CMR and LV Remodeling

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Introduction. Myocardial infarction (MI) continues to be a major cause of morbidity and mortality in Western societies. The most recent American Heart Association statistics show that approximately 7,200,000 Americans are now living with a history of MI, and this year an estimated 865,000 Americans will suffer a new or recurrent MI (1). Despite significant progress over the past 20 years leading to modern medical therapy with angiotensin converting enzyme (ACE) inhibitors and beta-blockers, of those patients that survive the acute phase of MI approximately 22% of men and 46% of women will be disabled with heart failure within 6 years (1). Additionally, the high incidence of atherosclerosis, obesity, diabetes, and an aging population combine to ensure that MI and the subsequent occurrence of heart failure will continue to grow as a major public health problem. The progression from acute MI to heart failure occurs through the process of post-MI left ventricular (LV) remodeling. Post-MI LV remodeling involves an early phase of infarct expansion and wound healing, followed by a later phase of progressive fibrosis, cardiomyocyte hypertrophy and dysfunction, wall thinning, LV dilatation, increasing sphericity of shape of the LV, and often mitral valve regurgitation (2). Increasing end diastolic volume (EDV) and end systolic volume (ESV) and decreasing ejection fraction (EF) are important negative clinical prognostic indicators for heart failure and mortality. In acute MI, the location and extent of the infarct, as well as the presence of microvascular obstruction, provide important early prognostic information. For noninvasive diagnosis, all of these parameters can be accurately assessed in post-MI patients by cardiac magnetic resonance (CMR). In addition to clinical application, CMR can be used in preclinical studies aimed at elucidating the molecular and cellular mechanisms underlying post-MI LV remodeling and to evaluate novel therapies aimed at reducing adverse post-MI LV remodeling.

CMR in clinical post-MI LV remodeling. The use of late gadolinium enhancement (LGE) CMR in acute MI has been shown to be a powerful predictor of subsequent LV remodeling and major adverse cardiac events (MACE). In the study by Wu et al (3), 44 patients with acute MI were imaged 10 ± 6 days after MI, 17 patients returned for CMR follow up at 6 months after MI, and clinical follow up was performed for 16 ± 5 months. The major findings of this study were that (a) patients with microvascular obstruction (MO) at initial CMR, defined as hypoenhanced regions with regions of LGE, had more MACE than patients without MO, and (b) for the patients with follow-up CMR, initial MO was associated with greater myocardial scar and more LV remodeling. Similar results demonstrating the importance of LGE in predicting LV remodeling were reported in additional studies by Tarantini (4) and Hombach (5). In the former study, CMR was performed 6 ± 2 days after MI and follow-up echocardiography was performed 6 ± 1 months after MI in 76 patients. At univariate analysis, infarct size, transmural extent of LGE, presence of MO, and troponin level all correlated directly with LV remodeling, defined as a 20% increase in EDV. At multiple regression, transmural extent of LGE and troponin level remained independent predictors of LV remodeling. In the latter study, 110 patients underwent CMR at 6 ± 2 days after MI, and 89 underwent follow-up CMR at 225 ± 92 days after MI. Infarct size, MO and transmural extent of LGE at the initial CMR study were predictive of adverse LV remodeling, and EDV, EF, and MO at initial CMR were predictive of MACE. Together, these studies clearly show that transmural LGE and MO early after MI are predictive of adverse long-term LV remodeling and clinical outcomes.

CMR in preclinical models of post-MI LV remodeling. While significant advances in medical therapy for MI have occurred over the last 20 years, post-MI LV remodeling is not completely understood, and further progress in reducing remodeling or even achieving reverse remodeling may be possible. Preclinical studies aimed at elucidating basic mechanisms of or evaluating novel therapies for post-MI LV remodeling can benefit from CMR imaging of infarction, scar, LV anatomy, and other measures. In particular, CMR in transgenic and knockout mice has recently provided new insights into the roles of specific genes in this disease process.

Fig. 1. Significant differences in EDV and ESV are appreciated as early as 7 days after MI in KO vs WT mice. These differences remained significant at day 28. Error bars represent SEM. *p < 0.05 versus WT.
In one example, Gilson et al used CMR to test the hypothesis that post-MI LV remodeling would be reduced in mice that lack the gene encoding for inducible nitric oxide synthase (iNOS) (6). Early after MI, the elaboration of proinflammatory cytokines and chemokines stimulates the expression of iNOS, which in turn produces large quantities of nitric oxide. Multiple studies had previously reported that cardiomyocytes express active iNOS in response to MI; however, previous studies using iNOS knockout (KO) mice had reported discordant results regarding the role of iNOS in post-MI cardiac dysfunction and mortality (7-9). In the study by Gilson et al, 12 wild-type (WT) and 12 KO mouse were studied by CMR at baseline and at days 1, 7, and 28 after MI. CMR detected no differences in baseline LV anatomy or function between WT and KO mice. However, at days 7 and 28 post-MI, cine MRI revealed decreased ESV and EDV and increased ET in KO vs. WT mice (Fig. 1). Also, wall thinning was reduced in KO mice and adjacent zone circumferential shortening was improved in some adjacent zones. Thus, CMR in mice demonstrated an important detrimental role for iNOS in post-MI LV remodeling.

Summary. Post-MI LV remodeling is integral to the progression from acute MI to heart failure and major adverse events. LGE CMR is prognostic for post-MI LV remodeling and provides important information for the clinical management of patients suffering acute MI. CMR also plays an important role in studies of basic mechanisms underlying post-MI LV remodeling and in studies that evaluate potential new therapies against post-MI LV remodeling.

References.


(7) Sam F, Sawyer DB, Xie Z et al. Mice lacking inducible nitric oxide synthase have improved left ventricular contractile function and reduced apoptotic cell death late after myocardial infarction,[see comment]. Circulation Research 2001; 89(4):351-356.
