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EDITORIAL

Identifying Patients at Risk Post-Infarct: Is it Time for Routine CMR?

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In this issue of *Heart, Lung and Circulation*, Costello et al. report a strong correlation between late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) and traditional biomarkers in patients post ST-elevation myocardial infarction (STEMI) [1]. LGE imaging obtained 6 months post STEMI is a marker of regional fibrosis and able to quantify infarct size using different image processing techniques. Using manual and semi-automated methods, they optimised the assessment of infarct size at 6 months and correlated this to biomarkers measured at the time of STEMI. This raises the question that if troponin, a widely available and inexpensive test, already used in clinical practice, is able to predict the results of CMR performed 6 months later, then what additional value does CMR bring to patient management post STEMI? If CMR is to have a role in the assessment of such patients then identifying the optimal time to perform such imaging and identifying the best methods to quantify infarct size are important considerations.

Incremental Benefit of CMR

Identifying patients at high risk of adverse outcomes following STEMI, such as repeat myocardial infarction and the need for urgent revascularisation, remains an important area in both clinical practice and research. Arguably, the risks associated with malignant arrhythmias and heart failure, that increase the risk of sudden death, chronic morbidity and long-term mortality, are more important. In patients with large infarcts, there is a risk of left ventricular (LV) thrombus formation and subsequent systemic embolism. Clinical scoring systems, cardiac biomarkers and echocardiographic LV ejection fraction (LVEF) are most commonly used for risk assessment of these outcomes. However, most of these assessments were developed in the pre-prcutaneous coronary intervention (PCI) era and subsequent improvements in both cardiac biomarkers and cardiac imaging techniques allow for more comprehensive patient assessment and risk stratification.

Cardiac magnetic resonance provides gold standard assessment of LV volumes and LVEF. However, LVEF measured early post infarct may not reliably predict long term systolic function. Patients with reduced LVEF may have significant recovery of function in regions of myocardial stunning [2]. Patients with a normal LVEF at the time of STEMI may progress to worse function due to a loss of compensatory hypercontractility of non-infarcted segments [3]. Due to its unique tissue characterisation properties, CMR offers additional prognostic information alongside the assessment of LV function. Regional fibrosis identified using LGE imaging predicts poor outcomes including ventricular arrhythmias in both ischaemic and non-ischaemic cardiomyopathy [4]. CMR imaging can identify microvascular obstruction (MVO) early post infarct, which is an independent predictor of adverse cardiac events, and is associated with increased LV volumes and lower LVEF at long-term follow-up [2,5]. Myocardial haemorrhage, due to extensive damage to the myocardial microcirculation, can

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be identified with early CMR imaging and in addition to MVO is closely associated with worse outcomes [6]. More recently, incorporation of CMR imaging techniques into a risk scoring system alongside established clinical risk factors in STEMI patients improved risk stratification and prediction of adverse cardiac events [7].

Even when CMR is performed early in STEMI patients (at a time when late infarct size is overestimated, as discussed further below), quantification by LGE is still a strong predictor for late systolic dysfunction and adverse outcomes when compared to traditional measures [3]. A meta-analysis of 10 randomised trials utilising early imaging performed at a median of 4 days post infarct demonstrated that, for every 5% increase in infarct size, there was a 20% increase in the relative hazard ratio for heart failure hospitalisation and all-cause mortality at one year [8].

Outside of those with definite STEMI, CMR is also useful in identifying alternative non-ischaemic causes such as myocarditis, stress induced cardiomyopathy or aortic dissection, as well as identifying small regions of ischaemic scar that may not have been evident on echocardiography [9]. Cardiac magnetic resonance allows for improved identification of LV apical thrombus compared to both contrast and non-contrast transthoracic echocardiography [10].

When to Perform CMR

In general, there are three time points to consider for performing CMR post STEMI – acute, sub-acute, and late. Acute assessment within the first 3–5 days allows assessment of myocardium at risk and potentially salvageable myocardium if there are questions about further revascularisation [11] but has the disadvantage that gadolinium kinetics in areas of early myocardial oedema leads to overestimation of infarct size [12]. In a rat model, early CMR imaging obtained within 48 hours post infarct overestimated the true infarct size by approximately 8% due to partial enhancement of the peri-infarct tissue [13]. In further animal models this effect has been shown to diminish significantly within the first 7 days with no significant difference in infarct size quantified at 7 days post infarct between histology and LGE techniques, likely reflecting early recovery of the peri-infarct zone [12,14].

The optimal timing for early CMR imaging estimated from a recent meta-analysis is between 3 and 5 days post infarct to allow for optimal balance between infarct estimation and assessment of myocardium at risk [15]. This corresponds to a typical length of stay for many inpatients following STEMI such that CMR imaging in this time period would have minimal impact on length of hospital stay.

Sub-acute assessment at 7–14 days allows time for the majority of the infarction-related myocardial oedema to resolve, improving the assessment of infarct size and regional myocardial dysfunction. Microvascular obstruction and intramyocardial haemorrhage are still detectable in the majority of patients, and LGE shows similar infarct size if assessed at in the chronic phase [6,16]. In addition, this is likely the optimum time frame to detect the majority of ventricular thrombi [17]. However, CMR performed at 7–14 days would likely follow discharge for patients, which may result in a loss to follow-up, due, for example, to mandatory driving license restrictions.

Late imaging assessment after 6 months allows assessment of ventricular volumes, cardiac function and infarct size, that is unlikely to change significantly in the future. However, given the large number of events that occur early post-MI, there is a significant survivor effect in the patients who would have CMR at this time point.

How to Quantify Infarct Size

A particular strength of the study by Costello et al. is the care with which they measured infarct size [1]. There is a lack of consensus about the optimal method [18], partly because there has been variation in the CMR techniques used in research trials in this area [15]. Quantitative and semi-quantitative methods currently require manual image processing that can be time consuming and require expertise that may not be available outside of reference centres. For most clinical indications, visual assessment of LGE images may be sufficient [18]. Manual contouring techniques performed by experienced operators in expert centres has been a favoured technique in clinical trials and shown to have low inter-observer variability of +/−2.2% [19]. Manual techniques have subsequently been demonstrated as being the most reproducible method for both myocardial oedema and infarct size [20].

Semi-automated intensity thresholding techniques, such as those assessed in the paper by Costello et al. may be simpler to use and reduce inter-observer variability [1]. Several techniques have been used in clinical research, but the accuracy and reproducibility of these techniques can be influenced by several factors including the imaging sequences used [21], magnetic field strength, image quality, contrast kinetics and contrast timing [22]. These techniques are also prone to artefact, particularly partial volume effects and slice thickness [21–23] Partial volume effects have been demonstrated in the peri-infarct zone where a mix of viable and nonviable tissue as well as oedema are present in the same voxel [23].

A recent paper comparing different semi-automated techniques in comparison to manual methods performed in an expert centre in both early and late imaging identified that the 6-SD technique was as accurate as manual processing for acute and chronic MI size quantification. The full width at half maximum method (FWHW) method, however, was affected depending on which LGE sequence was utilised and underestimated chronic infarct size in patients who had MVO on early imaging [21].

The paper by Costello et al. demonstrated a strong correlation between different methods for quantification of infarct size on late CMR imaging and cardiac biomarkers using manual and semi-automated techniques for all

methods [1]. The inter- and intra-observer variation for manual processing techniques in this study was low and comparable to those in other expert centres. This validates infarct size as measured by the manual method in this study as a reference for comparison with semi-automated methods. In this study, there was a particularly strong correlation for infarct size using thresholds at 5SD and 6SD and the FWHW method when compared to manual quantification and consistent with previous studies [24]. In this study, early imaging was not obtained to assess for micro-vascular obstruction, however all patients included had full revascularisation of the culprit vessel with restoration of TIMI 3 flow. Patients with cardiogenic shock or poor reperfusion who would have been at increased risk for MVO were excluded. This may account for the close correlation in the SD techniques and FWHW method to manual techniques which is in contrast to the recent findings of Bulluck et al. where the limitations of the FWHW method on late imaging were largely in those who had previously been found to have MVO [21].

What Does the Future Hold?

Cardiac magnetic resonance provides additional useful clinical information that may identify individuals at high risk for adverse cardiac events post STEMI and could potentially enable early implementation of disease modifying therapy. Amongst factors limiting routine use of this modality are a lack of consensus on the optimal timing for such imaging and lack of standardisation in imaging techniques used for quantification. The paper by Costello et al. demonstrates a correlation between manual quantification techniques and semi-automated techniques [1]. With ongoing development of imaging sequences these will continue to improve image quality, reduce artefact and improve the accuracy of semi-automated techniques. This would allow for implementation of a more standardised approach for quantification and the use of such techniques outside of reference centres, eventually placing powerful predictive tools in the hands of clinicians.

At present however, recommendations for routine use of CMR cannot be made as there are currently no randomised clinical trials that have implemented changes in therapy based on CMR findings. Cardiac magnetic resonance is not widely available for use in the post-STEMI population and it is likely that such high-grade evidence will be needed to persuade funders to allocate resources to this area. A welcome example of an approach mapping CMR assessment to treatment is the Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator (ICD) Implantation to Prevent Tachyarrhythmias Following Acute Myocardial Infarction (PROTECT-ICD) [25]. While this trial is using an invasive electrophysiological (EP) study to risk-stratify patients to an ICD in the early past post myocardial infarction, a sub-study is using CMR assessment, which may allow identification of those with high risk EP studies without the risk of an invasive procedure. Prior to such evidence, it is likely that the current practice of using CMR in selected patients to answer important diagnostic questions will continue, rather than routine CMR in all patients post-STEMI.

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