Chapter 1

*General Introduction and Outline of the Thesis*
A thirty-nine year old male with prior history of a percutaneous coronary intervention of the left anterior descending (LAD) coronary artery presented with progressive shortness of breath. His ECG showed loss of R-wave and negative T-waves in the precordial leads V1-V6. Echocardiography showed moderate impairment of LV function with wall thinning and akinesia of the mid and distal anterior and anteroseptal segments and apex. Coronary angiography revealed proximal occlusion of the LAD and 90% stenosis of the left circumflex artery. Attempts to cross the occlusion in the LAD with a guidewire were unsuccessful, and patient was accepted for coronary artery bypass grafting of both vessels if viability could be demonstrated in the territory of the occluded LAD. Cine Cardiovascular Magnetic Resonance (CMR) imaging confirmed the morphological and functional left ventricular (LV) changes (fig): LV end-diastolic volume (EDV) 147 mL, end-systolic volume (ESV) 84 mL, ejection fraction (EF) 43%. Late gadolinium enhanced (LGE) imaging showed absence of contrast enhancement in the dysfunctional area (fig). Patient underwent successful and uncomplicated total arterial revascularization using both internal mammary arteries. Six months after surgery, exercise tolerance had normalized. CMR examination revealed normalized wall thickness and recovery of contractile function of the previously dysfunctional and thinned segments (fig). EDV was now 102 ml, ESV 65 ml, and EF 64%.

Severe reductions in coronary flow may lead to myocardial dysfunction without co-existing necrosis. Stunning refers to a limited period of persistent dysfunction observed after transient total or near-total occlusion of a coronary artery. In a clinical context, it is typically encountered after timely reperfusion in patients with acute myocardial infarction. Hibernation refers to the situation where the reduction in myocardial flow occurs slowly and the chronically ischemic myocardium is able to adapt by decreasing contractile performance, and, subsequently, by morphological changes, all aimed at reducing metabolic demand. Initially, the myocardial dysfunction was thought to be the result of chronically reduced baseline myocardial blood flow. Later, a concept of severe impairment of vasodilator reserve was proposed, leading to repetitive myocardial
ischemia after any increase in oxygen demand (repetitive stunning)\(^2\). The typical clinical context portrays a patient with heart failure, severe left ventricular dysfunction and extensive coronary artery disease. Echocardiography generally shows regional and global dysfunction as well as myocardial wall thinning. Histological analysis of tissue samples obtained from these areas shows evidence of profound structural changes, including loss of contractile myofilaments with replacement by glycogen and a variable degree of intercellular fibrosis\(^3-5\). The relation between the reduced flow state, the adaptive processes and the potentially reversible left ventricular dysfunction remains incompletely understood. The adaptations are generally, although not unanimously, regarded as self preserving (‘the smart heart theory’)\(^1\). Several mechanisms have been suggested to play a role, like changes in adrenergic receptor density, upregulation of cardioinhibitory cytokines and the increased expression of cardioprotective genes and proteins \(^6-8\). Regardless of the mechanisms, recovery of function of hibernating myocardium may occur with revascularization. If myocardial flow remains low, irreversible myocardial damage and permanent dysfunction will eventually follow\(^9\).
The terms myocardial viability and hibernation are frequently used synonymously, however, they differ in point of view: viability is defined in a prospective manner and hibernation in a retrospective one. Viability characterizes the state of dysfunctional myocardium: it implies that dysfunctional myocytes are alive and have the potential to recover after revascularization. Lack of recovery does not exclude the presence of myocardial viability. The original concept of hibernation requires that functional recovery has occurred.

Chronic ischemic myocardial dysfunction is associated with a poor prognosis. Although patients might benefit from revascularization, peri-operative morbidity and mortality rates are high. Current guidelines therefore state that patient management should be guided by the non-invasive assessment of myocardial viability. Patients with dysfunctional, but viable myocardium should be considered for revascularization, whereas patients with irreversibly damaged, non-viable myocardium should be treated medically.

A number of different techniques (dobutamine stress echocardiography, single photon emission computed tomography, positron emission tomography, cardiovascular magnetic resonance imaging) can be used to demonstrate the presence of viable myocardium before revascularization.

**Dobutamine stress echocardiography** (DSE) is used to evaluate the presence of recruitable contractile reserve, i.e. improvement of wall motion or thickening. Low dose (5 to 10 µg • kg⁻¹ • min⁻¹) dobutamine can lead to increased contractility in dysfunctional segments that are viable. The incidence of contractile reserve is inversely related to degree of baseline wall motion abnormalities and severity of reduction of resting myocardial perfusion. The mean sensitivity and specificity values for low dose dobutamine echocardiography to predict regional functional recovery after revascularization are 82% and 79%, respectively. Higher doses may surpass the ischemic threshold, causing wall motion deterioration in these viable segments, reflecting inducible ischemia. This biphasic response is highly predictive of recovery of function after revascularization. The reported mean sensitivity and specificity values for high dose DSE are 79% and 85%, respectively.
Single-photon emission computed tomography (SPECT) uses Thallium-201 and Technetium-99m labeled tracers. Myocardial uptake of Thallium-201 is dependent on regional blood flow and myocyte cell membrane integrity. Imaging protocols require Thallium-201 injection at rest or immediately after (pharmacological) stress with subsequent late imaging following redistribution of the tracer. The initial distribution of Thallium-201 primarily reflects regional myocardial blood flow. Late images are a marker of sarcolemmal integrity and therefore reflect myocardial viability. Reported mean sensitivity and specificity for this technique to predict improvement in regional contractile function after revascularization are 87% and 55%, respectively. Intracellular uptake and retention of Technetium-labeled tracers, which are lipophilic molecules, is dependent on cell membrane integrity and intact mitochondrial function. Uptake of these agents provides information on both myocardial perfusion and viability. However, since the uptake depends on both perfusion and viability, viability may be underestimated in areas with reduced perfusion at rest. The mean sensitivity and specificity to detect regional functional recovery after revascularization are 79% and 58%, respectively.

Positron emission tomography (PET) has been considered as the gold standard for viability assessment using metabolic tracers. Under aerobic conditions, myocytes use predominantly fatty acids. With ischemia, fatty acid metabolism is diminished and glucose uptake is enhanced. Thus, hibernating myocardium is characterized by diminished perfusion and function and upregulation of glucose metabolism relative to flow. PET images are acquired using fluorine-18-deoxyglucose (FDG) to measure exogenous glucose uptake by myocardium in combination with a myocardial perfusion tracer. Regions that show a concordant reduction in both myocardial blood flow and FDG uptake (i.e. flow-metabolism match) are considered to be irreversibly injured, whereas regions in which FDG uptake is relatively preserved or increased despite of having a perfusion defect (i.e. flow-metabolism mismatch) are considered ischemic but still viable. Compared to SPECT and DSE, FDG PET has the highest sensitivity value of 93% for prediction of functional recovery after revascularization and a modest specificity of 58%.

The Perfusable tissue index (PTI) is an alternative method for detecting myocardial viability and has the advantages that metabolic imaging is not required. PTI reflects
the fraction of myocardium that is able to exchange water rapidly (i.e. perfusable by water). It can be obtained with PET using oxygen-15-labeled water ($H_2^{15}O$) and carbon monoxide ($C^{15}O$). Dysfunctional myocardium with normal or near normal PTI ($\pm 1.1$) is expected to be viable because the amount of scar tissue is limited. In contrast, dysfunctional myocardium with reduced PTI is less likely to be viable because more scar tissue is present. The optimal threshold value for PTI to predict functional recovery after revascularization is yet to be established with reported cutoffs varying between 0.70 and 0.90$^{18,21}$. The reported mean sensitivity and specificity values for prediction of regional functional recovery after revascularization are 89% and 94%, respectively$^{23}$.

**CARDIOVASCULAR MAGNETIC RESONANCE IMAGING IN THE ASSESSMENT OF MYOCARDIAL VIABILITY**

**Cardiovascular magnetic resonance imaging** is a versatile imaging technique that allows the one stop assessment of anatomy, function, flow, perfusion and scar in patients with ischemic heart disease. CMR can be used in a number of ways in the evaluation of myocardial viability. First, end-diastolic wall thickness can be assessed using cine imaging. Both echocardiographic and CMR studies have demonstrated that, in patients with chronic ischemic heart, disease thinned myocardium (with end-diastolic wall thickness < 5.5 – 6.0 mm) represents scar and will not improve after revascularization$^{24,25}$. Second, CMR cine imaging can be used in combination with low dose dobutamine, similar to DSE. Finally, the presence of myocardial scar can be studied by late gadolinium enhancement imaging (LGE). LGE accurately visualizes regional myocardial necrosis in patients with ischemic heart disease$^{26}$. Infarcted regions are easily identified as regions of high signal intensity within noninfarcted, non-enhanced myocardium. Excellent spatial resolution (1.5 x 1.5 mm in plane resolution) and high contrast between scarred and viable myocardium allow accurate and reproducible 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 CMR has the mean sensitivity and specificity of 81% and 83%, respectively, for predicting of functional recovery$^{27}$.
LGE CMR has several advantages compared to the other techniques used in the assessment of viability. Stress is not required, which makes it both safer and more practical than dobutamine stress cine imaging. Furthermore, CMR offers the simultaneous and detailed visualization of morphology (wall thickness, left ventricular shape), function (regional and global) and tissue characterization (side by side visualization of necrosis and viable myocardium). In addition, CMR does not expose the patient to the potentially harmful effects of ionizing radiation, which is even more relevant when doing follow-up studies.

Although the literature on the use of LGE CMR in patients with ischemic myocardial dysfunction is gradually expanding, clinical evidence is still limited in comparison to nuclear techniques and dobutamine stress echocardiography. The goal of this thesis is therefore to further evaluate and optimize LGE CMR in the assessment of myocardial viability and the prediction of functional outcome after revascularization in patients with chronic ischemic heart disease.

**OUTLINE OF THE THESIS**

Although visual assessment of LGE images is generally sufficient for clinical purposes, it is influenced by image window settings reflecting 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 studies from different centers. Chapters 1 and 2 address this issue. In Chapter 1 we compared visual analysis of hyperenhancement by team of experienced observers with quantitative analysis after thresholding window settings of the images at 2 – 6 standard deviations above the mean signal intensity of remote, non-scarred myocardium. In Chapter 2 we evaluated standardized quantification of late gadolinium enhancement in relation to the clinical standard of viability, i.e. functional outcome after revascularization.

In Chapters 3 and 4 we studied the relation between transmural extent of hyperenhancement and functional improvement after revascularization, using the standardized definition of hyperenhancement. In Chapter 3 functional outcome was assessed early (3 months) after revascularization. Predictive accuracy of LGE imaging was evaluated, combining data of transmural scar extent, viable rim thickness and occurrence of revascularization related necrosis. In Chapter 4 we studied long term (> 1 year) functional outcome and time course of functional improvement.
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In Chapters 5 and 6 we compared LGE imaging to PET perfusable tissue index. Chapter 5 provides a head to head comparison between the two techniques. Chapter 6 studies the diagnostic accuracy of both techniques to predict functional outcome after revascularization, as assessed by cine CMR. Finally, Chapter 7 provides an overview of our current understanding of the detection of myocardial viability by CMR.
General introduction and outline of the thesis

REFERENCES


