2-STIR approach for visualizing the edema can yield non-diagnostic quality images in 35% of the patients while CE-SSFP only in 3% of cases.(55)

T2 mapping techniques normally relay in the acquisition different TE after consecutive spin-echo pulses. There are two different approaches based on multi-echo gradient spin-echo or the combination of single shot steady state free precession sequence combined with spin-echo preparation pulses for different echo times. Reproducibility study demonstrated that both techniques are highly reproducible between consecutive measurements, different measurements along the day and at different days in a week interval.(93) On the other hand, detail review of the data showed a slightly higher T2 values for GraSE acquisition that for T2Prep approach probably due to difference in the number of sampling echo times.

Regarding T1 values, almost all vendors include an implementation of Modified Lock-Locker Inversion recovery technique and most of them provide a 5(3)3 MOLLI scheme as the default one.(50,94,95) This technique provides highly precise values with

minimal T1 underestimation. In all cases the image readout is based on steady-state free precession with flip angle of 35^{o} for 1.5T and 20^{o} for 3.0T systems to minimize readout effect on T1 estimation, maintaining proper SNR. Inversion recovery methods such as MOLLI have excellent precision and are highly reproducible when using tightly controlled protocols.(96) If equivalent T1 mapping techniques are not shared between the centers estimated T1 values can vary significantly, limiting the capability to pool data between different centers.

Considerations regarding CMR endpoints in experimental studies

The ultimate goal of new cardioprotective strategies is to reduce the extent of irreversible injury, thus infarct size is the natural primary outcome used in experimental studies. LGE has been demonstrated to be tightly correlated with areas of irreversible injury on pathology standards, being therefore the best surrogate for infarct size,(4) and the preferred CMR primary outcome measure in experimental studies. Recent evidence recommends against the use of edema-sensitive methodologies to estimate AAR,(64,97-99) (refer to main document for more details). The extent of edema after reperfusion (as evaluated by different T2 sequences(97)), as well as the signal intensity (T2W),(99) and T2 relaxation times,(64,97,98) can be affected by strong cardioprotective interventions. Therefore, edema development might be used as secondary endpoint in experimental studies (not as a surrogate for AAR when therapy can be expected to affect edema formation). MVO is another CMR endpoint that can be quantified in experimental studies and has prognostic implications in patients. Other CMR endpoints discussed in main document can be obtained in large animal studies, and could be used as secondary endpoints.

One important aspect to consider when deciding the primary outcome of a study is timing of the CMR scan. Infarct size, MVO, and other parameters are highly dynamic after reperfusion. Studies in different large animal species have shown that the extent of infarct size is much larger early after reperfusion when compared to days later. Jablonowski et al.(87) used a pig model of reperfused MI to estimate infarct size by 3 different methodologies (in vivo LGE CMR, ex-vivo LGE CMR, and pathology TTC staining) in 2 groups of animals, one being evaluated 6 hours after reperfusion, and the other 7 days later. Infarct size was larger at 6 hours than 7 days by all methodologies.(87) Fernández-Jiménez et. al performed a serial CMR study in a similar pig model of reperfused MI.(32) Animals underwent 4 different scans after reperfusion (2 hours, 1, 4, and 7 days). The extent of LGE was largest immediately after reperfusion, and since then there was a progressive reduction.(32) These experimental data are in agreement with clinical studies where patients underwent CMR from day 1 and up to 365 days later showing a reduction in infarct size with time.(100,101) The fact that LGE extension is larger at early time points does not mean that infarct size is overestimated. It rather reflects the biology of the processes occurring in the infarcted area; in fact, pathology evaluation of infarct size (TTC staining) also shows larger extension early after reperfusion than days later. LGE, MVO and other relevant CMR parameters are relatively stable in the time window of 3 to 7 days after reperfusion in the experimental setting.(97)

Evolving CMR methodologies

Evaluation of LV strain post-STEMI: Feature Tracking and DENSE

Feature tracking (FT) is a CMR post-processing analysis method that can be applied to routinely acquired long- and short-axis cine images by identifying features in the image, tracking them, and measuring the displacement of segments. Shetye et al demonstrated in 64 patients that global longitudinal strain (GLS) measured by both FT and tagging early after STEMI did not predict the development of LV remodelling. Although GLS had a good correlation with baseline infarct size, only the latter was a significant predictor of adverse LV remodelling.(102) In a study of 43 patients with STEMI, GLS demonstrated the strongest association with MVO and IMH (beta = 0.53, $p < 0.001$) compared to global circumferential strain (GCS) and global radial strain (GRS).(103)
The prognostic role of deformation imaging after STEMI has been investigated in few studies. In an initial cohort of 323 patients acutely after STEMI, GLS was an independent predictor of MACE but it did not improve risk reclassification beyond baseline characteristics (time to reperfusion, TIMI risk score) and CMR LVEF.(104) Yoon et al, later demonstrated that myocardial deformation (all 3 components of GLS, GCS, GRS) were significant predictors of adverse events.(105) Similar results were confirmed in a subsequent larger multicentre study on 1,235 patients reperfused with primary PCI (n=795 STEMI, n=440 NSTEMI), in which GLS was the strongest predictor of MACE even after adjustment for established prognostic markers such as LVEF and infarct size.(106). However, a recent study in 323 patients with STEMI and an external 190 patients validation cohort, analysis of strain failed to add prognostic information over traditional CMR indexes.(104) GLS and GCS have been shown to be sensible to detect the cardioprotective effects of early i.v. metoprolol before reperfusion in the METOCARD-CNIC trial at 2 two different timepoints: one week and 6 months.(107)

Displacement encoding with stimulated echoes (DENSE) or strain encoding (SENC)(108) are another non-contrast CMR methodology that evaluates strain with pixel-level resolution. Aletras et al. developed a phase contrast method for DENSE with the ability to extract myocardial motion data at high spatial density over segments of the cardiac cycle.(109) In a recent study of 259 STEMI patients undergoing CMR 2 days after reperfusion.(110) DENSE-, but not FT-derived strain provided incremental prognostic value above MI size for prediction of MACE.

Dark-blood infarct imaging

Conventional ‘dark-blood’ double-IR techniques were not designed to function after contrast administration since they rely on the long native T1 of blood and sufficient blood flow within this time period. Fortunately, dark-blood LGE techniques such as Flow-Independent Dark-blood DeLayed Enhancement (FIDDLE) allows visualization of tissue contrast-enhancement while simultaneously suppressing blood-pool signal. First described in 2010, FIDDLE uses a nonselective preparation pulse, an inversion pulse, and phase-sensitive reconstruction to suppress the blood-pool signal. The preparation pulse can be any pulse (e.g. T2, MT, T1rho, etc.) that has differential effects on the magnetization of myocardium compared with blood.
An MT-prep variant of FIDDLE has been validated against histopathology in a canine model of MI, and shown to have higher diagnostic accuracy than conventional LGE in

patients with MI.(111) Findings were similar at 1.5T and at 3T. A T2-prep variant of FIDDLE at 1.5T, which combined single-shot SSFP readout with motion correction to allow imaging during free breathing, demonstrated increased conspicuity of regions that were likely to represent subendocardial fibrosis,(112) and demonstrated a higher rate of detecting hyperenhanced myocardium than conventional LGE imaging.(113)
The prep pulse can be placed before (prep-IR) or after the inversion pulse (IR-prep), however, the IR-prep variant is more limited since the time required for the prep pulse itself will restrict the minimum inversion time that can be chosen. This constraint may not allow a short enough inversion time to result in a black-blood image, depending on the dose of contrast media given and the time elapsed after administration.
For either prep-IR or IR-prep FIDDLE, if the inversion time is extended beyond that needed to result in black-blood, a “grey-blood” image will result. Blood-pool signal will be higher than that of normal myocardium, however, grey-blood imaging could still be helpful since blood-pool signal will be suppressed relative to conventional LGE. This could improve the depiction of MI, unless the infarct is patchy and results in a similar grey myocardial image intensity to that of the blood-pool. Grey-blood imaging can be performed without phase-sensitive reconstruction.(114)

3D T1/T2 mapping

Cardiac mapping techniques have a unique ability to describe the underlying pathophysiology in cardiac muscle after MI. T2 and T1 mapping techniques of the cardiac muscle are typically acquired in a limited number of two-dimensional (2D) slices acquired in different breath-holds. However, the tissue characterization features often has a complex three-dimensional (3D) structure. Different expiration position for each breath-hold can make it difficult to follow this complex 3D structure. In recent years, some studieshave proposed 3D cardiac mapping techniques for T2(46,115-117) and T1.(117,118) Typically, 3D T2 mapping is measured with adiabatic spin-echo preparation pulses followed by a 3D steady-state free precession or stack-of-stars spoiled-gradient-echo readout. To avoid interaction between different spin-echo preparations and readouts on T2 estimation, a saturation pulse can be applied in the same heart-beat with the longest possible saturation time(115) or it is required to wait different heart-beats for fully magnetization recovery.(116)
The most suitable acquisition approach for 3D T1 mapping techniques is saturation recovery. Saturation pulses reset the magnetization before any experiment not requiring to wait until full magnetization recovery before a new saturation pulse. On the other hand, proton density signal is required for normalization and capturing this signal can take up to 25% of the acquisition time.(118) The main limitation with these techniques is the acquisition time that can last several minutes. These acquisition times limit the application of this technique particularly for post-contrast T1 maps due to dynamic wash out of the contrast.
There is very limited clinical experience with these techniques in MI. For T2 mapping techniques 3D sequenced show good agreement with 2D data in terms of estimated T2 values in healthy volunteers and acute ischemia reperfusion animal models.(115) For fast 3D T1 mapping techniques such as QALAS, some clinical examples were shown in the original study but in none of the works have evaluated the clinical performance of this techniques compared with more stablished 2D mapping techniques.

T1 and T1-rho

Native T1 mapping at 3T has been demonstrated to yield substantial improvement in image contrast, compared to native T1 mapping at 1.5T, towards accurate detection and characterization of chronic MI territories in large animal models of reperfused infarction.(119) Follow-up studies in STEMI and NSTEMI patients have reproduced the findings in animals, which show that compared to LGE, native T1 mapping have similar diagnostic performance (bias of < 1% of LV mass, sensitivity/specificity > 85%, and AUC above 95%).(120) Multi-center studies may provide the impetus to advance the approach toward clinical use, especially in those MI patients who are contraindicated for gadolinium-based contrast agents.

The T1-rho technique has also been proposed as an endogenous contrast to detect cardiac fibrosis. Although there is limited experience with T1-rho mechanism, it has been reported that T1-rho-weighted pulses on regular contrast enhanced cine images can improve the contrast between the acutely infarcted and remote myocardium after intra-venous contrast administration.(121) Native T1-rho maps have shown good agreement assessing the infarct size compare with LGE in a I/R swine model at 1 and 4 weeks.(122)

Perfusion mapping

Dynamic contrast CMR-enhanced CMR is a noninvasive imaging tool to evaluate myocardial perfusion. These studies acquire sequential saturation recovery images during the first pass of extracellular contrast media. The same experiment is acquired under rest and pharmacological stress conditions to evaluate myocardial perfusion reserve and to help differentiate artifacts from true perfusion defects.(123)
Semi-quantitative analysis based on contrast enhancement ratio(124,125) or upslope index(126,127) have been proposed to evaluate the difference between stress and rest conditions. However, these approaches systematically underestimate myocardial flow reserve (MFR) compared with fully quantitative methods.(128) Absolute quantification of myocardial blood flow (MBF) has been achieved with a dual-bolus contrast injection protocol(129) at the cost of complex contrast injection protocols.(130) In this protocol a first bolus of diluted contrast is injected followed by a second bolus of full contrast concentration. The Arterial Input Function (AIF) is estimated from the first bolus avoiding signal saturation due to high contrast concentration in the blood pool while conventional myocardial contrast enhancement is measured from the second bolus injection. To simplify patient preparation dual sequence techniques have been proposed to acquire the AIF. In this acquisition AIF information is captured from an additional low resolution image with very short saturation recovery time which reduces signal intensity saturation even under high contrast concentration in the blood pool.(131-133) One low resolution AIF image is acquired each heart beat followed by conventional high resolution images (longer saturation time) to evaluate the contrast uptake in the cardiac muscle. Such sequences can provide full quantitative data within less than two minutes and have been validated in patients against PET perfusion imaging.(134)
In addition to MBF estimation, quantitative techniques can also measure other physiological parameters as myocardial blood volume (MBV).(135) Although MBF and MBV are related, under dobutamine stress myocardial volume reserve (MVR) was able to distinguish between moderate and severe stenosis.(136) In addition, for equivalent MBF changes MBV was double for dobutamine stress compared with dipyridamole stress suggesting a better association of MBV with total myocardial oxygen demand.

Diffusion weighted and diffusion tensor imaging

Beyond the assessment of changes in MR relaxation times, reflecting alterations in tissue structure and composition,(137) diffusion weighted imaging (DWI) has been used to study microstructural changes of myocardial tissues in various pathologies. Early *ex-vivo* studies demonstrated that diffusion tensor imaging (DTI)(138,139) can reveal physiologically meaningful insights of the heart's microstructure (4-6) (138,140,141) Functional insights have been gained by studying the dynamics of myofiber configurations after arresting hearts in systole and diastole(142) Besides the ex-vivo and experimental in-vivo work in animals, DWI/DTI of the human heart in-vivo has successfully been implemented.(143,144)
The key technical challenge of *in-vivo* DWI/DTI relates to achieving sufficient sensitivity to diffusion of water molecules within the myocardium while, at the same time, avoiding image artefacts and signal cancellation due to bulk motion and strain of the cardiac muscle. Current approaches for imaging the *in-vivo* heart are either based on stimulated echo acquisition mode (STEAM) sequences(143) requiring two consecutive heart beats for a single diffusion encoding experiment or utilize spin-echo (SE) based diffusion encoding which allows single heart beat diffusion encoding.(145)

Oxygenation-Sensitive CMR

Oxygenation-sensitive CMR (OS-CMR) has emerged as a unique approach for monitoring changes of myocardial oxygenation without the use of contrast agents.(146) The approach is based on the known "BOLD (Blood-Oxygen-Level-Dependent) effect", i.e. the correlation of the T2* signal of tissue with blood oxygenation. Known for nearly 30 years, the application of OS-CMR to the heart has only slowly transitioned to the heart, given the technical challenges in imaging the heart while adequately sensitizing the CMR signals to oxygenation changes .(147) In OS-CMR, which typically employs T2*- or apparent T2-weighted protocols, the signal intensity is correlated with myocardial oxygenation. The technique has been applied to identify myocardial ischemia,(148) valvular disease, cardiomyopathies,(149) diabetes,(150) kidney disease(151) and hind-limb ischemia.
Recently, OS-CMR has been successfully used with breathing maneuvers or prospectively targeted alterations in arterial CO2 tension as a replacement for pharmacological vasodilator stress to assess coronary vascular function.(152) This approach has been validated in large animal models with flow-limiting(153) and non-flow limiting coronary stenoses. OS-CMR, particularly with breathing maneuvers has been shown to be clinically useful to detect regional and diffuse inducible oxygenation deficits in patients with coronary artery disease.(154) How this parameter changes within the infarct zone, salvaged myocardium, and remote myocardium following an acutely reperfused STEMI is not known, and would be interesting to investigate.

CMR spectroscopy

CMR spectroscopy (MRS) is the only non-invasive, non-radiation exposure technique for the investigation of cardiac metabolism in vivo providing comprehensive metabolic and biochemical information in reperfused post-infarction patients.(155) Such detailed pathophysiologic insights into the inter-relations among cardiac structure, function, perfusion and metabolism may be important in the near future to monitor patient responses to therapeutic interventions including pharmacologic, devices, or

interventional in patients with acute MI. However, this technology and expertise is currently not available in most centres.

CMR in clinical practice

CMR is already becoming an indispensable technique in the management of STEMI patients. In certain areas, such as the diagnosis and management of LV thrombi, the exact quantification of LVEF for evaluating qualification of patients for advanced therapies or for differential diagnosis of MI with non-obstructive coronary arteries (MINOCA), CMR has already become the reference technique. CMR is clinically useful not only in patients with STEMI(156,157), but also with NSTEMI.(158,159) Echocardiography is the standard of care cardiac imaging test in patients post-MI. However, it has some limitations, the main one being image quality, which is influenced by the availability of acoustic windows and the skill of the operator. When echocardiography is non-diagnostic, an alternative imaging test, such as CMR, is indicated and recommended by international guidelines.(157) CMR is an advanced cardiovascular imaging technology and access to CMR may be limited by logistics and costs. Some geographies have overcome this problem by providing access through regional networks of care.(160)

In STEMI patients, CMR is usually performed when the patient is stable and few days have passed since the acute episode. However, recent studies have shown that CMR can be safely performed in hemodynamically-stable patients at earlier timepoints following reperfusion therapy.(32,161)

CMR is useful in clinical practice to assess for myocardial viability, LVEF, LV thrombus, and mechanical complications following acute MI (ventricular rupture, ventricular septal defect, papillary muscle rupture leading to mitral regurgitation,..).(156-159) Greater local experience and availability as well as a decrease in scan times to roughly 30 minutes for a post-MI protocol significantly improved the practicability of CMR imaging.

CMR is diagnostically useful to identify patients with acute myocardial ischemia, and discriminate patients with recent MI from established, chronic MI.(158,159,162,163) Delineating the extent of myocardial edema is less straightforward in patients with recent NSTEMI and mapping methods are useful.(77,79) CMR aids clinical risk stratification of post-MI patients, and to this end, CMR-based risk scores have recently been developed.(164,165) Despite the demonstrated prognostic value of these scores, today they hold no definite implications in terms of management decision. CMR may reveal MI when coronary angiography is not diagnostic(158,159,166) and is also useful to identify incidental cardiac and non-cardiac problems.(156,157,167)

CMR has also the ability to assess the presence and extent of ischemic mitral regurgitation (MR) with phase contrast imaging, as well as the presence of papillary muscles infarction with the LGE technique. CMR is an accurate and reproducible method to quantify MR regardless of the jet(s) morphology or the presence of multiple valve lesions.(168,169) Studies indicate that CMR is more accurate than echocardiography in assessing the severity of MR with only modest agreement between the two modalities and with CMR better predicting post-surgical LV remodeling and outcome than echocardiography.(170)

Papillary muscles infarction is more frequently associated with infarction in the right and circumflex coronary artery and not necessarily associated with mitral regurgitation.(171) Although the prevalence of chronic ischemic mitral regurgitation is almost doubled in the presence of infarcted papillary muscles, the latter is not an independent predictor of chronic ischemic mitral regurgitation.(172)

CMR is diagnostically useful in patients who present with an acute MI and coronary angiography rules out obstructive coronary artery disease (i.e. MI with non-obstructive coronary arteries (MINOCA).(158,159) Accurate diagnosis is not only important for prognostic estimates but also to guide therapeutic considerations in these cases. Multiparametric CMR may yield information to rule-in or rule out an acute cardiomyopathy, Takotsubo syndrome, or myopericarditis. (158,159) A systematic review showed that CMR imaging reveals a final diagnosis in at least three-quarter of MINOCA patients, thus underscoring the diagnostic performance of CMR.(173)

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References

1. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977;56:786-94.
2. Reimer KA, Jennings RB, Tatum AH. Pathobiology of acute myocardial ischemia: metabolic, functional and ultrastructural studies. The American journal of cardiology 1983;52:72A-81A.
3. Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving Therapies for Myocardial Ischemia/Reperfusion Injury. J Am Coll Cardiol 2015;65:1454-1471.
4. Kim RJ, Fieno DS, Parrish TB et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992-2002.
5. Prabhu SD, Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis. Circ Res 2016;119:91-112.
6. Montecucco F, Carbone F, Schindler TH. Pathophysiology of ST-segment elevation myocardial infarction: novel mechanisms and treatments. Eur Heart J 2016;37:1268-83.
7. Lecour S, Botker HE, Condorelli G et al. ESC working group cellular biology of the heart: position paper: improving the preclinical assessment of novel cardioprotective therapies. Cardiovasc Res 2014;104:399-411.
8. Schaper W, Flameng W, Winkler B et al. Quantification of collateral resistance in acute and chronic experimental coronary occlusion in the dog. Circ Res 1976;39:371-7.
9. Sjoquist PO, Duker G, Almgren O. Distribution of the collateral blood flow at the lateral border of the ischemic myocardium after acute coronary occlusion in the pig and the dog. Basic Res Cardiol 1984;79:164-75.
10. Schaper W, Binz K, Sass S, Winkler B. Influence of collateral blood flow and of variations in MVO2 on tissue-ATP content in ischemic and infarcted myocardium. J Mol Cell Cardiol 1987;19:19-37.
11. Garcia-Dorado D, Theroux P, Elizaga J et al. Myocardial reperfusion in the pig heart model: infarct size and duration of coronary occlusion. Cardiovasc Res 1987;21:537-44.
12. Hedstrom E, Engblom H, Frogner F et al. Infarct evolution in man studied in patients with first-time coronary occlusion in comparison to different species - implications for assessment of myocardial salvage. J Cardiovasc Magn Reson 2009;11:38.
13. Gensini GG, Bruto da Costa BC. The coronary collateral circulation in living man. Am J Cardiol 1969;24:393-400.
14. Lobo M, Ibanez B. Take a deep (nitric oxide) breath and follow the reverse translational research pathway. Eur Heart J 2018.
15. Botker HE, Hausenloy D, Andreadou I et al. Practical guidelines for rigor and reproducibility in preclinical and clinical studies on cardioprotection. Basic Res Cardiol 2018;113:39.
16. Vilahur G, Gutierrez M, Casani L et al. Protective Effects of Ticagrelor on Myocardial Injury After Infarction. Circulation 2016;134:1708-1719.

17. Fernandez-Jimenez R, Ibanez B. CAESAR: One Step Beyond in the Construction of a Translational Bridge for Cardioprotection. Circ Res 2015;116:554-6.
18. Amado LC, Gerber BL, Gupta SN et al. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a canine myocardial infarction model. J Am Coll Cardiol 2004;44:2383-9.
19. Flett AS, Hasleton J, Cook C et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovasc Imaging 2011;4:150-6.
20. Bondarenko O, Beek AM, Hofman MB et al. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. J Cardiovasc Magn Reson 2005;7:481-5.
21. McAlindon E, Pufulete M, Lawton C, Angelini GD, Bucciarelli-Ducci C. Quantification of infarct size and myocardium at risk: evaluation of different techniques and its implications. Eur Heart J Cardiovasc Imaging 2015;16:738-46.
22. Vermes E, Childs H, Carbone I, Barckow P, Friedrich MG. Auto-threshold quantification of late gadolinium enhancement in patients with acute heart disease. J Magn Reson Imaging 2013;37:382-90.
23. Khan JN, Nazir SA, Horsfield MA et al. Comparison of semi-automated methods to quantify infarct size and area at risk by cardiovascular magnetic resonance imaging at 1.5T and 3.0T field strengths. BMC Res Notes 2015;8:52.
24. Engblom H, Tufvesson J, Jablonowski R et al. A new automatic algorithm for quantification of myocardial infarction imaged by late gadolinium enhancement cardiovascular magnetic resonance: experimental validation and comparison to expert delineations in multi-center, multi-vendor patient data. J Cardiovasc Magn Reson 2016;18:27.
25. Beek AM, Bondarenko O, Afsharzada F, van Rossum AC. Quantification of late gadolinium enhanced CMR in viability assessment in chronic ischemic heart disease: a comparison to functional outcome. J Cardiovasc Magn Reson 2009;11:6.
26. Klem I, Heiberg E, Van Assche L et al. Sources of variability in quantification of cardiovascular magnetic resonance infarct size - reproducibility among three core laboratories. J Cardiovasc Magn Reson 2017;19:62.
27. Zhou X, Rundell V, Liu Y et al. T(2) -weighted STIR imaging of myocardial edema associated with ischemia-reperfusion injury: the influence of proton density effect on image contrast. J Magn Reson Imaging 2011;33:962-7.
28. Francone M, Bucciarelli-Ducci C, Carbone I et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. J Am Coll Cardiol 2009;54:2145-53.
29. Raman SV, Simonetti OP, Winner MW, 3rd et al. Cardiac magnetic resonance with edema imaging identifies myocardium at risk and predicts worse outcome in patients with non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 2010;55:2480-8.
30. Eitel I, Desch S, Fuernau G et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. J Am Coll Cardiol 2010;55:2470-9.

31. Kim HW, Van Assche L, Jennings RB et al. Relationship of T2-Weighted MRI Myocardial Hyperintensity and the Ischemic Area-At-Risk. Circ Res 2015;117:254-65.
32. Fernandez-Jimenez R, Barreiro-Perez M, Martin-Garcia A et al. Dynamic Edematous Response of the Human Heart to Myocardial Infarction: Implications for Assessing Myocardial Area at Risk and Salvage. Circulation 2017;136:1288-1300.
33. Fernandez-Jimenez R, Garcia-Prieto J, Sanchez-Gonzalez J et al. Pathophysiology Underlying the Bimodal Edema Phenomenon After Myocardial Ischemia/Reperfusion. J Am Coll Cardiol 2015;66:816-828.
34. Fernandez-Jimenez R, Sanchez-Gonzalez J, Aguero J et al. Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: imaging and histological tissue characterization. J Am Coll Cardiol 2015;65:315-323.
35. Kellman P, Aletras AH, Mancini C, McVeigh ER, Arai AE. T2-prepared SSFP improves diagnostic confidence in edema imaging in acute myocardial infarction compared to turbo spin echo. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2007;57:891-7.
36. Payne AR, Casey M, McClure J et al. Bright-blood T2-weighted MRI has higher diagnostic accuracy than dark-blood short tau inversion recovery MRI for detection of acute myocardial infarction and for assessment of the ischemic area at risk and myocardial salvage. Circ Cardiovasc Imaging 2011

4:210-9.
37. Shea SM, Deshpande VS, Chung YC, Li D. Three-dimensional true-FISP imaging of the coronary arteries: improved contrast with T2-preparation. J Magn Reson Imaging 2002;15:597-602.
38. Aletras AH, Kellman P, Derbyshire JA, Arai AE. ACUT2E TSE-SSFP: a hybrid method for T2-weighted imaging of edema in the heart. Magn Reson Med 2008;59:229-35.
39. Fernandez-Jimenez R, Sanchez-Gonzalez J, Aguero J et al. Fast T2 gradient-spin-echo (T2-GraSE) mapping for myocardial edema quantification: first in vivo validation in a porcine model of ischemia/reperfusion. J Cardiovasc Magn Reson 2015;17:92.
40. Giri S, Chung YC, Merchant A et al. T2 quantification for improved detection of myocardial edema. J Cardiovasc Magn Reson 2009;11:56.
41. Verhaert D, Thavendiranathan P, Giri S et al. Direct T2 quantification of myocardial edema in acute ischemic injury. JACC Cardiovasc Imaging 2011

4:269-78.
42. Baessler B, Schaarschmidt F, Stehning C, Schnackenburg B, Maintz D, Bunck AC. Cardiac T2-mapping using a fast gradient echo spin echo sequence - first in vitro and in vivo experience. J Cardiovasc Magn Reson 2015;17:67.
43. Messroghli DR, Moon JC, Ferreira VM et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19:75.
44. Roujol S, Basha TA, Weingartner S et al. Impact of motion correction on reproducibility and spatial variability of quantitative myocardial T2 mapping. J Cardiovasc Magn Reson 2015;17:46.

45. Giri S, Shah S, Xue H et al. Myocardial T(2) mapping with respiratory navigator and automatic nonrigid motion correction. Magn Reson Med 2012;68:1570-8.
46. Yang HJ, Sharif B, Pang J et al. Free-breathing, motion-corrected, highly efficient whole heart T2 mapping at 3T with hybrid radial-cartesian trajectory. Magn Reson Med 2016;75:126-36.
47. Bonner F, Janzarik N, Jacoby C et al. Myocardial T2 mapping reveals age- and sex-related differences in volunteers. J Cardiovasc Magn Reson 2015;17:9.
48. von Knobelsdorff-Brenkenhoff F, Prothmann M, Dieringer MA et al. Myocardial T1 and T2 mapping at 3 T: reference values, influencing factors and implications. J Cardiovasc Magn Reson 2013;15:53.
49. Rauhalammi SM, Mangion K, Barrientos PH et al. Native myocardial longitudinal (T1) relaxation time: Regional, age, and sex associations in the healthy adult heart. J Magn Reson Imaging 2016;44:541-8.
50. Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. Magn Reson Med 2004;52:141-6.
51. Piechnik SK, Ferreira VM, Lewandowski AJ et al. Normal variation of magnetic resonance T1 relaxation times in the human population at 1.5 T using ShMOLLI. J Cardiovasc Magn Reson 2013;15:13.
52. Chow K, Flewitt JA, Green JD, Pagano JJ, Friedrich MG, Thompson RB. Saturation recovery single-shot acquisition (SASHA) for myocardial T(1) mapping. Magn Reson Med 2014;71:2082-95.
53. Viallon M, Mewton N, Thuny F et al. T2-weighted cardiac MR assessment of the myocardial area-at-risk and salvage area in acute reperfused myocardial infarction: comparison of state-of-the-art dark blood and bright blood T2-weighted sequences. J Magn Reson Imaging 2012;35:328-39.
54. Ferreira VM, Piechnik SK, Dall'Armellina E et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012;14:42.
55. Nordlund D, Klug G, Heiberg E et al. Multi-vendor, multicentre comparison of contrast-enhanced SSFP and T2-STIR CMR for determining myocardium at risk in ST-elevation myocardial infarction. Eur Heart J Cardiovasc Imaging 2016;17:744-53.
56. Hammer-Hansen S, Leung SW, Hsu LY et al. Early Gadolinium Enhancement for Determination of Area at Risk: A Preclinical Validation Study. JACC Cardiovasc Imaging 2017;10:130-139.
57. McAlindon EJ, Pufulete M, Harris JM et al. Measurement of myocardium at risk with cardiovascular MR: comparison of techniques for edema imaging. Radiology 2015;275:61-70.
58. Berry C, Kellman P, Mancini C et al. Magnetic resonance imaging delineates the ischemic area at risk and myocardial salvage in patients with acute myocardial infarction. Circ Cardiovasc Imaging 2010;3:527-35.
59. Whalen DA, Jr., Hamilton DG, Ganote CE, Jennings RB. Effect of a transient period of ischemia on myocardial cells. I. Effects on cell volume regulation. The American journal of pathology 1974;74:381-97.
60. Jennings RB. Historical perspective on the pathology of myocardial ischemia/reperfusion injury. Circ Res 2013;113:428-38.

61. Jennings RB, Schaper J, Hill ML, Steenbergen C, Jr., Reimer KA. Effect of reperfusion late in the phase of reversible ischemic injury. Changes in cell volume, electrolytes, metabolites, and ultrastructure. Circ Res 1985;56:262-78.
62. Garcia-Dorado D, Oliveras J. Myocardial oedema: a preventable cause of reperfusion injury? Cardiovasc Res 1993;27:1555-63.
63. Aletras AH, Tilak GS, Natanzon A et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. Circulation 2006;113:1865-70.
64. Dongworth RK, Campbell-Washburn AE, Cabrera-Fuentes HA et al. Quantifying the area-at-risk of myocardial infarction in-vivo using arterial spin labeling cardiac magnetic resonance. Sci Rep 2017;7:2271.
65. Wright J, Adriaenssens T, Dymarkowski S, Desmet W, Bogaert J. Quantification of myocardial area at risk with T2-weighted CMR: comparison with contrast-enhanced CMR and coronary angiography. JACC Cardiovascular imaging 2009;2:825-31.
66. Carlsson M, Ubachs JF, Hedstrom E, Heiberg E, Jovinge S, Arheden H. Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography. JACC Cardiovascular imaging 2009;2:569-76.
67. Ubachs JF, Engblom H, Erlinge D et al. Cardiovascular magnetic resonance of the myocardium at risk in acute reperfused myocardial infarction: comparison of T2-weighted imaging versus the circumferential endocardial extent of late gadolinium enhancement with transmural projection. J Cardiovasc Magn Reson 2010;12:18.
68. Kumar A, Beohar N, Arumana JM et al. CMR imaging of edema in myocardial infarction using cine balanced steady-state free precession. JACC Cardiovascular imaging 2011;4:1265-73.
69. Nordlund D, Heiberg E, Carlsson M et al. Extent of Myocardium at Risk for Left Anterior Descending Artery, Right Coronary Artery, and Left Circumflex Artery Occlusion Depicted by Contrast-Enhanced Steady State Free Precession and T2-Weighted Short Tau Inversion Recovery Magnetic Resonance Imaging. Circ Cardiovasc Imaging 2016;9.
70. Ugander M, Bagi PS, Oki AJ et al. Myocardial edema as detected by pre-contrast T1 and T2 CMR delineates area at risk associated with acute myocardial infarction. JACC Cardiovasc Imaging 2012;5:596-603.
71. Bulluck H, White SK, Rosmini S et al. T1 mapping and T2 mapping at 3T for quantifying the area-at-risk in reperfused STEMI patients. J Cardiovasc Magn Reson 2015;17:73.
72. Mewton N, Rapacchi S, Augeul L et al. Determination of the myocardial area at risk with pre- versus post-reperfusion imaging techniques in the pig model. Basic Res Cardiol 2011;106:1247-57.
73. Hammer-Hansen S, Ugander M, Hsu LY et al. Distinction of salvaged and infarcted myocardium within the ischaemic area-at-risk with T2 mapping. Eur Heart J Cardiovasc Imaging 2014;15:1048-53.
74. Naruse S, Horikawa Y, Tanaka C, Hirakawa K, Nishikawa H, Yoshizaki K. Proton nuclear magnetic resonance studies on brain edema. J Neurosurg 1982;56:747-52.

75. Brown JJ, Peck WW, Gerber KH, Higgins CB, Strich G, Slutsky RA. Nuclear magnetic resonance analysis of acute and chronic myocardial infarction in dogs: alterations in spin-lattice relaxation times. Am Heart J 1984;108:1292-7.
76. Lin W, Paczynski RP, Venkatesan R et al. Quantitative regional brain water measurement with magnetic resonance imaging in a focal ischemia model. Magn Reson Med 1997;38:303-10.
77. Dall'Armellina E, Piechnik SK, Ferreira VM et al. Cardiovascular magnetic resonance by non contrast T1-mapping allows assessment of severity of injury in acute myocardial infarction. J Cardiovasc Magn Reson 2012;14:15.
78. Langhans B, Nadjiri J, Jahnichen C, Kastrati A, Martinoff S, Hadamitzky M. Reproducibility of area at risk assessment in acute myocardial infarction by T1- and T2-mapping sequences in cardiac magnetic resonance imaging in comparison to Tc99m-sestamibi SPECT. Int J Cardiovasc Imaging 2014;30:1357-63.
79. Layland J, Rauhalammi S, Lee MM et al. Diagnostic Accuracy of 3.0-T Magnetic Resonance T1 and T2 Mapping and T2-Weighted Dark-Blood Imaging for the Infarct-Related Coronary Artery in Non-ST-Segment Elevation Myocardial Infarction. Journal of the American Heart Association 2017;6.
80. van der Pals J, Hammer-Hansen S, Nielles-Vallespin S et al. Temporal and spatial characteristics of the area at risk investigated using computed tomography and T1-weighted magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2015;16:1232-40.
81. Sorensson P, Heiberg E, Saleh N et al. Assessment of myocardium at risk with contrast enhanced steady-state free precession cine cardiovascular magnetic resonance compared to single-photon emission computed tomography. J Cardiovasc Magn Reson 2010;12:25.
82. Nordlund D, Kanski M, Jablonowski R et al. Experimental validation of contrast-enhanced SSFP cine CMR for quantification of myocardium at risk in acute myocardial infarction. J Cardiovasc Magn Reson 2017;19:12.
83. Ubachs JF, Sorensson P, Engblom H et al. Myocardium at risk by magnetic resonance imaging: head-to-head comparison of T2-weighted imaging and contrast-enhanced steady-state free precession. Eur Heart J Cardiovasc Imaging 2012;13:1008-15.
84. Zhou X, Rundell V, Liu Y et al. On the mechanisms enabling myocardial edema contrast in bSSFP-based imaging approaches. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2011;66:187-91.
85. Arheden H, Saeed M, Higgins CB et al. Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with 99mTc-DTPA autoradiography in rats. Radiology 1999;211:698-708.
86. Arheden H, Saeed M, Higgins CB et al. Reperfused rat myocardium subjected to various durations of ischemia: estimation of the distribution volume of contrast material with echo-planar MR imaging. Radiology 2000;215:520-8.
87. Jablonowski R, Engblom H, Kanski M et al. Contrast-Enhanced CMR Overestimates Early Myocardial Infarct Size: Mechanistic Insights Using ECV Measurements on Day 1 and Day 7. JACC Cardiovasc Imaging 2015;8:1379-1389.
88. Hammer-Hansen S, Bandettini WP, Hsu LY et al. Mechanisms for overestimating acute myocardial infarct size with gadolinium-enhanced

cardiovascular magnetic resonance imaging in humans: a quantitative and kinetic study. Eur Heart J Cardiovasc Imaging 2016;17:76-84.
89. Ortiz-Perez JT, Meyers SN, Lee DC et al. Angiographic estimates of myocardium at risk during acute myocardial infarction: validation study using cardiac magnetic resonance imaging. Eur Heart J 2007;28:1750-8.
90. Versteylen MO, Bekkers SC, Smulders MW et al. Performance of angiographic, electrocardiographic and MRI methods to assess the area at risk in acute myocardial infarction. Heart 2012;98:109-15.
91. Fuernau G, Eitel I, Franke V et al. Myocardium at risk in ST-segment elevation myocardial infarction comparison of T2-weighted edema imaging with the MR-assessed endocardial surface area and validation against angiographic scoring. JACC Cardiovasc Imaging 2011;4:967-76.
92. Lonborg J, Engstrom T, Mathiasen AB, Vejlstrup N. Myocardial area at risk after ST-elevation myocardial infarction measured with the late gadolinium enhancement after scar remodeling and T2-weighted cardiac magnetic resonance imaging. Int J Cardiovasc Imaging 2011.
93. Baessler B, Schaarschmidt F, Stehning C et al. Reproducibility of three different cardiac T2 -mapping sequences at 1.5T. J Magn Reson Imaging 2016;44:1168-1178.
94. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. J Cardiovasc Magn Reson 2012;14:63.
95. Kellman P, Arai AE, Xue H. T1 and extracellular volume mapping in the heart: estimation of error maps and the influence of noise on precision. J Cardiovasc Magn Reson 2013;15:56.
96. Kellman P, Hansen MS. T1-mapping in the heart: accuracy and precision. J Cardiovasc Magn Reson 2014;16:2.
97. Fernandez-Jimenez R, Galan-Arriola C, Sanchez-Gonzalez J et al. Effect of Ischemia Duration and Protective Interventions on the Temporal Dynamics of Tissue Composition After Myocardial Infarction. Circ Res 2017;121:439-450.
98. White SK, Frohlich GM, Sado DM et al. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2015;8:178-88.
99. Thuny F, Lairez O, Roubille F et al. Post-Conditioning Reduces Infarct Size and Edema in Patients With ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol 2012;59:2175-81.
100. Ibrahim T, Hackl T, Nekolla SG et al. Acute myocardial infarction: serial cardiac MR imaging shows a decrease in delayed enhancement of the myocardium during the 1st week after reperfusion. Radiology 2010;254:88-97.
101. Engblom H, Hedstrom E, Heiberg E, Wagner GS, Pahlm O, Arheden H. Rapid initial reduction of hyperenhanced myocardium after reperfused first myocardial infarction suggests recovery of the peri-infarction zone: one-year follow-up by MRI. Circ Cardiovasc Imaging 2009;2:47-55.
102. Shetye AM, Nazir SA, Razvi NA et al. Comparison of global myocardial strain assessed by cardiovascular magnetic resonance tagging and feature tracking to infarct size at predicting remodelling following STEMI. BMC Cardiovasc Disord 2017;17:7.
103. Garg P, Kidambi A, Swoboda PP et al. The role of left ventricular deformation in the assessment of microvascular obstruction and intramyocardial haemorrhage. Int J Cardiovasc Imaging 2017;33:361-370.

104. Gavara J, Rodriguez-Palomares JF, Valente F et al. Prognostic Value of Strain by Tissue Tracking Cardiac Magnetic Resonance After ST-Segment Elevation Myocardial Infarction. JACC Cardiovasc Imaging 2018;11:1448-1457.
105. Yoon YE, Kang SH, Choi HM et al. Prediction of infarct size and adverse cardiac outcomes by tissue tracking-cardiac magnetic resonance imaging in ST-segment elevation myocardial infarction. Eur Radiol 2018.
106. Eitel I, Stiermaier T, Lange T et al. Cardiac Magnetic Resonance Myocardial Feature Tracking for Optimized Prediction of Cardiovascular Events Following Myocardial Infarction. JACC Cardiovasc Imaging 2018.
107. Podlesnikar T, Pizarro G, Fernandez-Jimenez R et al. Effect of Early Metoprolol During ST-Segment Elevation Myocardial Infarction on Left Ventricular Strain: Feature-Tracking Cardiovascular Magnetic Resonance Substudy From the METOCARD-CNIC trial. JACC Cardiovasc Imaging 2018.
108. Neizel M, Lossnitzer D, Korosoglou G et al. Strain-encoded (SENC) magnetic resonance imaging to evaluate regional heterogeneity of myocardial strain in healthy volunteers: Comparison with conventional tagging. J Magn Reson Imaging 2009;29:99-105.
109. Aletras AH, Ding S, Balaban RS, Wen H. DENSE: displacement encoding with stimulated echoes in cardiac functional MRI. J Magn Reson 1999;137:247-52.
110. Mangion K, Carrick D, Carberry J et al. Circumferential Strain Predicts Major Adverse Cardiovascular Events Following an Acute ST-Segment-Elevation Myocardial Infarction. Radiology 2018:181253.
111. Kim HW, Rehwald WG, Jenista ER et al. Dark-Blood Delayed Enhancement Cardiac Magnetic Resonance of Myocardial Infarction. JACC Cardiovasc Imaging 2018;11:1758-69.
112. Kellman P, Xue H, Olivieri LJ et al. Dark blood late enhancement imaging. J Cardiovasc Magn Reson 2016;18:77.
113. Francis R, Kellman P, Kotecha T et al. Prospective comparison of novel dark blood late gadolinium enhancement with conventional bright blood imaging for the detection of scar. J Cardiovasc Magn Reson 2017;19:91.
114. Fahmy AS, Neisius U, Tsao CW et al. Gray blood late gadolinium enhancement cardiovascular magnetic resonance for improved detection of myocardial scar. J Cardiovasc Magn Reson 2018;20:22.
115. Ding H, Fernandez-de-Manuel L, Schar M et al. Three-dimensional whole-heart T2 mapping at 3T. Magn Reson Med 2015;74:803-16.
116. van Heeswijk RB, Piccini D, Feliciano H, Hullin R, Schwitter J, Stuber M. Self-navigated isotropic three-dimensional cardiac T2 mapping. Magn Reson Med 2015;73:1549-54.
117. Kvernby S, Warntjes MJ, Haraldsson H, Carlhall CJ, Engvall J, Ebbers T. Simultaneous three-dimensional myocardial T1 and T2 mapping in one breath hold with 3D-QALAS. J Cardiovasc Magn Reson 2014;16:102.
118. Nordio G, Henningsson M, Chiribiri A, Villa ADM, Schneider T, Botnar RM. 3D myocardial T1 mapping using saturation recovery. J Magn Reson Imaging 2017;46:218-227.
119. Kali A, Cokic I, Tang RL et al. Determination of location, size, and transmurality of chronic myocardial infarction without exogenous contrast media by using cardiac magnetic resonance imaging at 3 T. Circ Cardiovasc Imaging 2014;7:471-81.

120. Kali A, Choi EY, Sharif B et al. Native T1 Mapping by 3-T CMR Imaging for Characterization of Chronic Myocardial Infarctions. JACC Cardiovasc Imaging 2015;8:1019-1030.
121. Muthupillai R, Flamm SD, Wilson JM, Pettigrew RI, Dixon WT. Acute myocardial infarction: tissue characterization with T1rho-weighted MR imaging--initial experience. Radiology 2004;232:606-10.
122. Stoffers RH, Madden M, Shahid M et al. Assessment of myocardial injury after reperfused infarction by T1rho cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2017;19:17.
123. Klem I, Heitner JF, Shah DJ et al. Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. J Am Coll Cardiol 2006;47:1630-8.
124. Wilke N, Simm C, Zhang J et al. Contrast-enhanced first pass myocardial perfusion imaging: correlation between myocardial blood flow in dogs at rest and during hyperemia. Magn Reson Med 1993;29:485-97.
125. Kraitchman DL, Wilke N, Hexeberg E et al. Myocardial perfusion and function in dogs with moderate coronary stenosis. Magn Reson Med 1996;35:771-80.
126. Al-Saadi N, Nagel E, Gross M et al. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. Circulation 2000;101:1379-83.
127. Nagel E, Klein C, Paetsch I et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. Circulation 2003;108:432-7.
128. Hsu LY, Rhoads KL, Holly JE, Kellman P, Aletras AH, Arai AE. Quantitative myocardial perfusion analysis with a dual-bolus contrast-enhanced first-pass MRI technique in humans. J Magn Reson Imaging 2006;23:315-22.
129. Christian TF, Rettmann DW, Aletras AH et al. Absolute myocardial perfusion in canines measured by using dual-bolus first-pass MR imaging. Radiology 2004;232:677-84.
130. Ishida M, Schuster A, Morton G et al. Development of a universal dual-bolus injection scheme for the quantitative assessment of myocardial perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2011;13:28.
131. Kellman P, Hansen MS, Nielles-Vallespin S et al. Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. J Cardiovasc Magn Reson 2017;19:43.
132. Gatehouse PD, Elkington AG, Ablitt NA, Yang GZ, Pennell DJ, Firmin DN. Accurate assessment of the arterial input function during high-dose myocardial perfusion cardiovascular magnetic resonance. J Magn Reson Imaging 2004;20:39-45.
133. Sanchez-Gonzalez J, Fernandez-Jimenez R, Nothnagel ND, Lopez-Martin G, Fuster V, Ibanez B. Optimization of dual-saturation single bolus acquisition for quantitative cardiac perfusion and myocardial blood flow maps. J Cardiovasc Magn Reson 2015;17:21.
134. Engblom H, Xue H, Akil S et al. Fully quantitative cardiovascular magnetic resonance myocardial perfusion ready for clinical use: a comparison between cardiovascular magnetic resonance imaging and positron emission tomography. J Cardiovasc Magn Reson 2017;19:78.
135. Wilke N, Kroll K, Merkle H et al. Regional myocardial blood volume and flow: first-pass MR imaging with polylysine-Gd-DTPA. J Magn Reson Imaging 1995;5:227-37.

136. McCommis KS, Goldstein TA, Abendschein DR et al. Roles of myocardial blood volume and flow in coronary artery disease: an experimental MRI study at rest and during hyperemia. Eur Radiol 2010;20:2005-12.
137. Bull S, White SK, Piechnik SK et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart 2013;99:932-7.
138. Helm PA, Tseng HJ, Younes L, McVeigh ER, Winslow RL. Ex vivo 3D diffusion tensor imaging and quantification of cardiac laminar structure. Magn Reson Med 2005;54:850-9.
139. Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. J Magn Reson B 1994;103:247-54.
140. Schmid P, Jaermann T, Boesiger P et al. Ventricular myocardial architecture as visualised in postmortem swine hearts using magnetic resonance diffusion tensor imaging. Eur J Cardiothorac Surg 2005;27:468-72.
141. Strijkers GJ, Bouts A, Blankesteijn WM et al. Diffusion tensor imaging of left ventricular remodeling in response to myocardial infarction in the mouse. NMR Biomed 2009;22:182-90.
142. Chen J, Liu W, Zhang H et al. Regional ventricular wall thickening reflects changes in cardiac fiber and sheet structure during contraction: quantification with diffusion tensor MRI. Am J Physiol Heart Circ Physiol 2005;289:H1898-907.
143. Reese TG, Weisskoff RM, Smith RN, Rosen BR, Dinsmore RE, Wedeen VJ. Imaging myocardial fiber architecture in vivo with magnetic resonance. Magn Reson Med 1995;34:786-91.
144. Wu MT, Su MY, Huang YL et al. Sequential changes of myocardial microstructure in patients postmyocardial infarction by diffusion-tensor cardiac MR: correlation with left ventricular structure and function. Circ Cardiovasc Imaging 2009;2:32-40, 6 p following 40.
145. Gamper U, Boesiger P, Kozerke S. Diffusion imaging of the in vivo heart using spin echoes--considerations on bulk motion sensitivity. Magn Reson Med 2007;57:331-7.
146. Friedrich MG, Karamitsos TD. Oxygenation-sensitive cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2013;15:43.
147. Bauer WR, Nadler W, Bock M et al. The relationship between the BOLD-induced T(2) and T(2)(*): a theoretical approach for the vasculature of myocardium. Magn Reson Med 1999;42:1004-10.
148. Wacker CM, Bock M, Hartlep AW et al. BOLD-MRI in ten patients with coronary artery disease: evidence for imaging of capillary recruitment in myocardium supplied by the stenotic artery. Magma (New York, NY 1999;8:48-54.
149. Karamitsos TD, Dass S, Suttie J et al. Blunted myocardial oxygenation response during vasodilator stress in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;61:1169-76.
150. Levelt E, Rodgers CT, Clarke WT et al. Cardiac energetics, oxygenation, and perfusion during increased workload in patients with type 2 diabetes mellitus. Eur Heart J 2016;37:3461-3469.
151. Parnham S, Gleadle JM, Bangalore S et al. Impaired Myocardial Oxygenation Response to Stress in Patients With Chronic Kidney Disease. Journal of the American Heart Association 2015;4:e002249.

152. Fischer K, Guensch DP, Friedrich MG. Response of myocardial oxygenation to breathing manoeuvres and adenosine infusion. Eur Heart J Cardiovasc Imaging 2015;16:395-401.
153. Fischer K, Guensch DP, Shie N, Lebel J, Friedrich MG. Breathing Maneuvers as a Vasoactive Stimulus for Detecting Inducible Myocardial Ischemia - An Experimental Cardiovascular Magnetic Resonance Study. PLoS One 2016;11:e0164524.
154. Huber AT, Bravetti M, Lamy J et al. Non-invasive differentiation of idiopathic inflammatory myopathy with cardiac involvement from acute viral myocarditis using cardiovascular magnetic resonance imaging T1 and T2 mapping. J Cardiovasc Magn Reson 2018;20:11.
155. Hudsmith LE, Neubauer S. Magnetic resonance spectroscopy in myocardial disease. JACC Cardiovasc Imaging 2009;2:87-96.
156. American College of Emergency P, Society for Cardiovascular A, Interventions et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-140.
157. Ibanez B, James S, Agewall S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-177.
158. Amsterdam EA, Wenger NK, Brindis RG et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139-228.
159. Roffi M, Patrono C, Collet JP et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.
160. Menacho K, Ramirez S, Segura P et al. INCA (Peru) Study: Impact of Non-Invasive Cardiac Magnetic Resonance Assessment in the Developing World. Journal of the American Heart Association 2018;7:e008981.
161. Carrick D, Haig C, Ahmed N et al. Temporal Evolution of Myocardial Hemorrhage and Edema in Patients After Acute ST-Segment Elevation Myocardial Infarction: Pathophysiological Insights and Clinical Implications. Journal of the American Heart Association 2016;5.
162. Kwong RY, Schussheim AE, Rekhraj S et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. Circulation 2003;107:531-7.
163. Cury RC, Shash K, Nagurney JT et al. Cardiac magnetic resonance with T2-weighted imaging improves detection of patients with acute coronary syndrome in the emergency department. Circulation 2008;118:837-44.
164. Pontone G, Guaricci AI, Andreini D et al. Prognostic Stratification of Patients With ST-Segment-Elevation Myocardial Infarction (PROSPECT): A Cardiac Magnetic Resonance Study. Circ Cardiovasc Imaging 2017;10.

165. Stiermaier T, Jobs A, de Waha S et al. Optimized Prognosis Assessment in ST-Segment-Elevation Myocardial Infarction Using a Cardiac Magnetic Resonance Imaging Risk Score. Circ Cardiovasc Imaging 2017;10.
166. Moon JC, Oldershaw PJ, Pennell DJ. Microvascular obstruction and missed infarction. Heart 2002;88:330.
167. McGeoch RJ, Payne AR, Woodward R et al. Diagnostic utility of cardiac magnetic resonance imaging in STEMI survivors after emergency PCI. Int J Cardiol 2013;168:2933-4.
168. Uretsky S, Argulian E, Narula J, Wolff SD. Use of Cardiac Magnetic Resonance Imaging in Assessing Mitral Regurgitation: Current Evidence. J Am Coll Cardiol 2018;71:547-563.
169. Penicka M, Vecera J, Mirica DC, Kotrc M, Kockova R, Van Camp G. Prognostic Implications of Magnetic Resonance-Derived Quantification in Asymptomatic Patients With Organic Mitral Regurgitation: Comparison With Doppler Echocardiography-Derived Integrative Approach. Circulation 2018;137:1349-1360.
170. Uretsky S, Gillam L, Lang R et al. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial. J Am Coll Cardiol 2015;65:1078-88.
171. Tanimoto T, Imanishi T, Kitabata H et al. Prevalence and clinical significance of papillary muscle infarction detected by late gadolinium-enhanced magnetic resonance imaging in patients with ST-segment elevation myocardial infarction. Circulation 2010;122:2281-7.
172. Bouma W, Willemsen HM, Lexis CP et al. Chronic ischemic mitral regurgitation and papillary muscle infarction detected by late gadolinium-enhanced cardiac magnetic resonance imaging in patients with ST-segment elevation myocardial infarction. Clin Res Cardiol 2016;105:981-991.
173. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015;131:861-70.