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**Title: Advances in magnetic resonance imaging of the myocardial area-at-risk and salvage**

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## **Cardiac magnetic resonance - role in infarct characterization**

Cardiac magnetic resonance (CMR) imaging in survivors of acute ST-elevation myocardial infarction (STEMI) provides accurate and precise measurements of left ventricular dimensions, and infarct pathologies are uniquely characterised. Acute coronary artery occlusion initiates a 'wavefront phenomenon' of ischemia (1) commencing from the endocardial layer and propagating radially towards the epicardium, and typically, myocardial infarction will supervene unless coronary reperfusion is achieved in a timely manner. The myocardial area-at-risk is the jeopardised perfusion territory of the culprit artery.

Ischemia results in an increase in myocardial water content manifesting as myocardial edema, and the local changes in T1 and T2 relaxation times (milliseconds) can be revealed by CMR (2). Myocardial salvage is calculated by subtracting the infarct size on contrast-enhanced CMR from the myocardial area-at-risk, revealed by T1 or T2-weighted CMR and predicts the likelihood of functional recovery (2). On the other hand, edema imaging has limitations since the area-at-risk diminishes in size from approximately 5 days post-reperfusion (3,4) and T2 relaxation times within the ischemic zone vary as infarct pathologies evolve (5,6)

### **Imaging myocardial edema**

Several CMR methods are now available for imaging myocardial edema (7), the most established of which is the T2-weighted short tau inversion recovery (T2-STIR) black blood technique. This method has the advantage of being generically available across all major vendors. However, image quality may be limited when using T2-STIR CMR, due to low contrast-to-noise ratio between normal and abnormal myocardium, and a propensity for sub-endocardial bright rim artefacts due to static blood and surface coil issues (8,9). In recent clinical trials involving optimized core laboratory analyses, T2-STIR has not been of diagnostic value in at least one quarter of all scans (10,11). In our opinion, this limitation is

unacceptable. New alternative methods include T1- (12) and T2-mapping (13), which like T2-STIR, require additional breath-hold acquisitions specifically for the purpose of imaging edema. Contrast-enhanced cine steady-state free precession (SSFP) (CE-SSFP) (14) depicts edematous myocardium as a region of higher T2:T1 signal than normal myocardium (15). This new method has recently gained traction as an alternative approach for assessing the area-at-risk after being validated against SPECT (14) and T2-STIR (16).

### **Relationship between the culprit artery, the myocardial-area-at-risk and infarct size and location.**

Knowledge of the distribution and size of the coronary artery perfusion territories is clinically relevant. For example, identification of the culprit artery and estimation of salvageable myocardium subtended by that artery could promote novel applications such as 1) the development of automated software for area-at-risk and infarct analysis, 2) be used as a surrogate outcome measure in therapeutic clinical trials, 3) provides tools to aid clinicians in practice e.g. validation of novel ECG algorithms.

Nordlund et al (17) compared CE-SSFP against T2 STIR for the assessment of the ischemic area-at-risk and myocardial salvage in 215 survivors of an index acute STEMI enrolled into two clinical trials (CHILL-MI NCT01379261; MITOCARE NCT01374321). The in-plane resolution of both methods was ~1.5 mm x 1.5 mm x 8 mm. The temporal resolution of CE-SSFP was 20 – 30 frames per second. Nordlund et al (17) also set out to compare their results with previous publications on identifying the culprit artery utilizing SPECT (18,19). The CMR image analyses were performed in a core laboratory utilizing software designed by the same group in the University of Lund, Sweden. The CMR findings for assignment of the culprit artery territory were compared with the reference findings from the invasive coronary angiogram, taking into account the Rentrop collateral grade, and infarct assessment using late

gadolinium enhancement imaging with CMR. The study builds on previous work done by Ortiz-Pérez et al. (20) who used contrast-enhanced CMR to map infarct distribution to identify the culprit artery in 93 STEMI survivors.

The first main finding was, as compared with CE-SSFP, a higher number of T2-STIR scans were not of diagnostic value (86 (40% vs 13 (6%)). Of those scans that were interpretable, the area-at-risk (% LV mass) was similar. CE-SSFP had a higher rate of agreement with angiography in assigning the culprit artery than T2-STIR (97% vs 89%). The area-at-risk revealed by CE-SSFP was greater than infarct size in all of the subjects. The second main finding was that the CE-SSFP may reflect the true perfusion territory of the reperfused culprit artery. The third finding was that area-at-risk revealed by CE-SSFP and T2-STIR (using the sub-set of scans that were of diagnostic value) were similar to findings in previous studies of culprit artery distribution using myocardial perfusion scintigraphy (18,19).

The results provide evidence that CE-SSFP is an emerging alternative to T2-STIR for edema imaging. It is intriguing that a non-invasive multi-modality CMR scan can be used to identify the location of the culprit artery, its perfusion territory, and the amount of residual myocardium amenable to salvage.

Some potential limitations of the CE-SSFP method include the fact that diagnostic accuracy will likely be reduced in non-reperfused STEMI, since the intra-vascular contrast agent would not be expected to perfuse the infarct territory. Since the study involved patients with a first STEMI, in whom coronary collateral connections may be minimal, the diagnostic accuracy of CE-SSFP merits further assessment in a less selected and more heterogeneous population of STEMI patients.

## **Advances in imaging the myocardial area-at-risk**

There is a divergence of opinion in the cardiovascular imaging community (5,6,7,21,22) on whether the hyper-intense area revealed by T2-weighted imaging in patients with recent STEMI reflects the ischemic area-at-risk or instead may simply reflect infarct size. We recognise the theoretical limitations of edema imaging, especially with T2-STIR. The new applications with T1-mapping, T2-mapping and CE-SSFP represent important advances which strengthen the case for imaging the myocardial area-at-risk and salvage with CMR.

## **Utility of contrast enhanced cine SSFP imaging**

In the study by Nordlund et al (17), out of 215 CMR scans that acquired using technology from different vendors, only eleven CE-SSFP sets were not of diagnostic quality. The scans from two other patients were of diagnostic quality but the area-at-risk was not apparent. The CE-SSFP approach seems reasonably robust. It is particularly attractive since the data can be acquired from the standard cine scans that are acquired for LV mass and function, without the need for additional breath-hold edema imaging acquisitions. Therefore, the overall duration of the CMR scan would be shorter using CE-SSFP (17) as compared to when additional scans are acquired for edema imaging. Further validation of the accuracy and performance of CE-SSFP (17) against T2-parametric mapping (13) and T1 mapping techniques (12) are warranted.

## **Conflict of interest**

Disclosure: The University of Glasgow holds research agreements with Siemens Healthcare.

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