Summary and Clinical Implications of the Thesis

This thesis describes several clinical studies on the subject of cardiovascular magnetic resonance (CMR) in patients after percutaneous coronary intervention (PCI) with stent implantation for acute myocardial infarction (MI). CMR is a noninvasive imaging technique, which combines anatomical, functional and tissue specific information in one single examination, with high (spatial and temporal) resolution and excellent accuracy. In clinical practice, it is used for precise assessment of myocardial function and volumes, the size and transmural extent of infarction, and sequelae of MI. Since several cardiac parameters important for clinical decision making in ischemic heart disease can be obtained in a single-stop examination, an increasing number of cardiologists have adapted CMR in their diagnostic work-up.

Myocardial Function and Acute Myocardial Infarction

In the first part, we evaluated myocardial function and infarction in patients treated with primary PCI. We compared the safety and feasibility of CMR scanning in patients with coronary stents at high magnetic field (3.0 T) with the current clinical standard at 1.5 T in Chapter 2. CMR scanning at high magnetic field offers improved image quality by higher spatial and temporal resolution, which shortens examination times and increases diagnostic accuracy. However, high field CMR is also more sensitive to disturbances in homogeneity of the magnetic field which translates into image artifacts. These effects may counteract the gain in scan duration and image quality. Also, it is unknown whether 3.0 T scanning is safe in patients with stents, with regard to the potential risks associated with migration, the induction of an electrical current and heating of the stent by the high magnetic field.

Our study demonstrated that it is safe and feasible to perform CMR at 3.0 T in the acute (within 7 days) and chronic (around 4 months) phase after stent implantation for acute MI. Although the image quality at 3.0 T is sufficient to assess myocardial function for clinical purposes, quantitative segmental analysis and infarct imaging is less reliable compared to 1.5 T. This is mainly due to dark band, flow and stent artifacts. An important conclusion of this chapter is that further optimization of pulse sequences at 3.0 T is essential to make 3.0 T CMR scanning suitable for clinical cardiology.

The assessment of myocardial function and viability using electromechanical endocardial mapping (EEM) is compared with CMR in Chapter 3. Therapies aiming at enhancing the repair of infarcted myocardium rely on the evaluation of the underlying target tissue. Identification and quantification of viable myocardium is therefore of great interest in ischemic heart disease, and especially the combination with targeted delivery of myocardial therapies is
promising. EEM is a system that provides information on regional electrical and mechanical properties of the ventricular cavity. Since infarcted regions of myocardium have reduced electrical characteristics, the local endocardial electrocardiogram has been proposed as an indicator of viability. Also, the ability of EEM to provide 3D real-time images enables the combination of viability assessment with direct myocardial treatment. In this chapter, we validated the accuracy of the EEM system to assess myocardial function and viability against CMR.

Although a relatively large underestimation in global myocardial function was found using EEM, total infarct size correlated well between EEM and CMR. Regional analyses demonstrated that EEM can be used to determine both regional function and transmural extent of infarction in patients with previous MI, however, reliable cut-off values could not be established. Therefore, exact pinpointing of myocardial areas benefiting from direct injection of therapeutics may remain difficult with EEM.

Since CMR imaging is not restricted to anatomical orientations, it has the ability of 3D quantification of function of the right ventricle with high accuracy. Right ventricular function has proven to be of significant importance in a wide range of cardiac disease, but acquisition and analysis using CMR remain time consuming. In Chapter 4, we investigated whether a more simple and rapid semi-quantitative method which is adapted from echocardiography can be applied in CMR, and evaluated its diagnostic performance for identifying right ventricular dysfunction.

Our data demonstrated that the semi-quantitative approach correlates well with the full 3D volumetric assessment of right ventricular function, and may thus be regarded as a reliable and easy method to screen for patients with right ventricular dysfunction in clinical practice. The reproducibility between two semi-quantitative measurements in one study by one investigator (intra-observer variability) was better than between the same semi-quantitative measurement in one study by two different investigators (inter-observer variability). However, semi-quantitative measurements were overall less reproducible than the full 3D volumetric approach, and therefore, the full quantitative method is preferred for research purposes or to evaluate treatment response.

**Microvascular Injury in Acute Myocardial Infarction**

In the second part of the thesis, different tools and techniques to assess the incidence and clinical significance of microvascular injury (microvascular obstruction, MVO) were evaluated, with respect to functional recovery after primary PCI for acute MI. T2-weighted CMR imaging is evaluated for the identification of microvascular injury in patients after acute MI in Chapter 5. Unenhanced T2-weighted spin echo imaging can be used for the visualization of acute
Chapter 13.1

infarction by visualizing infarct-related edema, which generates a higher signal intensity in necrotic myocardium compared to healthy, non-ischemic myocardium. Additionally, hemorrhage in areas with microvascular injury may attenuate the high signal intensity of T2-weighted images, by the magnetic effects of deoxygenated hemoglobin and its degeneration products. In this chapter, we explored the relation between hemorrhage, infarct size and MVO in patients after reperfused acute MI.

Our study showed that in patients with MVO, T2-weighted signal intensity in the core of the infarct was lower than in the peripheral part of the infarcted myocardium in the majority of patients. The attenuated core T2-weighted signal can be attributed to intramyocardial hemorrhage, and the difference between core and peripheral signal intensity was strongly related to markers of myocardial function, infarct size and MVO size. Thus, T2-weighted CMR imaging visualizes both infarct-related edema and intramyocardial hemorrhage, and when used in combination with late gadolinium-enhanced imaging, provides a comprehensive characterization of the acutely infarcted and reperfused myocardium.

The accuracy to visualize MVO of several gadolinium-enhanced CMR imaging techniques is evaluated in Chapter 6. Two techniques have been described to detect MVO using CMR in the clinical setting: first pass perfusion and late gadolinium enhancement. First pass perfusion provides dynamic information on the rapid wash-in of the gadolinium contrast agent, however, with limited image quality and incomplete coverage of the myocardium. The late enhancement technique on the other hand, offers information on a more equilibrated distribution of the contrast agent in the infarct area with excellent image quality, but is limited by a longer examination time since it requires at least 10 minutes to reach equilibrium of the contrast agent and multiple breath holds to fully cover the left ventricle. We have compared both techniques in this chapter, together with a third (intermediate) method, consisting of a static imaging technique early after contrast administration with excellent image quality and complete coverage of the myocardium in a single breath hold.

Our results suggest that areas of MVO as depicted on late gadolinium-enhanced images best predict remodeling of the left ventricle, and show the highest difference in signal intensity between the infarct and MVO area. Additionally, late gadolinium enhancement offers information on size and extent of infarction, right ventricular involvement and thrombus formation, which assists the cardiologist in clinical decision making. We therefore recommend late gadolinium enhancement as the preferred technique to evaluate microvascular injury in patients after acute MI.

Chapter 7 investigated infarct size, presence and extent of MVO, and changes over time in relation to myocardial function in a uniform, optimally treated patient group after acute MI. Clinical studies have demonstrated improvement of myocardial function and infarct size involution during follow-up in patients after acute MI. However, these studies were performed
in heterogeneous patient groups with a variety of revascularization strategies, and lacked
detailed information on (anti-thrombotic) medication.
In this study, we used late gadolinium enhancement and cine CMR imaging to monitor infarct
size, microvascular injury and left ventricular volumes and function in a patient group with
optimal reperfusion therapy. Using standardized analysis, we found a significant involution of
infarct size of approximately 20% at 4 months, and the majority of patients had evidence of
MVO despite optimal therapy. Although its presence identified patients with larger infarcts
and worse myocardial function, the change in myocardial function over time was comparable
to patients without MVO. Additionally, there were no differences between patients with small
or large areas of microvascular injury, suggesting that the mere presence of MVO may be
clinically more relevant than its extent.

The relation between CMR characteristics of microvascular injury and the currently used
angiographic and electrocardiographic measures of incomplete reperfusion were studied in
Chapter 8. In previous studies it has been demonstrated that MVO determined by
gadolinium-enhanced CMR is predictive of left ventricular remodeling and major adverse
cardiac events after acute MI, but it is not well known how it compares to commonly used
criteria of microvascular injury. Thrombolysis In Myocardial Infarction (TIMI) flow grade and
myocardial blush grade from angiography and the degree of ST-segment recovery (ST-
segment resolution) from electrocardiography were compared with first pass perfusion (early
MVO) and late gadolinium enhancement (late MVO) imaging in a uniformly treated patient
group, after primary stenting and optimal medical therapy.
ST-segment resolution, but not TIMI flow grade and myocardial blush grade, correlated well
with the presence of MVO on CMR. Of all angiographic, electrocardiographic and CMR
variables, late MVO was the strongest predictor of change in left ventricular global volumes
and myocardial function at 4 months follow-up. Regional analysis showed that late MVO had
incremental diagnostic value to transmural extent of infarction (odds ratio 0.18, p<0.0001).
These results suggest that, in the acute setting after MI, MVO might be more relevant than
infarct size or transmural extent.

In Chapter 9, the functional characteristics of microvascular injury as assessed with coronary
Doppler flow velocity measurements were compared with the anatomical severity of MVO as
determined by CMR, in patients treated with primary PCI for acute MI. Previous Doppler flow
studies have established that early systolic retrograde flow, a rapid deceleration of the
diastolic flow velocity and a reduced coronary flow velocity reserve are typical findings
associated with microvascular injury, whereas CMR is able to directly visualize size and extent
of MVO using late gadolinium enhancement.
In this study, we showed that the extent and size of microvascular injury as assessed by late
gadolinium-enhanced CMR correlated well with the coronary Doppler flow parameters.
Furthermore, after adjusting for MVO (size or extent), infarct size and transmural extent of infarction were no longer associated with systolic retrograde flow and deceleration of the diastolic flow velocity, while MVO remained the only factor independently related to these flow parameters. These findings support the hypothesis that the changes in coronary blood flow velocity patterns are the result of an injured microvasculature rather than a mere reflection of larger or more transmural infarcts.

In current clinical practice, an electrocardiogram is routinely obtained shortly after PCI for acute MI, to evaluate the success of reperfusion by means of ST-segment resolution. ST-segment resolution is an established predictor of clinical outcome in acute MI, whereas the presence of pathologic Q waves is related to larger infarcts and an increased mortality in patients with old infarction. It is unknown whether early Q wave assessment provides additional prognostic value to standard ST-segment evaluation in patients after primary PCI for acute MI. Therefore, we have undertaken a more detailed study of the electrocardiogram early after primary PCI, including the change of ST-segment elevation between pre and post PCI (ST-segment resolution), the degree of persistent ST-segment resolution post PCI (residual ST-segment elevation), and Q wave assessment post PCI (number of pathological Q waves) in relation to a full quantitative CMR assessment in Chapter 10. The principal findings of the study were that residual ST-segment elevation and the number of Q waves on the post-procedural electrocardiogram are complementary in predicting myocardial function and necrosis. Residual ST-segment elevation and the number of Q waves were strong, independent predictors of left ventricular function. Additionally, residual ST-segment elevation was the single and best predictor of microvascular injury, while Q wave count best predicted infarct size and transmural extent of infarction. Intriguingly, ST-segment resolution was neither predictive for myocardial function or necrosis, nor for microvascular injury.

A Novel Treatment Strategy in Acute Myocardial Infarction

The third part of the thesis concerns the first Dutch multicenter cell therapy study: The HEBE trial, named after the goddess of youth in Greek mythology. Recently, several preliminary reports have demonstrated that cell transplantation after acute MI in humans is safe, preserves myocardial function and improves myocardial perfusion. Different mechanisms have been suggested by which bone marrow-derived progenitor cells may induce a beneficial effect: 1. enhanced neovascularization following release of angiogenic and arteriogenic cytokines by the injected cells, 2. enhanced scar tissue formation following the inflammatory response, 3. decreased apoptosis, and 4. myocardial regeneration. Although there is an ongoing dispute regarding the regeneration hypothesis, neovascularization is generally accepted to be an
important mechanism of the documented functional recovery after cell treatment. The principle limitation of most previously conducted studies is that these studies are small and/or non-controlled, and/or have not included an appropriate control group, and all were performed single center. Chapter 11 provides the rationale and design for the randomized and controlled HEBE trial, which determined the effect of intracoronary infusion of mononuclear cells in patients with acute MI treated by PCI, in a multicenter design. Additionally, to distinguish between the effect of progenitor cells and other mononuclear cells on myocardial function, patients were randomized to be treated with either intracoronary infusion of bone marrow-derived mononuclear cells or mononuclear blood cells derived from peripheral blood. The primary end point of the study was the change in regional myocardial function after 4 months, as measured with CMR.

A non-randomized pilot HEBE trial was described in Chapter 12, in which all patients were treated with bone marrow-derived mononuclear cells after acute MI, to assess the safety and feasibility of intracoronary cell infusion in a multicenter setting. Our results showed that intracoronary infusion of autologous bone marrow-derived mononuclear cells appears to be safe and feasible in a multicenter setting. Furthermore, a summary was given of the changes in myocardial function in published randomized trials of intracoronary infusion of bone marrow cells in a meta-analysis, which demonstrated an overall significant treatment benefit of 2.2% in left ventricular ejection fraction compared to control patients. In the pilot trial, we observed a modest, but significant increase in myocardial function as well. The most notable result of our analysis of regional function was that improvement of myocardial function in regions with almost transmural extent of infarction is similar to regions with less transmural infarction. However, efficacy of cell therapy was not the aim of the study, since a control group was not included. With great curiosity we await the results of the main trial.

Future Perspectives

Evaluation of microvascular injury is useful for risk stratification of patients with an acute myocardial infarction after successful percutaneous coronary intervention. It may facilitate decision making regarding the necessity of additional interventions, such as cell therapy. Theoretically, improvement of microvascular perfusion may have beneficial effects on infarct healing, myocardial remodeling and collateral formation, which may ultimately lead to better outcome. Finally, besides selecting patients for adjunctive therapy, measurements of MVO can be very useful in evaluating the efficacy of novel treatment strategies aiming at preserving the microvasculature when treating acute MI in both clinical and experimental studies. This thesis demonstrated that the presence of MVO at late gadolinium enhancement is the best prognosticator for functional recovery, superior to angiography and electrocardiography,
and even exceeding the predictive value of the size and transmural extent of infarction. It should therefore play a pivotal role as an endpoint assessment tool in trials of putative mechanical, pharmacologic and biologic therapeutics aiming at reducing infarct size and myocardial injury in the setting of acute MI.

Further studies may be valuable to investigate the long-term outcome of optimally treated patients with MVO, to confirm the results of this thesis with respect to adverse events and mortality. Additionally, detection of MVO in patients with left ventricular ejection fraction of 30% or below may influence the timing of internal cardioverter-defibrillator implantation. Since these patients have a low likelihood of functional recovery, they could be considered for direct implantation rather than to wait for the 40-days re-evaluation. However, randomized trials are necessary to confirm this hypothesis.

Since the prognosis of patients after acute MI strongly depends on the presence of microvascular injury, different treatment strategies focus on the maintenance of microvascular perfusion after reperfusion. However, the significance and contribution of different mechanisms responsible for microvascular injury during acute MI are not fully understood, and need to be evaluated in order to provide optimal therapy. Further studies should therefore focus on the relationship between the coronary microcirculation and pathogenesis of ischemic heart disease, in order to understand the complex mechanism of MI and reperfusion injury.