Manuscript No.:47381-Review-HTML **EDITORIAL**

Cardiovascular magnetic resonance: Stressing the future

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Abstract

Non-invasive cardiac stress imaging plays a central role in the assessment of patients with known or suspected coronary artery disease. The current guidelines suggest estimation of the myocardial ischaemic burden as a criterion for revascularisation on prognostic grounds despite the lack of standardised reporting of the magnitude of ischaemia on various non-invasive imaging methods. Future studies should aim to accurately describe the relationship between myocardial ischaemic burden as assessed by cardiovascular magnetic resonance imaging and mortality.

Key words: Coronary artery disease; Myocardial ischaemic burden; Non-invasive imaging; Cardiac stress; Magnetic resonance imaging

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Core tip: Further studies should aim to accurately describe the relationship between myocardial ischaemic burden as assessed by stress cardiovascular magnetic resonance and mortality.

INTRODUCTION

Non-invasive cardiac stress imaging plays a central role in guiding the treatment of patients with known or suspected coronary artery disease (CAD). Stress testing techniques performed include stress echocardiography, single photon emission computed tomography (SPECT) myocardial perfusion imaging and more recently cardiovascular magnetic resonance imaging (CMR). All functional tests support diagnosis, risk stratification and subsequent management decisions[1] and thus allow myocardial ischaemia to play a crucial role in the management of patients with CAD[2]. As the availability and use of CMR increases, it is increasingly emerging as the gold standard method of safe, radiation-free perfusion imaging providing functional assessment and tissue characterisation.

In this editorial, we focus on a recent article by Heitner *et al*[3] published in JAMA Cardiology as we feel it is an important study adding credence to the growing role of pharmacological stress CMR in the assessment of patients with known or suspected CAD . We will also provide our perspective for the future direction of stress CMR.

STUDY ANALYSIS

Heitner *et al*[3] provided real-world data for 9151 patients referred for evaluation of myocardial ischaemia with stress CMR across 7 participating centres followed for a total of 48000 patient-years. Their analysis demonstrated a strong association of abnormal CMR results with all-cause mortality over long-term follow-up up to 10 years with a hazard ratio of 1.8 between the patients who had abnormal scans and those that did not. This hazard ratio remained significant in all 8 patient subpopulations (presence/absence of history of CAD, normal/abnormal left ventricular ejection fraction (LVEF), presence/absence of typical chest pain, presence/absence of Late Gadolinium Enhancement). The multivariate analysis also showed that addition of stress CMR in two different models significantly increased the χ^2 from 581.8 to 687.4 ($P < 0.001$) and from 620.7 to 721.1 ($P < 0.001$) respectively, indicating that the addition of stress CMR in the model significantly predicts mortality over and above the other variables (including age, sex, diabetes, hypertension, hyperlipidaemia, smoking status, history of CAD or Myocardial Infarction, body mass index, family history of CAD and LVEF).

Whilst this was not a randomised control trial, it crucially provides real-world data and demonstrated for the first time that stress CMR is significantly associated with mortality. The major strengths of the study lie in the large number of patients included and the high number of outcomes over long-term follow up. It is important to consider however, that there were certain limitations. The cause of death is not known in the study and future studies will have to investigate if stress CMR is able to predict specific cardiovascular events rather than all-cause mortality. Nevertheless, as discussed by the authors, all-cause mortality is an objective, unbiased and clinically relevant hard end point. The authors also acknowledged that they had not been able to determine if patients were revascularised after the stress CMR. They reasonably anticipated that revascularisation would occur more commonly in patients with abnormal stress CMR and that revascularisation would improve prognosis and not increase mortality. Another important limitation is that the study CMRs did not assess the extent of ischaemic burden but instead categorised ischaemia into "negative" or "positive" even if just one segment showed abnormal perfusion. Although full quantified perfusion[4] is not yet part of routine practice, visual semi-quantitative methods have been described[5] and might have further improved the association with mortality. Furthermore, information about patient revascularisation in combination with myocardial ischaemic burden (MIB) might had allowed estimation of a threshold for MIB, similarly to the way it was estimated in the SPECT studies originally [6], providing valuable information regarding the threshold of ischaemic burden as assessed with stress CMR .

Hachamovitch *et al*[6] for the first time in 2003 successfully estimated the 10% MIB threshold with SPECT above which revascularisation offers a survival benefit over medical therapy, using propensity match scoring of observational data. In 2011, the same group used SPECT to demonstrate in a slightly larger observational series that patients with significant ischaemia but without extensive scar were likely to benefit from revascularisation in contrast to patients with minimal ischaemia[7]. The 10% threshold for myocardial ischaemia based on SPECT has correlated with perfusion defect in 2/16 segments on CMR[8] and has been incorporated in the ESC 2018 guidelines as a criterion for revascularisation on prognostic grounds and in the ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 guidelines as a high-risk indicator[1,9]. Despite the significance of ischaemia in decision making, there is a lack of standardized reporting of the magnitude of ischaemia on non-invasive testing, which contributes to the variability in translating the severity of ischaemia across stress imaging modalities[8]. Given the high diagnostic and prognostic yield of pharmacological stress CMR with regards to CAD, it will be valuable for future studies to attempt to delineate the relationship between MIB and prognosis. Nonetheless, Heitner *et al*[3] should be highly commended for contributing to the medical literature; a very well undertaken and described study including a significant number of patients and an extended follow up, supporting the prognostically beneficial use of CMR perfusion in the routine evaluation of patients with suspected coronary artery disease.

FUTURE DIRECTIONS

Over the last few years, adenosine stress CMR has been established as a highly accurate non-invasive and radiation-free method for the diagnosis and prognosis of CAD. The initial CE-MARC study demonstrated that stress CMR was superior to SPECT regarding the diagnostic accuracy for CAD[10]. It has also been shown that compared with stress echocardiography, stress CMR was the strongest independent predictor of significant CAD among patients with intermediate probability of CAD presenting to emergency department[11]. The 5-year follow up data from CE-MARC study demonstrated that stress CMR was the only significant predictor of MACE in addition to major cardiovascular risk factors, angiographic findings or the effect of initial treatment[12]. Even though stress CMR is not universally, easily available currently, the increasing number of studies demonstrating its cost effectiveness over other non-invasive imaging modalities indicate that it will become more widely available in the near future[13-15]. In addition to accurate assessment of ischaemia, stress CMR offers accurate localisation of ischaemic segments and the extent of myocardial scar, which have prognostic implications[16]. It has been shown that ischaemia in ≥ 1.5 myocardial segments (in a 16 segment model) is significantly associated with poor prognosis as is the presence of myocardial scar, albeit to a lesser degree[17]. Two potential drawbacks of stress CMR perfusion include the visual assessment of perfusion defects as well as the incomplete myocardial coverage. The continuous development of quantified myocardial perfusion reserve aims to reduce the inherent interpreter-bias of visual assessment and to increase the diagnostic ability in the presence of triple-vessel disease. Comparison of quantitative myocardial perfusion reserve with qualitative assessment of stress CMR has demonstrated that quantitative assessment differentiates significantly better the MIB particularly in the context of triple-vessel disease[18]. More recently, it was also shown that quantitative assessment of MIB was superior to visual assessment with respect to prognosis[4]. The ongoing development of whole-heart perfusion aims to address the limited, non-contiguous coverage of 2D stress CMR and ultimately provide a non-invasive, non-ionizing radiation method for accurate measurement of MIB. It has been demonstrated that whole-heart perfusion CMR has high diagnostic accuracy for the detection of significant CAD as defined by Fractional Flow Reserve, while estimation of MIB by whole-heart perfusion has very good correlation with SPECT[19,20]. Comparison of whole-heart perfusion with high-resolution 2D perfusion has shown that there is strong correlation between the two techniques for the estimation of MIB however, there is still uncertainty around the clinically relevant threshold of 10%[21].

In summary, non-invasive accurate assessment of myocardial ischaemic burden is a clinical necessity with significant implications for prognosis and clinical decision making. In the near future, further development of stress CMR perfusion techniques may reveal that quantified, whole-heart perfusion is the most accurate non-invasive method for the diagnosis and prognosis of CAD.

CONCLUSION

Heitner *et al*[3] showed for the first time that stress CMR is significantly associated with worse mortality in a large study of real-world data. This is an important study that confirms the prognostic significance of stress CMR in terms of mortality in the real world. The study is a valuable addition to the growing volume of data that supports the central role of CMR in the diagnosis and stratification of CAD in routine clinical practice. However, as information about MIB as assessed by stress CMR was not available, future studies could aim to describe accurately the relationship between MIB, revascularisation and mortality.

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Figure Legends