Chapter 8

Revascularization in patients with chronic ischemic myocardial dysfunction: Insights from Cardiovascular Magnetic Resonance Imaging

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Submitted

ABSTRACT

In patients with chronic ischemic left ventricular dysfunction, revascularization may lead to symptomatic and prognostic improvement[1]. Myocardial viability and hibernation (i.e. myocardial dysfunction due to chronic hypoperfusion or repetitive ischemia)[2, 3] provide the rationale for revascularization: contractile function will improve with restoration of adequate blood flow. This reversible state should be clearly distinguished from irreversibly injured or infarcted myocardium, in which case the restoration of coronary blood flow would not be justified. Cardiovascular magnetic resonance (CMR) imaging with its high spatial resolution provides qualitative and quantitative, global and regional information on myocardial anatomy and function. In combination with a gadolinium-based contrast agent CMR allows accurate quantification of myocardial scar[4] and predicts likelihood of functional recovery after revascularization[5-9]. The aim of this review is to summarize our current understanding of the detection of myocardial viability using CMR, and why it may be the preferred technique in the assessment of patients with ischemic cardiomyopathy.

CMR TECHNIQUES IN THE ASSESSMENT OF MYOCARDIAL VIABILITY

Several CMR techniques can be used in the evaluation of myocardial viability. Currently, late gadolinium enhancement (LGE) imaging is by far the most frequently used technique. Alternative techniques are the assessment of end-diastolic wall thickness using cine imaging and the evaluation of contractile reserve using cine imaging in conjunction with low dose dobutamine stress.

End-diastolic wall thickness

Both echocardiographic and CMR studies have demonstrated that in patients with chronic ischemic myocardial dysfunction, segments with thinned myocardium (end-diastolic wall thickness ≤ 5.5 – 6.0 mm) represent scar and therefore have low likelihood of improved contractile function after revascularization[10, 11]. However, as reported on several previous occasions[12, 13], even segments with significant wall thinning (<5 mm) may regain wall thickness and thickening, as long as there is no or minimal regional scarring at LGE imaging.

Dobutamine stress cine CMR

Similar to dobutamine stress echocardiography, low dose dobutamine stress cine CMR is an accurate technique to predict functional recovery after revascularization with sensitivity and specificity values of 86% en 92%, respectively[14]. To date there are no reports on viability assessment with high dose dobutamine cine CMR.

Late gadolinium enhancement

Late gadolinium enhancement imaging (LGE) accurately visualizes regional myocardial necrosis in ischemic heart disease[4]. Gadolinium is an extracellular contrast agent that resides in interstitial space. In chronically infarcted regions, interstitial space is increased as a result of replacement fibrosis. These areas are easily identified as regions of high signal intensity within or surrounded by non-enhancing, non-infarcted myocardium. In ischemic heart disease, hyperenhancement typically has a subendocardial or transmural distribution. Excellent spatial resolution (1.5 x 1.5 mm in plane resolution) and high contrast between scarred and viable myocardium allow quantification of the transmural extent of myocardial necrosis. The high resolution of LGE permits the assessment of viability in segments with advanced wall thinning, which makes it superior to the simple

assessment of wall thickness. LGE imaging is a simple and robust technique, and stress is not required, which makes it both safer and more practical than dobutamine cine imaging. The risk of nephrogenic systemic fibrosis in patients with renal failure is extremely low with the use of cyclical agents and lower doses, although careful consideration of the indication in patients on hemodialysis is still needed[15, 16].

PREDICTING FUNCTIONAL IMPROVEMENT AFTER REVASCULARIZATION

Kim et al[7] were the first to show that in patients with chronic ischemic myocardial dysfunction the likelihood of regional functional improvement is inversely related to the transmural extent of hyperenhancement on LGE images. They found that 78% of dysfunctional segments without hyperenhancement improved, compared to 1 of 58 segments with >75% hyperenhancement[7]. Using a cut-off value of ≤25% of scar transmurality to define viability, sensitivity and specificity were, respectively, 71% and 79%, when regions with any degree of dysfunction were evaluated. Expressing diagnostic utility as sensitivity and specificity (or positive and negative predictive values) using a single cut-off is appealing to the clinician and facilitates clinical decision making. However, the gradual relation between functional improvement and scar transmurality emphasizes that the concept of viability as a binary process is an artificial one. LGE CMR is the only technique that allows the side-by-side visualization and quantification of scarred and viable myocardial tissue. Thus, it may be used to further refine the assessment of viability and potential of functional recovery in patients with ischemic cardiomyopathy.

As an example, LGE imaging provides more insight into why contractile function does not always recover after revascularization. First, it may be used to assess both likelihood as well as time course of functional improvement. In patients with chronic ischemic myocardial dysfunction improvements of dysfunctional but viable myocardium may be considerably delayed: it may take more than one year to improve after successful revascularization[6]. Extensive structural changes[17-19] found by histological analysis of tissue samples obtained from areas of myocardial hibernation, including loss of myofilaments with replacement by glycogen and increasing degree of fibrosis, impede timely functional improvement. In accordance with these data, we recently showed that the time course of improvement is more delayed in segments with more extensive

hyperenhancement at baseline[6]. As a consequence, follow-up examination scheduled at 3 or 6 months after revascularization, may not be long enough to assess the full potential of recovery. Second, hypokinetic regions with intermediate scar extent (e.g. 50% of transmural extent of hyperenhancement) contain viable myocardial tissue and might appear viable when examined with nuclear techniques and show (pseudo-) improvement in response to dobutamine stress. However, they may not be hibernating, i.e., since their full potential of function is already used, these segments will not demonstrate further improvement in resting contractility after revascularization. Third, the high reproducibility of LGE imaging allows the identification of new, clinically undetected areas of necrosis between the baseline and follow-up examinations. Procedure related necrosis may offset the improvement in regional function in viable segments and has been shown an important negative predictor of functional outcome[5]. Thus, a considerable amount of viable tissue, a successful revascularization procedure as well as patience are required for global functional improvement. It has been estimated that at least 25% viable myocardial tissue is necessary for significant (generally defined as a ≥5% increase in EF) improvement in global left ventricular function[20, 21]. Pegg et al[22] recently examined the diagnostic accuracy of LGE CMR to predict recovery of global LV function in 33 patients six months after surgical revascularization. The majority of patients with improved EF did not meet the conventional 5% improvement criterion, again illustrating that the degree of global functional improvement is only limited. Also, this implies that only techniques with high reproducibility (such as cine CMR) should be used to evaluate functional changes. The presence of 25% viability (4 segments in a 16-segment model, with viability arbitrarily - and binary - defined as < 50% transmural extent of hyperenhancement) proved a poor predictor of global functional recovery, defined as a 3% increase in EF (sensitivity 76%, specificity 42%). The presence of ≥10 viable + normal segments (i.e. normokinetic with < 50% scar transmurality) was the only independent predictor of global functional improvement (sensitivity 95%, specificity 75%).

VIABILITY ASSESSMENT IN THE MANAGEMENT OF PATIENTS WITH ISCHEMIC CARDIOMYOPATHY

According to current guidelines on myocardial revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, the detection

of myocardial viability should be included in the diagnostic work-up of patients with systolic left ventricular dysfunction and known coronary artery disease, and surgical revascularization should be considered in the presence of viable myocardium[23]. The level of evidence for this recommendation is limited and based on retrospective studies. The recently published STICH trial was the first randomized trial evaluating the prognostic effect of CABG on top of optimal medical therapy in patients with ischemic cardiomyopathy[24]. Results from the viability substudy[25] showed that, regardless of the presence of significant amounts of viable myocardium, surgery did not contribute to improved overall survival. However, the methodology of the viability subtrial study has been questioned. After slow initial patient recruitment, the study protocol was modified and referral for viability testing was left to the discretion of the treating physician. This may have resulted in selection bias which is suggested by the fact that the large majority of the patients in the viability subtrial (81%) met the stringent viability criteria. In addition, 4 different SPECT protocols and dobutamine stress echocardiography were allowed as viability test. Differences in the viability information provided by these two methods (one related to membrane integrity and the other to contractile reserve) and in analytic approaches pose further limitations on the outcome of the trial. Data on functional (ejection fraction, volumes) outcome might have allowed better interpretation of the results, but, unfortunately, these were not included in the recent publications. Finally, the gradual relation between hyperenhancement and both functional outcome after revascularization as well as its time course strongly favor the present concept of hibernation. More randomized studies are necessary to fully establish the place of revascularization in patients with heart failure and ischemic cardiomyopathy. CMR, including cine and LGE imaging, might be the optimal technique to assess pre-operative viability status, peri-operative injury and long-term functional changes. Quantification of LGE images should be standardized to optimize reproducibility and reliability, and to facilitate comparison between different centers. Novel methods such as T1 mapping, which bypass the influences of windowing and variations in signal enhancement by directly measuring the underlying T1 relaxation times of the different areas of the myocardium, might further expand the use of CMR in patients with ischemic cardiomyopathy[5, 26].

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