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Cardiac MRI Anatomy and Function as a Substrate for Arrhythmias

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Cardiovascular Magnetic Resonance (CMR) is a multi-parametric non-invasive imaging technique with high spatial and good temporal resolution. By providing accurate assessment of ventricular volumes and function (1)(2) and precise in vivo tissue characterization (3)(4)(5)(6), the use of CMR has been implemented in the diagnostic and prognostic work-up of patients with cardiomyopathies (7)(8)(9)(10) (11)(12)(13).

Ventricular arrhythmias are the major cause of sudden cardiac death (14), which often represents the first manifestation of an underlying disease. CMR has recently emerged as a powerful tool to better identify the substrate for fatal arrhythmias, showing to be superior to non-CMR imaging techniques (15).

Cardiovascular Magnetic Resonance for Tissue Damage

CMR has the ability to provide non-invasive tissue characterisation of the myocardium. In particular it can identify the presence and extent of myocardial fibrosis, myocardial oedema and microvascular obstruction. All these imaging biomarkers of myocardial damage can represent substrates for arrhythmias.

Imaging myocardial tissue damage has therefore important clinical implications, not just for the diagnosis and the management of patients but also because it can provide novel pre-clinical biomarkers of disease that could be useful either for early diagnosis or as a therapeutic target.

Myocardial Fibrosis

Late gadolinium enhancement (LGE) technique

Among the non-invasive imaging techniques, CMR is unique in its ability to provide myocardial tissue characterisation. Traditionally, CMR is able to accurately identify myocardial fibrosis, based on the analysis of the distribution of contrast agent within the myocardium, 10-15 minutes after its administration (late gadolinium enhancement, LGE) (**Figure 1**). CMR uses gadolinium chelates

contrast agent, an extra-cellular agent, which is quickly washed out by normal myocardium, whereas it accumulates in expanded extra-cellular space typically associated with damaged myocardium (4). Whether the extra-cellular space is expanded due to myocardial cell rupture in the setting of acute myocardial infarction or due to collagen deposition in the setting of chronic myocardial scarring, the contrast agent accumulates and its presence and extent is imaged with the LGE technique.

The ability of CMR to detect myocardial fibrosis has been validated by histology studies on animal models of ischemic cardiomyopathy (16) and as diagnostic tool in the clinical setting (17)(18). Due to its high spatial resolution, CMR can identify myocardial scars of variable size and location, proving to be superior also in detecting small amounts of myocardial scars (i.e. focal subendocardial myocardial infarction) that are not detectable by other techniques such as single photon emission tomography (19) because of lower spatial solution (~10mm vs ~2mm by CMR).

Types of myocardial fibrosis

There are three types of myocardial fibrosis that include infarct fibrosis, replacement fibrosis and diffuse interstitial fibrosis (**Figure 2**). It has been shown that these distinct patterns represent a continuum of tissue damage: for example, in end-stage ischemic heart disease (IHD) replacement and interstitial fibrosis account for up to 70% of fibrotic tissue, thus representing the major cause of left ventricular (LV) remodelling, while focal myocardial infarction only accounts for 30% (20).

Infarct fibrosis is the result of the myocyte necrosis following myocardial infarction, and its LGE distribution pattern follows the pathophysiological process of the "ischemic-necrotic wavefront phenomenon", therefore extending from the subendocardium to the entire wall thickness (4)(9), depending on the duration of ischemia. The presence of large transmural myocardial scar visualised as a large area of LGE, determines the lack of viability of the affected myocardial segments.

This accumulation of contrast agent in damaged areas of the heart resulting in areas of myocardial enhancement (LGE) was first observed in ischemic heart disease and exemplified as "bright is

dead". However, in the last decade it was observed that LGE was present also in the setting of non-ischemic heart diseases, albeit with a different pattern of distribution, leading to a paradigm shift to "bright is bad" as LGE in cardiomyopathies also carried prognostic significance (21).

Studies on IHD have shown that recovery, in terms of improved myocardial contractility after myocardial revascularization is proportional to the transmural extent of LGE on CMR. In particular, Kim et al. described a correlation between the extent of dysfunctional but viable myocardium and improvement in ejection fraction after successful revascularization (22). More recently, Shah et al. (23) showed that even thinned and severely dysfunctional myocardium can fully recover after revascularization, both in terms of wall thickness and contractility, if LGE (scar extent) is <50% transmurality.

Myocardial fibrosis and arrhythmic risk

Left ventricular ejection fraction (LVEF) is an indirect measure of scar size and is the best known predictor of arrhythmic risk. However, it is also established that both myocardial scar and viable myocytes within myocardial scar represent the substrate of re-entrant arrhythmias. Different studies have shown that the extent of myocardial scar by LGE is predictive of arrhythmic risk, irrespective of LVEF: in a population evaluated for implantable cardioverter defibrillator (ICD) implantation, Klem et al. (24) showed that a smaller scar (<5%) is correlated with lower rate of events (ICD discharge, all-cause mortality), also in patients with severely impaired LVEF. Infarct size appears to be a better predictor of ventricular arrhythmias than LVEF (25)(26) and scar heterogeneity (i.e. interaction between the dense scar core and the peri-infarct border zone) demonstrates to be the strongest determinant of ventricular arrhythmias inducibility (27).

The LGE technique is able to identify the critical isthmus site, and in particular the central isthmus, which is localised in close proximity to a > 75% transmural ventricular scar, thus providing guidance on the ventricular tachycardia (VT) ablation site in patients with ischemic and non-ischemic cardiomyopathy (28).

Based on the analysis of LGE distribution patterns, replacement fibrosis can appear as mid-wall, epicardial or global, leading to different differential diagnosis (4), mainly in the setting of non-ischemic cardiomyopathies (29). The identification of replacement fibrosis, with the mid-wall distribution pattern, has been shown to be the strongest predictor of sudden cardiac death or ICD discharge in patients with systolic dysfunction, also after adjusting for LVEF, ischemic pathogenesis and total LGE (30). In patients with non-ischemic dilated cardiomyopathy, ventricular scarring assessed by LGE predicts monomorphic but not polymorphic VT or ventricular fibrillation (31).

Piers et al. demonstrated that two typical myocardial scar patterns (anteroseptal and inferolateral) accounted for 89% of the arrhythmogenic substrates associated with ventricular tachycardia in patients with non-ischemic cardiomyopathy (31). In addition, the substrate location has an implication for intervention as the ablation site of the anteroseptal scar-related VT was localised in the aortic root or anteroseptal ventricular endocardium, whilst in the inferolateral scar-related VT the target site required an epicardial approach.

Infarct transmurality by LGE can identify patients that might benefit from a first-line endo-epicardial approach as in these patients the sole endocardial approach was associated with an increased risk of recurrence (32)(33).

Non-invasive visualisation of conducting channels is increasingly representing a new target for VT ablation. Initial experience suggested that ventricular scar architecture is able to visualise conducting channels as corridors within scar border zone identifying 74% of the critical isthmus of clinical VTs and 50% of all the conducting channels identified in electroanatomic maps (34). Further experience on 30 patients with structural heart disease referred for VT ablation confirmed the ability to image conducting channels when using an advanced 3D CMR technique on a high-resolution 3T MRI platform (35). Based on this technique, scar de-channeling (elimination of the conducting channels by ablating their entrance) resulted in non-inducibility of the VT in 54% of

patients, increasing to 78% with additional residual VT ablation and with recurrences mainly related to incomplete conducting channels (CC) electrogram elimination . (36)

Atrial fibrosis

Traditionally the visualisation of myocardial fibrosis has been confined to the ventricles. More recently, there is evidence that LGE can also be observed in the left atrial wall, identifying atrial fibrosis as an arrhythmic substrate for atrial fibrillation (AF) (37). Imaging fibrosis is more challenging in the atrial wall compared to the ventricles due to the limited CMR spatial resolution in thinned structures.

The DECAAF study is a recent multi-centre prospective trial that reported the association between atrial scarring and the recurrence of arrhythmia after AF ablation (38). In particular, the arrhythmia recurrences significantly correlated with the amount of atrial fibrosis on presentation (Utah stage I: 15%, stage II: 36%, stage III: 46%, and stage IV: 69%). A further analysis of the architecture of atrial fibrosis demonstrated that the largest atrial fibrosis patch was associated with post-ablation arrhythmia recurrence, independent from total atrial fibrosis. Marrouche therefore suggested a CMR-guided patient selection for AF trigger ablation where Utah stage I patients show a high chance of ablation success, as well as patients in Utah stages II and III, provided a limited fibrosis patch size is present, whereas patients with a larger patch size, as well as Utah stage IV patients, have a low chance of success and may be eligible for substrate ablation or no ablation at all (37).

Recurrences of AF after pulmonary vein (PV) isolation may be related to gaps at the ablation lines. Several groups have demonstrated that LGE CMR can identify radiofrequency lesions and gaps down to 1mm (39)(40). Bisbal et al. demonstrated that the site of electrical PV reconnection (assessed by circular mapping catheter) matched with a CMR gap in 79% of PVs and that CMR-guided ablation led to re-isolation of 95.6% of reconnected PVs, with the potential to reduce procedural duration and radiofrequency application time (41).

Novel CMR techniques for tissue characterisation

CMR relaxometry (T1- and T2-mapping) is a new technique, recently emerged for the assessment of myocardial and interstitial fibrosis. In particular, T1 mapping can be performed with and without contrast (native T1 mapping, and post-contrast T1-mapping, respectively). Native T1 mapping provides a quantitative (ms), rather than qualitative, assessment of both myocardial and interstitial fibrosis, only by measuring myocardial longitudinal magnetic relaxation (T1) and obviating to the need of contrast administration. (42)

The measurement of interstitial fibrosis (the extra-cellular volume, ECV) requires the acquisition of both native and post-contrast T1 mapping, and it is based on the assumption that there is a steady-state equilibrium of gadolinium between blood and myocardium after contrast administration (43). This provides a unique opportunity to measure non-invasively interstitial myocardial fibrosis. ECV has been shown to have a good correlation with histological collagen volume fraction (44) and there is initial evidence that it is a good predictor of mortality (45). In particular, in the Cox regression models, ECV related to all-cause mortality (hazard ratio, 1.55; 95% confidence interval, 1.27–1.88) and the composite end-point (mortality/cardiac transplant/ventricular assist implantation) (hazard ratio 1.48; 95% confidence interval, 1.23–1.78) for every 3% increase in ECV (adjusting for age, LVEF, and size of myocardial infarction size) (45).

Myocardial Oedema

CMR can also assess the presence of myocardial oedema. The most used sequences are the T2 weighted, which measure the transverse relaxation of the myocardium (T2): increased water content within the myocardium lengthens the T2 relaxation time, so that a bright signal is detected on CMR images. Traditionally oedema imaging is performed with a sequence called T2-STIR, but many

other sequences have been developed and used, such as the ACUT2E, the early gadolinium enhancement sequences and the most recent T2 mapping techniques. A recent study has shown that the most accurate and reproducible assessment of myocardial oedema is provided by T2 mapping (46). Assessment of myocardial oedema has an established role in IHD. The extent of oedema early after acute myocardial infarction represents the myocardium "at risk" (the myocardial area related to an occluded coronary artery with complete absence of blood flow). Using oedema imaging, the amount of "myocardial salvage" can also be calculated by subtracting the infarcted area from the "area at risk" (**Figure 3**); these parameters are both independent predictors of adverse LV remodelling and major adverse cardiac events (47). Myocadial oedema is a parameter assessed duing acute coronary syndome. Intra-myocardial haemorrhage and micro-vascular obstruction (MVO) are frequent complications after successful myocardial revascularization of an acute coronary syndrome. Both these parameters are independent predictors of adverse LV remodelling, irrespective of the initial infarct size (48). Due to the paramagnetic properties of deoxyemoglobin, in areas of myocardial haemorrhage there is a selective shortening of T2, which appears as a hypo-intense signal on T2 weighted images for myocardial oedema.

Myocardial oedema is also predictive of arrhythmic risk. Tako-Tsubo cardiomyopathy (TTC), which is considered a rather benign disease, can present or be associated with life-threatening ventricular arrhythmias or sudden cardiac death (49): this has been attributed to myocardial oedema and subsequent tissue heterogeneity. It has also been shown that the apico-basal oedema gradient in TTC linearly correlates with transient T-wave inversion and QT prolongation, as an expression of transient tissue inhomogeneity.

Ventricular Function

Cardiovascular magnetic resonance is the gold-standard non-invasive technique for the assessment of biventricular volumes and function (1) (2). The ventricles are sampled from base to apex by a short-axis stack of cine sequences, and ventricular volumes and ejection fraction are then derived

from the endocardial and epicardial contouring of each slice. This provides with a real three-dimensional (3D) assessment of ventricular function, which is free from any geometric assumption, and this represents the major advantage of CMR over 2D echocardiography (50)(51).

Left ventricular ejection fraction is the strongest predictor of adverse cardiovascular events (mortality, heart failure and arrhythmias) and the main determinant of the clinical indication to an ICD implantation. Many studies have shown an increased mortality risk in patients with reduced ejection fraction after acute myocardial infarction (MI): the Canadian Assessment of Myocardial Infarction (CAMI) trial (52) has shown that the odds ratio for one year mortality after MI was 9.48 for patients with LVEF ≤30% and 2.94 for patients with LVEF 30-40%, compared with patients with LVEF >50%, while there was no significant difference for patients with LVEF of 40-50%. The Multicenter Automatic Defibrillator Implantation Trial (MADIT I and II) (53)(54) reported a reduction in mortality in patients with reduced LVEF wearing prophylactic implantable cardioverter defibrillators (ICD). Accurate assessment of LVEF is thus fundamental, not only in diagnosis but also in guiding best treatment strategy; CMR plays a primary role in this setting.

Limitations of CMR

The common limitations of CMR are related to its limited availability and expertise, and to its cost. The main absolute contraindications are the presence of non-CMR conditional cardiac device, and cerebral metallic clips. Relative contraindications are low eGFR (glomerular filtration rate < 30mL/min/1.73 m^2) for patients due to receive contrast agent, and claustrophobia.

The spatial resolution of LGE imaging is ~1.5mm although improved spatial resolution can be achieved with using 3D technique and high field CMR systems such as 3T scanners.

Good quality LGE images can only be achieved by optimizing the time to null the signal in the normal myocardium (time of inversion, TI) which is achieved most reproducibly by using a T1 scout technique. Failure to identify the correct TI can lead to suboptimal image quality in which

artefact can mimic areas of myocardial late enhancement. Oedema imaging can be challenging in patients with elevated heart rate and enhanced cardiac motion.

Conclusion

Cardiac magnetic resonance is a comprehensive, one-stop-shop imaging technique, which provides accurate data on cardiac function and tissue characterization. Given that analysis of myocardial function and structure has shown to have important implications in prognosis, CMR has a promising role also in patients' management and risk stratification. The unique capability of CMR to perform tissue characterisation allows the detection and quantification of myocardial fibrosis which represents a substrate for arrhythmias.

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Figures

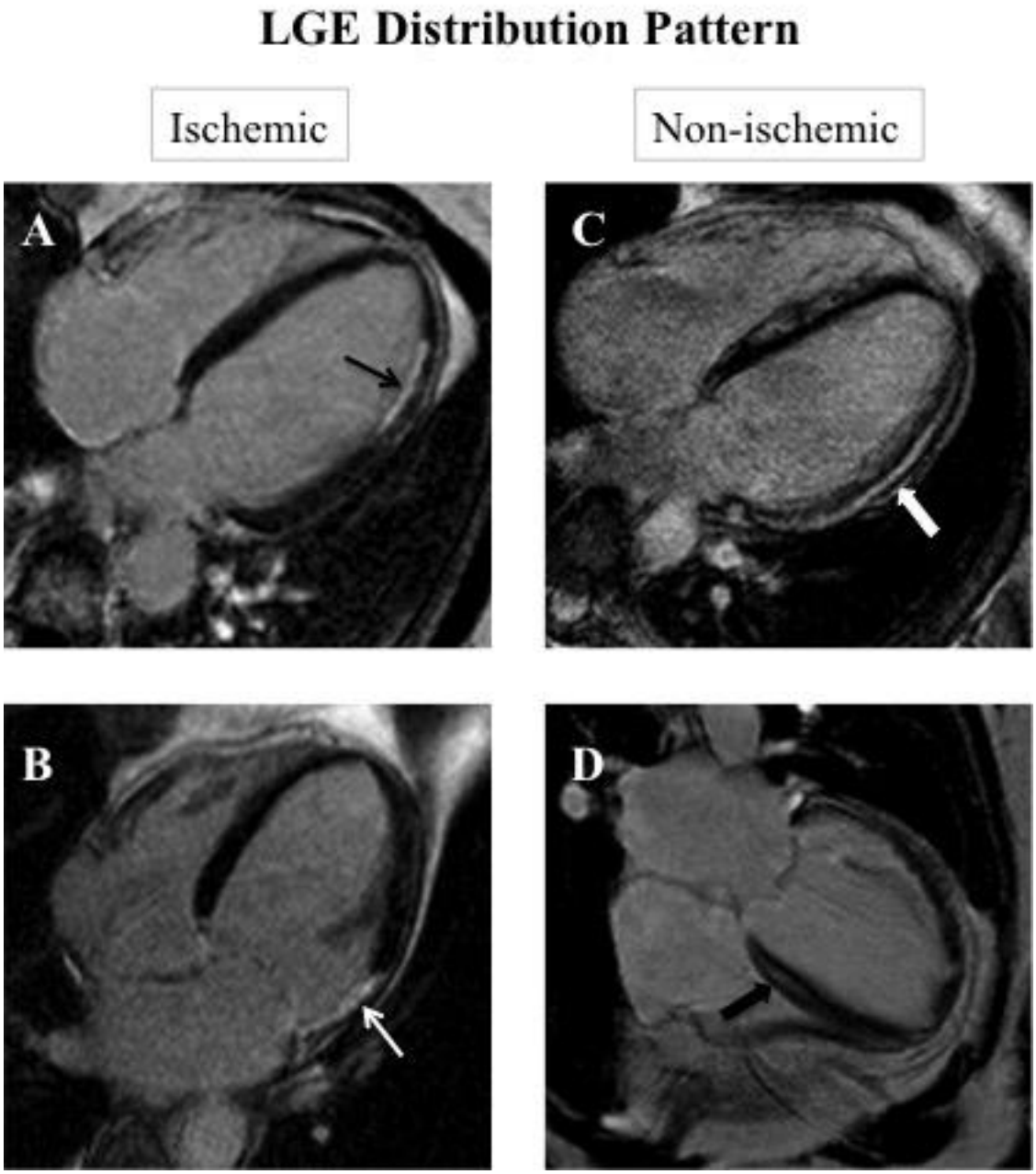

Figure 1. LGE distribution patterns in ischemic and non-ischemic heart disease. A) Four chamber post-contrast long axis view showing subendocardial myocardial late enhancement in the mid-cavity anterolateral wall (black arrow). B) Four chamber post-contrast long axis view showing showing trasnmural myocardial late enhancement in the basal anterolateral wall (white arrow). C) Four chamber post-contrast long axis view showing extensive epicardial late enhacement of the basal to apical anterolateral wall (thick white arrow). D) Four chamber post-contrast long axis view showing mid-wall late enhacement in the basal inferospetum (thick black arrow). LGE, late gadolinium enhancement.

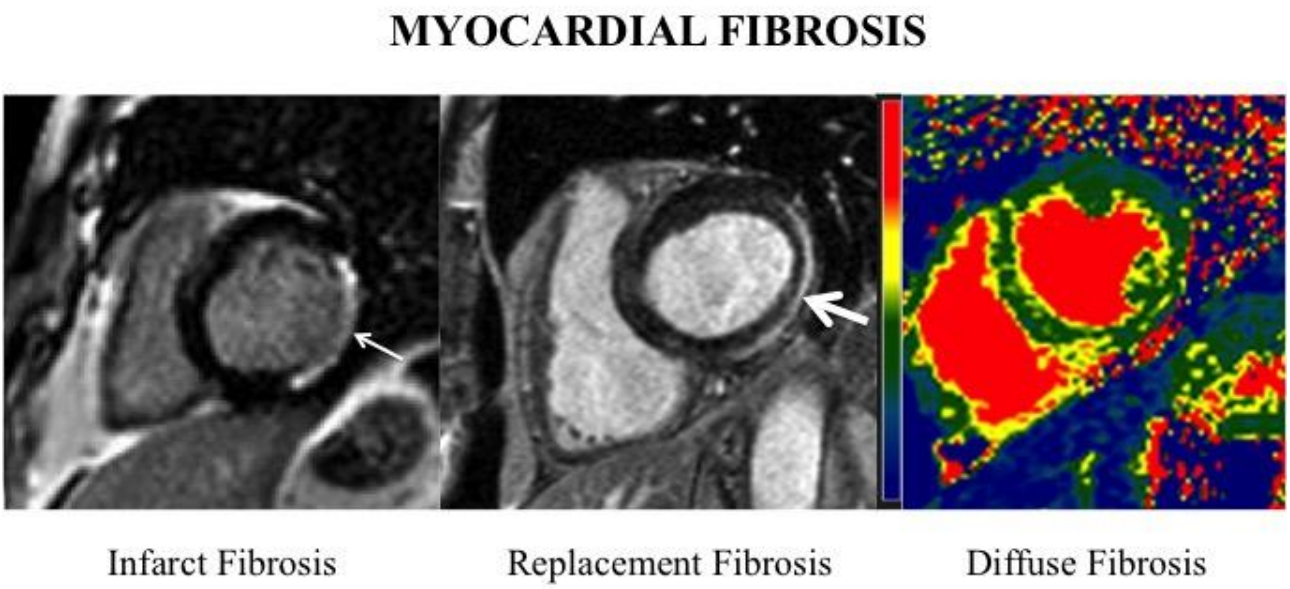

Figure 2. **Types of myocardial fibrosis detected by CMR.** Infarct fibrosis: short axis post-contrast sequence showing almost transmural myocardial infarction in the basal lateral wall (thin white arrow). Replacement fibrosis: short axis post-contrast sequence showing epicardial late enhancement of the basal lateral wall in a patient with myocarditis (thick white arrow). Diffuse fibrosis: native T1 mapping showing increased T1 values in the septum and inferior wall (yellow); normal myocardium green.

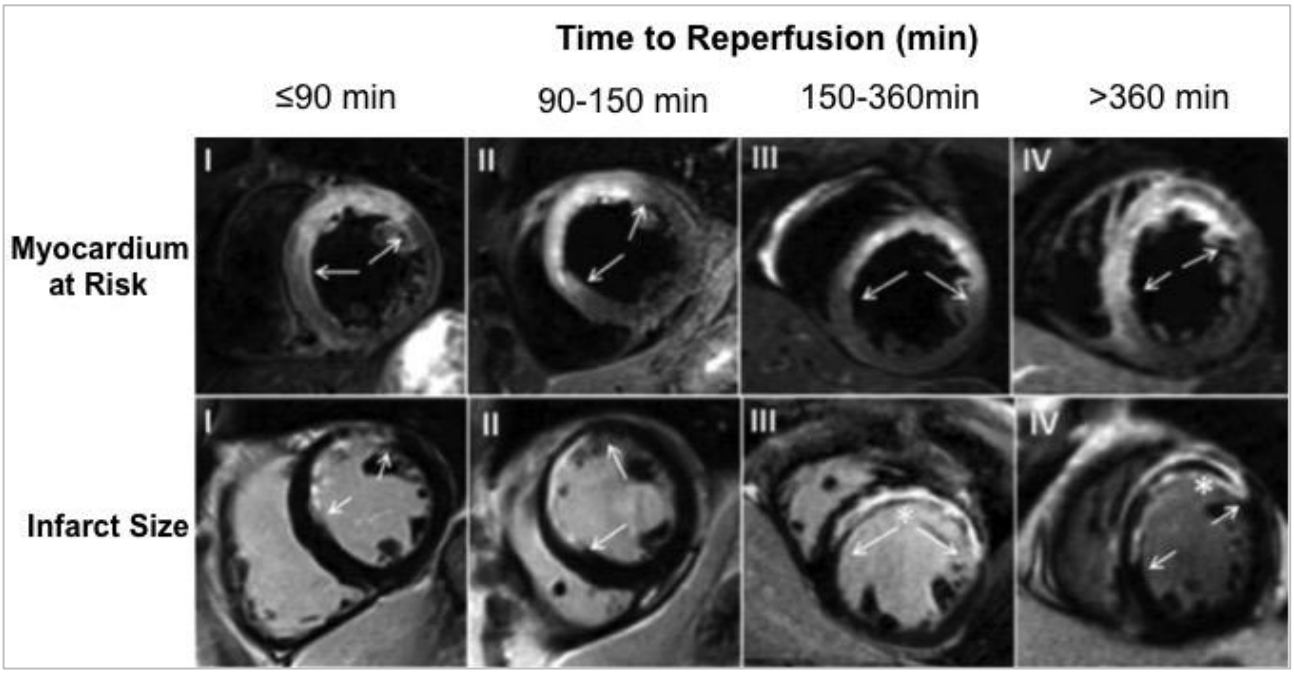

Figure 3. **Effect of time to reperfusion on tissue damage**. Top panel, T2 weighted images showing increased extent of myocardial oedema (arrows) with increased time to reperfusion. Bottom panel, post-contrast sequences showing increased infarct size (arrows) and MVO **(*)** as time to reperfusion progresses, with reduced myocardia salvage. Adapted from (47).