

## Chapter 9

### *Summary and future perspectives*

## SUMMARY

In patients with ischemic cardiomyopathy, revascularization of dysfunctional but viable myocardium may lead to improved functional status and prognosis. Cardiac magnetic resonance (CMR) imaging is a non-invasive imaging technique that enables assessment of myocardial morphology, function and viability with high spatial resolution and reproducibility. The main goal of this thesis was to evaluate late gadolinium enhanced (LGE) CMR in the assessment of myocardial viability and the prediction of functional outcome after revascularization in patients with myocardial dysfunction due to chronic ischemic heart disease.

Although visual evaluation of LGE images is sufficient for clinical purposes, it is influenced by image window settings personal preferences of the investigator. An objective, standardized analysis of hyperenhancement would improve reproducibility and facilitate scar quantification, and allow for comparison of results between follow-up studies within the same patient as well as between different centers. In **Chapter 1**, we performed a comparison between visual (qualitative) and standardized (quantitative) analysis of delayed hyperenhancement. For the qualitative analysis, image settings were left at the discretion of the observers. For the standardized analysis, window settings were thresholded at 2-6 standard deviations (SD) above the signal intensity of remote, normal myocardium. In 15 patients with a history of an old myocardial infarction total infarct size and segmental infarct extent were calculated using both visual and standardized methods. The best agreement between visual and standardized analysis was found after thresholding the images at 5 SD above normal signal intensity. The usual cut-off of 2 SD resulted in considerable (i.e. 40%) overestimation of infarct size. In **Chapter 2**, the standardized quantification of late gadolinium enhancement was evaluated in 38 patients in relation to the clinical standard of viability, i.e. functional outcome after revascularization. CMR was performed 1 month before and 6 months after intervention. Enhancement was quantified by thresholding window setting at 2-8 SD above mean signal intensity of a remote normal region, and according to the full width at half maximum (FWHM) method. We found that, although total and segmental extents of hyperenhancement were strongly affected by quantification method, there was no significant difference between the methods predicting functional outcome. With each method the inverse relation between transmural extent of hyperenhancement and

likelihood of functional recovery remained intact, making it difficult to detect small differences in predictive power.

Functional improvement after revascularization is inversely related to the transmural extent of hyperenhancement: segments with no or minimal hyperenhancement are more likely to recover than segments with more extensive scarring. Previous work has suggested that a minimal amount of residual viable cardiomyocytes is required to allow functional recovery. This segmental viable myocardial rim can be quantified using LGE CMR. The likelihood of functional recovery can also be influenced by myocardial infarction occurring at the time of the revascularization. In **Chapter 3**, using a standardized definition of hyperenhancement ( $>5$  SD above signal intensity of remote normal myocardium), we evaluated the effect of the residual, non-enhanced viable myocardial rim and revascularization procedure related necrosis on segmental functional recovery. Forty-five patients were studied 1 month before and 3 months after percutaneous or surgical revascularization. We confirmed that likelihood of functional improvement after revascularization was inversely related to the degree of transmural extent of hyperenhancement. In our study population, thickness of the viable rim was inversely related to the transmural extent of hyperenhancement and, therefore, its presence did not provide additional diagnostic value. Procedure related necrosis was found in 12 (27%) patients, and, in this study group, it was the only (negative) predictor of changes in left ventricular volumes and ejection fraction.

Functional recovery of hibernating regions, especially those with more advanced structural damage, may be considerably delayed. In **Chapter 4**, we studied long-term functional outcome after revascularization. Myocardial function was assessed 1 month before and 3, 6 and  $24 \pm 12$  months after revascularization, and temporal changes were related to baseline extent of hyperenhancement. We found that improvement of viable but dysfunctional myocardium can be considerably delayed and that both likelihood and time course of long-term functional improvement were related to the baseline amount of scar.

The relation between the reduced flow state, the adaptive processes and the potential reversibility of left ventricular dysfunction remains incompletely understood. Therefore, we investigated the level of matching between perfusion, myocardial fibrosis and contraction. The perfusable tissue index (PTI) is a viability marker that does not require metabolic imaging. PTI can be obtained with PET using oxygen-15-labeled water and

carbon monoxide and it reflects the fraction of myocardium that is able to exchange water rapidly (i.e. perfusable by water). The ability to exchange water rapidly requires presence of viable myocardium. Theoretically, PTI in normal myocardium is 1, and previous animal studies have found a close correlation between reduction in PTI and the amount of histochemically defined infarcted tissue. Chapters 5 and 6 are dedicated to the comparison between LGE CMR and PTI. In **Chapter 5**, we studied 20 patients with chronic ischemic left ventricular dysfunction and found that the extent of scar tissue estimated by LGE CMR was inversely related to PTI. However, PTI underestimated LGE CMR with increasing quantities of scar tissue. The optimal correlation between the two techniques was found with LGE viability defined as <25% transmural extent and PTI of 0.89. In **Chapter 6**, we compared LGE CMR and PTI in 14 patients in relation to functional outcome 6 months after revascularization. There were no significant differences between the techniques regarding their diagnostic accuracy in predicting of segmental functional improvement. In agreement with our previous study, LGE cut-off of <25% transmural extent of hyperenhancement and a cut-off value of 0.89 for PTI yielded the best sensitivity and specificity for prediction of functional outcome.

The current role of CMR for the detection of myocardial viability is reviewed in **Chapter 7**. Due to its high spatial resolution, CMR provides qualitative and quantitative, global and regional information on myocardial anatomy and function. In combination with a gadolinium-based contrast agent, CMR is the only technique that allows accurate side by side visualization of myocardial scar and viable tissue, even in regions with advanced wall thinning. Therefore, it may be used to further refine the assessment of viability and the potential of functional recovery in patients with ischemic cardiomyopathy. In addition, LGE imaging provides more insight into processes that may explain lack of functional recovery after revascularization.

## FUTURE PERSPECTIVES

According to the current guidelines on myocardial revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (Wijns et al. European Heart Journal 2010; 31, 2501-2555), assessment 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. The level of evidence for this recommendation is limited and based on retrospective studies. The first randomized trial was recently published (Velazquez et al. N. Engl. J. Med. 2011; 364(17), 1607-1616) and failed to show benefit from surgical revascularization over optimal medical therapy. In the viability substudy (Bonow et al. N. Engl. J. Med. 2011; 364(17), 1617-1625), the investigators found that pre-operative viability assessment did not help to identify a subgroup of patients who might have benefited from surgery. However, the study had several important limitations which make it difficult to translate the results directly to a change in guidelines. As an example, both the indication to viability assessment and the method of testing were non-randomized. Also, the results do not challenge the current basic concept of viability and hibernation. It seems therefore premature to pronounce viability assessment dead. More randomized studies are urgently required to fully establish the role of revascularization in patients with heart failure and ischemic cardiomyopathy. With a rapidly increasing availability, CMR may be the optimal technique to use. A simple protocol using cine and LGE imaging provides the quick and reproducible assessment of pre-operative viability and functional status. The examination can be repeated at various time points postoperatively without harm to the patient to assess functional recovery and to detect clinically unsuspected re-infarction. All analysis should be quantitative, using a standardized definition of hyperenhancement. Using these basic techniques, CMR will help to interpret the results of future studies. In addition, novel methods are currently being developed for the detection of diffuse myocardial fibrosis, which might further refine viability assessment in patients with ischemic cardiomyopathy.