Infarct Size and Myocardial Function
A methodological study

Lene Rosendahl

Division of Cardiovascular Medicine
Department of Medical and Health Sciences
Linköping University, Sweden

Linköping 2010
This work has been conducted in collaboration with the Center for Medical Image Science and Visualization (CMIV, http://www.cmiv.liu.se/) at Linköping University, Sweden. CMIV is acknowledged for provision of financial support and access to leading edge research infrastructure.

Infarct Size and Myocardial Function – A methodological study

Faculty of Health Science, Linköping University
Dissertation, No. 1169

Copyright © by Lene Rosendahl, 2010

http://www.liu.se/cmr

Published article has been reprinted with the permission of the copyright holder.

Printed in Sweden by LiU-Tryck, Linköping, Sweden, 2010

ISBN 978-91-7393-437-4
ISSN 0345-0082

Cover picture: Jennie Palmér.
LGE images displaying short axis (front page) and long axis views (back page) of the left ventricle. The white area indicates scar and the black area healthy myocardium.
To

Malin, Sara, Anna

&

Jan

If we really knew what we were doing, it would not have been called research, would it?

Albert Einstein
## Contents

Abstract 1

Svensk Sammanfattning 3

List of Original Papers 5

Abbreviations 7

1 Introduction 9

2 Coronary Artery Disease 11
   Epidemiology.................................................................11
   Pathophysiology.............................................................11
   Infarct size and prognosis................................................12
   Diagnosis...........................................................................13
   Myocardium-at-risk and treatment.....................................14

3 Myocardial Dysfunction 15
   Left ventricular systolic function........................................15
   The ischemic cascade........................................................15
   The effects of ischemia.......................................................16

4 Magnetic Resonance Imaging 19
   General principles............................................................20
   Signal and contrast.............................................................21
   Scar visualization with the Late Gadolinium Enhancement technique...........................................22
   A comparison between a fast and a segmented scar sequence......................................................23
   Segmentation of myocardium and of scar........................................24

5 Cardiac Ultrasound 27
   General principles............................................................27
   Echocardiographic techniques..........................................28
   Myocardial deformation or “Strain”......................................29
6 Myocardial Perfusion SPECT 31
   General principles.................................................................31
   Radioactive tracers...............................................................32
   Imaging protocols and perfusion defect size........................32

7 Aims of the Study 35

8 Material and Methods 37
   Study population........................................................................37
   Magnetic Resonance Imaging.......................................................38
   Magnetic Resonance Imaging Analysis........................................39
   Echocardiography........................................................................41
   Myocardial Perfusion SPECT......................................................43
   Statistics....................................................................................44

9 Results 47
   Paper I: Infarct size is comparable when determined with LGE and MPS........47
   Paper II: The semi-automatic method shortens the evaluation time with maintained clinical accuracy.........................................................49
   Paper III: SS_SSFP displays better imaging quality and equal infarct size compared to IR_FGR, in patients with ongoing atrial fibrillation........52
   Paper IV: WMSI is more sensitive that strain in detecting area-at-risk........55

10 Discussion 59
   Infarct size..................................................................................59
   Functional measurements of the left ventricle................................63
   Future developments and clinical implications..........................65

Conclusions 69

Acknowledgements 71

References 73

Papers I – IV 87
Abstract

The size of a myocardial infarction (MI) and the concurrent effect on left ventricular (LV) function are essential for decisions regarding patient care and treatment. Images produced with the late gadolinium enhancement (LGE) technique visualize the scar with high spatial resolution. The general aim of this thesis was to study methods to assess scar size in chronic MI, primarily with the use of LGE, and to relate area-at-risk and LV function to scar size.

Myocardial perfusion single photon emission computed tomography (MPS) is a well-established technique for the assessment of MI size. Our study showed that there is a fairly good agreement between MPS and LGE in the determination of scar size. Wall motion score index (WMSI) correlated moderately with both infarct size and infarct extent determined with LGE.

Manual delineation of myocardium and scar is time-consuming and subjective and there is a need for help in objective assessment. We showed that the semi-automatic computer software, Segment, reduced the evaluation time ≥50% with maintained clinical accuracy.

The segmented scar sequence - inversion recovery fast gradient echo, IR_FGRE, is a well-documented sequence for scar determination, however, the sequence requires regular heart rhythm and breath holding for good imaging. We showed that a single shot scar sequence - steady state free precession, SS_SSFP - acquired under free breathing in patients with ongoing atrial fibrillation, had significantly better image quality than IR_FGRE. The scar size and the error of determination were equal for both sequences and the examination time was shorter with SS_SSFP.

In an acute MI it is essential to know the myocardial area-at-risk. WMSI is clinically the most common way of assessing LV function, but is highly subjective. Tissue Doppler imaging with strain measurements is considered objective and quantitative in assessing both global and regional LV function compared to WMSI. Our results showed that WMSI is superior to strain for the detection of scar with transmurality ≥50% in patients with acute MI. Also WMSI correlated better than strain on all levels (global, regional, segmental) with final scar size determined with LGE.

LGE images visualize myocardial scar much more distinctly than any other modality. This new technique needs clinical validation but promises intense competition with existing modalities such as myocardial scintigraphy and echocardiography. However, in individual patient care all modalities should be used according to their own advantages and limitations.
SVENSK SAMMANFATTNING

Vid kranskärlssjukdom uppstår förändringar i kranskärlen som kan leda till att syrerikt blod hindras från att nå hjärtmuskulaturen, vilket kan ge upphov till hjärtinfarkt. Hos patienter som har drabbats av hjärtinfarkt är det viktigt att bedöma dess storlek vilken kommer att påverka patientens prognos och därmed behandling. Att bedöma hjärtinfarktstorleken med magnetkamera (MR) är en relativt ny teknik som med stor noggrannhet visar utbredningen av en infarkt i hjärtmuskuléväggen. Undersökningar har visat att om infarkten omfattar mindre än halva väggtjockleken är sannolikheten hög för framgångsrik effekt av flödesbefrämjande behandlingar. Om utbredningen av hjärtinfarkten överskridet halva väggtjockleken minskar sannolikheten för god effekt av revaskularisering på väggrörlighet och därmed på hjärtats pumpförmåga. Syftet med denna studie var att i lugnt skede efter hjärtinfarkt bedöma infarktstorleken, huvudsakligen med kontrastförstärkt MR. Vi har även värderat effekten av akut hjärtinfarkt på vänsterkammares pumpförmåga och försökt bedöma hur mycket hjärtmuskel som kan rådhas.

I första delstudien jämfördes infarktstorleken bestämd med den nya MR-metoden med en väldokumenterad referensmetod, myokardscintigrafi. Vid bedömning av infarktstorleken med myokardscintigrafi användes ett helautomatiserat program, PERFIT®, medan utvärderingarna av infarktbilderna från MR gjordes manuellt. Vi fann, i likhet med andra författare, en god överensstämmelse mellan infarktstorleksbedömningarna med de två olika metoderna, även om myokardscintigrafi visade något större infarktstorlek.


Den mest väldokumenterade MR sekvensen för infarktbedömning, IR_FGRE, kräver att patienten har regelbunden rytm samt kan hålla andan upprepade gånger under undersökningstiden. Detta gör att undersökningstekniken inte passar sig för svaga och påverkade patienter. I
delstudie tre jämförde vi en snabb MR sekvens, SS_SSFP, där patienten inte behöver ha regelbunden hjärtrytm eller kunna hålla andan, med IR_FGRE hos patienter med kronisk hjärtinfarkt och pågående förmaksslimer. Vi fann att SS_SSFP hade signifikant högre bildkvalitet jämfört IR_FGRE och att det inte vara någon signifikant skillnad mellan infarktstorleks- och infarktutbredningsbedömningen mellan de två sekvenserna. Även undersökningsstiden reducerades betydligt med den snabbare sekvensen, från knappt 9 minuter med IR_FGRE, minuter till drygt 4 minuter med SS_SSFP.

LIST OF ORIGINAL PAPERS

This thesis is based in the following four papers, which will be referred to by their Roman numerals:


(Articles reprinted with permission)
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>201Tl</td>
<td>Thallium 201</td>
</tr>
<tr>
<td>2D</td>
<td>2-dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>3-dimensional</td>
</tr>
<tr>
<td>99mTc</td>
<td>Technetium 99m</td>
</tr>
<tr>
<td>b-SSFP TFE</td>
<td>Balanced Steady State Free Precession Turbo Field Echo</td>
</tr>
<tr>
<td>BW</td>
<td>bandwidth</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
</tr>
<tr>
<td>CCTA</td>
<td>Cardiac Computed Tomographic Angiography</td>
</tr>
<tr>
<td>CKMB</td>
<td>the MB fraction of creatine kinase</td>
</tr>
<tr>
<td>CNR</td>
<td>Contrast-to-Noise ratio</td>
</tr>
<tr>
<td>COV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>CardioVascular Disease</td>
</tr>
<tr>
<td>ECG</td>
<td>ElectroCardioGram</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection Fraction</td>
</tr>
<tr>
<td>FA</td>
<td>Flip Angle</td>
</tr>
<tr>
<td>FGRE</td>
<td>Fast Gradient Echo</td>
</tr>
<tr>
<td>FOV</td>
<td>Field-of-View</td>
</tr>
<tr>
<td>Gd</td>
<td>Gadolinium</td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>Gadopentetate dimeglumine</td>
</tr>
<tr>
<td>IR</td>
<td>Inversion Recovery</td>
</tr>
<tr>
<td>IR_FGRE</td>
<td>Inversion Recovery - Fast Gradient Echo</td>
</tr>
<tr>
<td>LAD</td>
<td>Left Anterior Descending Artery</td>
</tr>
<tr>
<td>LCx</td>
<td>Left Circumflex Artery</td>
</tr>
<tr>
<td>LGE</td>
<td>Late Gadolinium Enhancement</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>MAM</td>
<td>Mitral Annular Movement</td>
</tr>
<tr>
<td>MCE</td>
<td>Myocardial Contrast Echocardiography</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>MPS</td>
<td>Myocardial Perfusion SPECT</td>
</tr>
<tr>
<td>MR(I)</td>
<td>Magnetic Resonance (Imaging)</td>
</tr>
<tr>
<td>NEX</td>
<td>Number of Excitations</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>RCA</td>
<td>Right Coronary Artery</td>
</tr>
<tr>
<td>RF</td>
<td>Radio Frequency Pulse</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver-Operating-Characteristics</td>
</tr>
</tbody>
</table>
### Infarct Size and Myocardial Function

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SI</td>
<td>Signal Intensity</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-Noise ratio</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
</tr>
<tr>
<td>SS_SSFP</td>
<td>Single Shot Steady State Free Precession</td>
</tr>
<tr>
<td>SSFP</td>
<td>Steady State Free Precession</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-Elevation Myocardial Infarction</td>
</tr>
<tr>
<td>TDI</td>
<td>Tissue Doppler Imaging</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TI</td>
<td>Inversion Time</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
</tr>
<tr>
<td>WMSI</td>
<td>Wall Motion Score Index</td>
</tr>
</tbody>
</table>
1. **INTRODUCTION**

Coronary artery disease (CAD) is very common and affects many people worldwide and in Sweden. The technical advances during the last decades in diagnosing cardiac diseases are tremendous and contribute with the improved treatment to a longer patient survival. After the development of fast magnetic resonance imaging (MRI) sequences, MRI has entered the field of cardiac diagnostic imaging. Contrast enhancement and a high spatial resolution enables cardiac MRI to visualize myocardial infarct (MI) scar\(^1\). The presence of scar in the myocardium is a strong prognostic factor predicting mortality\(^2\), and the transmurality of the scar is of great importance in determining the chance of recovery from left ventricle (LV) dysfunction after intervention\(^3\).

This thesis is a methodological study for assessing myocardial scar size, with late gadolinium enhancement (LGE) MRI. First a comparison of infarct size was made with myocardial perfusion single photon emission computed tomography (MPS, where the S stands for single photon emission computed tomography, SPECT). Secondly a semi-automatic software for infarct size determination was evaluated and, furthermore, different sequences were tested in patients with arrhythmia. Finally, the effect of scar on LV function was investigated and area-at-risk in acute MI was evaluated by using echocardiography. The obtained functional measurements were compared with final scar size assessed with LGE.

The thesis consists of two parts. Part one is an introduction to CAD and LV dysfunction followed by a presentation of the three techniques and their use in this thesis. The methods used in the studies and a summary of the results are presented followed by a discussion of the results. In part two each individual paper is presented.
2. CORONARY ARTERY DISEASE

2.1 Epidemiology

Cardiovascular disease (CVD) is the main cause of death worldwide and accounts for approximately 40% of all the deaths in high-income countries and 28% in low- and middle-income countries. CVD causes nearly half of all the deaths in Europe (48%) and in the European Union (42%). The cost of CVD to the economy of the European Union is estimated at €192 billion per year (2006), which corresponds to approximately 10% of the entire health care budget of the European Union. For each resident of the union this is about €223 per year. Cardiovascular diseases are also one of the main reasons for long-time sick leave. Of the various cardiovascular diseases, CAD is the single most common cause of death in the European Union and accounts for approximately 15-16% of all the deaths. Also in Sweden CAD is the leading cause of death.

2.2 Pathophysiology

MI can be defined from a number of different perspectives related to clinical, electrocardiographic (ECG), biochemical and pathologic characteristic. In a consensus document from the European Society of Cardiology and American College of Cardiology myocardial infarction is defined as myocardial cell death due to prolonged ischemia. Several processes can result in an oxygen supply inadequate to meet myocardial demand, but the most common cause of acute MI is the rupture of an atherosclerotic plaque leading to the formation of a thrombus causing partial or total occlusion of a coronary artery. Atherosclerotic lesions, composed primarily of a lipid-rich core and a fibrous cap, develop in virtually all major arteries. The process starts early in life, but becomes clinically important only later in life.

Lesions are initiated when endothelial cells recruit inflammatory leucocytes, such as monocytes and T lymphocytes, after being activated by factors such as hyperlipoproteinaemia and then express adhesion- and chemo attractant molecules. Extracellular lipid begins to accumulate in the intima and progressively fibro fatty lesions develop. As lesions progress inflammatory mediators cause expression of tissue factor and of matrix-degrading proteinases that weaken the cap of the plaque. The rupture of a plaque results...
in the exposure of collagen, lipids, smooth muscle cells and tissue factor into the blood leading to activation of platelets and the coagulation system. In acute MI, plaque disruption results in a persistent thrombotic vessel occlusion that prevents the oxygenated blood from reaching the myocytes and the oxygen available for metabolism decreases. This results in ischemia in the myocardium supplied by the thrombotic artery unless there is collateral blood supply. Cell death progresses gradually in an irregular wave front from the endocardium towards the epicardium. It takes several hours before myocardial necrosis can be identified by standard macroscopic or microscopic post-mortem examinations. Complete necrosis of all myocardial cells at risk requires at least 4 to 6 hours or longer, depending on the collateral blood flow, persistent or intermittent coronary occlusion and the sensitivity of the myocytes (pre- or post conditioning). Infarcts are classified temporally according to the different pathologic appearance, acute infarct (6 hours to 7 days), healing infarct (7 to 28 days) and healed infarct (29 days or more).

2.3 Infarct size and prognosis

Depending on the size of the threatening MI, varying degrees of wall motion disturbance will appear heralding the onset of heart failure. In early studies, LV ejection fraction (EF) and LV end-systolic volume were shown to be the strongest predictors of cardiac death. However, recent findings show that acute infarct size directly relates to LV remodelling and is a stronger predictor of future events than the measurement of LV systolic performance. Also, in patients with healed MI the size of the infarction may be superior to left ventricular EF and LV volumes for predicting long-term mortality. Unrecognized myocardial scar shown by LGE in patients without a history of MI are more frequent than expected, and among patients with clinical suspicion of CAD prognostic. LGE uptake indicating myocardial scar is a strong predictor for major adverse cardiac events and cardiac mortality.

There have been attempts to classify infarct size depending on the relative mortality risk and also in relation to other major cardiac events. Kelle et al found that patients with high risk of mortality had a spatial extent ≥ 6 segments assessed with LGE. Based on LGE exams, Wu et al found that small infarcts, < 18% of the LV myocardium, have good prognosis. Infarct size measured with MPS has also been shown to predict outcome in regard to ventricular function, cardiac events and cardiac deaths.
Although impaired LV function is a predictor of arrhythmias in general the presence of scar tissue provides the substance for re-entrant ventricular arrhythmias. Both Yukinaka et al and Hachamovitch et al demonstrated that patients with previous large perfusion reductions, detected with MPS, had a higher risk for ventricular arrhythmias and cardiac death compared with patients with less profound and fixed defects. In many studies multiple end points, such as global LV function, regional function, early arterial patency and clinical outcome, have been used as measurements of the efficacy of reperfusion therapy in acute MI. Clearly, the most important clinical outcome is the survival of the patient. However, the use of mortality as an end point requires large sample size. Studies have shown that the determination of infarct size may be an attractive surrogate endpoint.

2.4 Diagnosis

In the clinical setting there are several ways of diagnosing MI. Myocardial necrosis results in and can be recognized by the appearance in the blood of different proteins released into the circulation due to the damage of the myocytes. Most frequently used are cardiac troponin T, cardiac troponin I and previously the MB fraction of creatine kinase (CKMB). The cardiac troponins T and I have nearly absolute myocardial tissue specificity as well as high sensitivity. Like the other biomarkers they reflect myocardial damage but do not indicate the mechanism. CKMB is less tissue-specific than cardiac troponins. ECG is an inexpensive, easily accessible and non-invasive method that is easy to use. It may show signs of myocardial ischemia, specifically ST segment and T wave changes, as well as signs of myocardial necrosis, specifically changes in the QRS pattern, and has a reasonably good diagnostic performance.

Echocardiography cannot characterize scar tissue in distinction from myocardial muscle, but it is used to evaluate wall motion and wall thickness after an infarct. Injury involving > 20% of myocardial wall thickness can be detected by echocardiography. One of the major advantages of echocardiography is its availability and ease of use, even though the method is dependent on the scanning and interpreting skill of the operator. With MPS the infarct size can be evaluated acutely, as a perfusion deficit, to estimate the immediate area-at-risk, and also in the chronic setting. In general >10 g of myocardial tissue must be threatened before a radionuclide perfusion defect.
can be resolved. Coronary angiography is an x-ray method where contrast is injected into the coronary arteries to visualize lumen obstruction. One major advantage is the possibility to combine the examination with an intervention such as stenting or balloon angioplasty to open up the blood flow in the artery. LGE in MRI visualizes the necrotic scar\(^1\) and it is possible to evaluate the transmurality of the scar, which is of importance when estimating viability\(^2\). Other methods are less frequently used in the daily work and are mostly reserved for research. Cardiac computed tomography (CT) can visualize the coronaries and possibly assess perfusion. Positron emission tomography (PET), may achieve an absolute quantification of the perfusion deficit\(^3\).

### 2.5 Myocardium-at-risk and treatment

Several studies have shown that a short time to percutaneous coronary intervention (PCI) in patients with acute MI lowers the mortality\(^4\-^6\) and is associated with a high degree of myocardial salvage\(^7\). The shortest delay possible also improves the procedural success rate of PCI, the functional recovery of the LV and the clinical outcome\(^8\). Myocardium-at-risk, collateral flow, and the duration of coronary occlusion each are independently associated with final infarct size\(^9\). Commonly used methods for the evaluation of area-at-risk are MRI, with determination of myocardial oedema\(^10\), and MPS for the determination of myocardial perfusion\(^11\). The aim of infarct limiting therapies is to reduce the size of the final scar – the current goal is to limit final scar size to \(< 40\%\) of the initial risk area\(^12\). To reach this goal, the coronary blood flow as well as myocardial perfusion needs to be restored. In some cases, oedema will prevent reperfusion even if the vessel has been opened. Additionally, reperfusion itself may damage ischemic cells by providing free radicals that may further aggravate myocardial injury. If the microvasculature of the myocardium is damaged, reperfusion leads to the development of hemorrhagic infarct\(^13\). Primary PCI allows mechanical opening of the infarct related coronary artery. If that option is not available, medical thrombolysis can be used. During PCI, a guide wire opens the occlusion, passes the underlying stenosis and a balloon is deployed over the wire and inflated repeatedly until the stenosis is expanded\(^14\). A stent may be placed at the site of the stenosis to prevent restenosis\(^15\).
3. MYOCARDIAL DYSFUNCTION

3.1 Left ventricular systolic function

Infarct size reduces LV function, which can be expressed in terms of the many different measures that are available, such as EF, strain, and the rise of the systolic pressure curve, expressed as dP/dT. The systolic function of the LV is very complex with motion in several directions due to the three different fiber orientations of the LV. Fibers in the inner layer of the ventricle are forming a right-handed helix, whereas in the outer layer the fibers spiral left-handedly. Functionally these layers work together resulting in long- and short axis shortening as well as short axis rotation. The middle layer consists of fibers which are oriented circumferentially in the LV. Contraction of these fibers reduces the circumference and diameter of the heart. Hence systolic thickening is a result of both longitudinal and circumferential shortening. During systole there is a difference in the thickening of the three fiber layers where the thickening of the inner layer is 52%, the middle layer 27% and the outer layer 18%.

LV systolic function is influenced by various hemodynamic conditions such as preload, after-load, myocardial contractility and heart rate. Preload is the load present before contraction has started and reflects the venous filling pressure of the left atrium. After-load is the force against which the muscle contracts, generally systolic blood pressure. An occlusion of a coronary artery results in an immediate decrease in oxygen saturation and within less than a minute a reduction in regional wall motion. On a global level, LV dysfunction is characterized by a decrease in EF and an increase in the diastolic filling pressures. EF is defined as the ratio of stroke volume to end-diastolic volume [(EDV-ESV)/EDV x 100] and has been shown to be of great prognostic value.

3.2 The ischemic cascade

The ischemic cascade, figure 3.1, is a term used to explain a sequence of pathophysiological events occurring during myocardial ischemia. Ischemia is defined as an imbalance between oxygen supply and demand. It starts with decreased myocardial perfusion that first alters diastolic function, with reduced relaxation of the LV. As the ischemia continues, impairment in
systolic contraction will be observed. This wall motion abnormality occurs early and before abnormalities of the ECG will be seen. The impairment in myocardial function causes increased filling pressure which is often experienced by the patient as dyspnoea. ECG-changes will occur due to alterations in the membrane potential and finally chest pain due to the accumulation of metabolites. Symptoms of chest pain are variable and usually the last event to occur in the evolution of ischemia. The sequence is reversed with restored perfusion and chest pain will resolve before the hemodynamic changes will return, but abnormal wall motion might remain for several days as an effect of stunned myocardium.

Figure 3.1

3.3 The effects of ischemia

Dysfunctional but viable myocardium can be categorized into subgroups depending on different characteristics, see table 3.1.

Reversible stress induced ischemia: Reversible ischemia is caused by an imbalance in supply and demand for oxygen in the myocardium. Most often calcified lesions in the coronary arteries prevent exercise-induced increase in coronary blood flow. Asymmetric atherosclerotic lesions may display areas along the circumference where coronary vasospasm may further diminish the
available flow area and induce ischemic chest pain. Frequently, provocative testing is needed for the diagnosis of vasospasm. Symptoms of ischemia, induced by an increase in oxygen demand, are identical to those that herald the onset of an infarction. Due to the anatomy of the epicardial coronary arteries and the distribution of intramural pressure, ischemia is induced first in the endocardium (subendocardial ischemia) and later on, encompassing the entire wall including the epicardium (transmural ischemia). During the ischemic period wall motion is severely reduced.

**Stunned myocardium:** Myocardial function will normalize rapidly if the duration of the single ischemic period is short, less than 2 minutes. However, as the duration and/or the severity of ischemia increases, recovery will be delayed despite the return to normal of myocardial perfusion. The definition of stunned myocardium requires that myocardial function remains decreased despite normal myocardial perfusion. Thus, a mis-match will develop between perfusion and function. Stunned myocardium may occur after an increase in oxygen demand that induces ischemia e.g. in conjunction with physical exercise. If ischemia is prolonged it can progress to cell death and scar53. Stunned myocardium can also be seen postoperatively where it can cause LV dysfunction for several weeks. Stunned myocardium has contractile reserve i.e. wall motion normalizes when stimulated with inotropic agents. It is important to remember that stunned myocardium can coexist with irreversibly injured myocardium after an infarction and time-dependent improvement can be seen over a longer time.

**Hibernating Myocardium:** Hibernating myocardium is dysfunctional but viable, and seen in the setting of chronic ischemic heart disease54. Hibernating myocardium per definition requires the need for an intervention such as revascularization for recovery. However, it has been suggested that medical treatment also might be effective in relieving hibernation by decreasing ischemia55. Patients with viable myocardium undergoing revascularization have a potential for improved survival56. The presence of a large amount of dysfunctional but viable myocardium identifies patients where treatment has the best potential for improving prognosis57.
### Table 3.1 The characteristics of different categories of myocardial ischemia.

<table>
<thead>
<tr>
<th></th>
<th>Acute Ischemia</th>
<th>Stunning</th>
<th>Hibernation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>reduced ↓↓</td>
<td>reduced ↓</td>
<td>reduced ↓</td>
</tr>
<tr>
<td><strong>Perfusion</strong></td>
<td>reduced ↓↓</td>
<td>normal –</td>
<td>reduced ↓</td>
</tr>
<tr>
<td><strong>Response to low</strong></td>
<td>contractility ↓</td>
<td>contractility ↑</td>
<td>contractility ↑</td>
</tr>
<tr>
<td><strong>dose β-blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Need for</strong></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td><strong>intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. MAGNETIC RESONANCE IMAGING

In late 1972 the British scientific journal, Nature, returned a manuscript to the author Paul C. Lauterbur, Professor of Chemistry at the State University of New York at Stony Brook that read as follows.

» With regret I am returning your manuscript which we feel is not of sufficiently wide significance for inclusion in Nature. «

The paper was describing a new technique called 
zeugmatography, an analytical technique used in chemistry since late 1940s, called nuclear magnetic resonance. The author wanted this paper published in Nature and wrote back suggesting a change of the style of the paper that was dry and spare. The editor answered:

» Would it be possible to modify the manuscript so as to make the application more clear? «

Finally the manuscript was accepted and published in Nature 1973 under the title: Image formation by Induced Local Interaction: Examples Employing Magnetic Resonance.

from: Magnetic Resonance in Medicine

Today MRI is an established imaging modality. MRI has several advantages compared to other imaging modalities, being non-invasive and without ionizing radiation, displaying excellent contrast and enabling tissue characterization. An additional advantage of MRI is the ability to capture slices of the body in every imaginable plane. The high cost and limited availability are the draw-backs.
4.1 General principles

The most important element used for MRI is hydrogen (\(1^H\), containing one single proton) since the two major components of the human body, water and fat, both are rich in hydrogen. Hydrogen has weak magnetic properties caused by the positively charged proton that spins (precesses) around its axis, see figure 4.1. Spinning charged particles create an electromagnetic field analogous to that from a bar magnetic. When placed in a magnetic field they align themselves to the external magnetic field in two different orientations. Either they align parallel- (low energy level), or anti-parallel (high energy level) to the magnetic field lines (\(B_0\)). The magnetic moment vector, \(\mu\), precesses at a frequency that depends on the strength of the magnetic field according to the Larmor equation:

\[
\omega_0 = \gamma B_0
\]

where \(\omega_0\) is the Larmor frequency, \(B_0\) the strength of the external magnetic field and \(\gamma\) is the gyro-magnetic ratio. The gyro-magnetic ratio is different for different materials and is 42.58 MHz/T for \(1^H\). The sum of all magnetic vectors can be added in an M-vector that is aligned with the external \(B_0\) vector, see figure 4.1. However, this M-vector can only be detected when it is tilted in the x-y plane, perpendicular to the z-plane, by a radio frequency (RF) pulse (the excitation process). When the RF pulse is turned off the M-vector will gradually return to its original position (the relaxation process), sending out a radiofrequency signal that can be detected by the induction of a current in a coil. This transverse component of the M-vector that occurs during the relaxation process is referred to as the free induction decay, FID, and is the basis of MRI.

The relaxation process can be divided into two parts, T1 and T2- relaxation. T1 is defined as the time it takes for the longitudinal magnetization (\(M_L\)) to reach 63% of the original magnetization. T2 describes what happens in the x-y plane since the RF pulse not only flips the magnetization from the z plane into the x-y plane, but also causes the protons to start spinning in-phase, which they did not do before excitation. T2 is defined as the time it takes for the spins to de-phase to 37% of the original value. T2 relaxation occurs much faster than T1 relaxation. T2 relaxation develops in milliseconds, while T1 can take up to seconds. T1 relaxation will give T1 weighted images and T2 relaxation will give T2 weighted images. It needs to be emphasized that T1 and T2 relaxation are two independent processes. The one has nothing to do with the other. T1
relaxation describes what happens in the z direction, while T2 relaxation describes what happens in the x-y plane.

![Diagram](image)

Figure 4.1 Schematic drawing of proton spin (image M. Cohen) and the M-vector and its relationship to the coordinate system.

4.2 Signal and contrast

The stronger the MR signal intensity (SI), the better the image quality will be. The SI in MR images is often low and frequently severely influenced by background noise. The quality of the signal is described as the signal-to-noise ratio (SNR, SI divided by noise). Optimization in medical imaging aims at achieving the best possible SNR in combination with the best available contrast in the shortest time possible. SNR is proportional to the size of the voxel, but with increasing voxel size, noise will increase and the spatial resolution decrease. A reduction in SNR can be overcome at the price of longer scanning time that might be inconvenient for the patient. The human eye is more affected by the contrast-to-noise ratio (CNR) than SNR. CNR is defined as the difference in SI between different tissues divided by the background noise. If voxel size is increased for the purpose of improving SNR, CNR will decrease due to increasing noise. Thus there are numerous interdependencies between the different factors influencing image quality and contrast. If speed is chosen as the main factor, SNR and spatial resolution are proportional to the voxel size. Spatial resolution is linked to contrast and artefact reduction, such as field inhomogeneity and chemical shift. Contrast is related to SNR and artefacts.
4.3 Scar visualization with the Late Gadolinium Enhancement technique

The gadolinium chelates are the dominant class of contrast media for MRI. They are clear, colourless fluids for intravenous administration and are used for improved detection of lesions and for characterization of tissue. Gadolinium (Gd) is a rare metal that is extremely toxic in the elemental form (Gd³⁺). However, in medical use Gd is bound very tightly to a chelate (DTPA) almost neutralizing the toxicity of the ion. Gd is a paramagnetic substance which means that the ion causes a small local magnetic field that shortens the relaxation times, T1 and T2, of surrounding protons. In normal, healthy myocardium the contrast agent has an extracellular distribution. In reperfused MI, the extracellular volume is increased, mainly due to loss of cellular membrane integrity thus allowing the contrast agent to accumulate. An additional factor increasing the presence of Gd is oedema. Also, kinetics for wash-in and wash-out of Gd change when the myocardium is injured.

An inversion recovery (IR) sequence can be used to accentuate differences between tissues. This sequence uses an inversion pulse followed by a time delay, inversion time (TI) before imaging. The SI for a given TI is strongly dependent on inversion and repetition time (TR). TI can be chosen in order to null a signal from normal myocardium. However, scarred myocardium contains more contrast agent than healthy tissue increasing the signal and the scar becomes easily visible, figure 4.2.

![Graph showing T1 recovery](image)

Figure 4.2 Graph shows a faster recovery of T1 in infarct areas (red line) than in healthy myocardium (black line) due to a higher level of gadolinium-contrast in the scar area.
In 1999 Kim et al showed that LGE accurately determined infarct size and distinguished between reversible and irreversible ischemic injury\(^1\). LGE has also been shown to have a high reproducibility\(^{31, 65}\) and it compares well with both MPS\(^{30, 66, 67}\) and PET\(^{68}\). Another study from Kim et al showed that reversible myocardial dysfunction can be identified by measuring the transmurality of the scar\(^3\). If transmurality exceeds 50% of the myocardial wall thickness, recovery of wall motion after revascularization is unlikely. Thus, the high spatial resolution of MRI enables the assessment of viable myocardium\(^{69-72}\), figure 4.3.

![Figure 4.3 Left ventricle in short- and long axis view. Dark myocardium indicating healthy myocardium. White myocardium indicating scar.](image)

**4.4 A comparison between a fast and a segmented scar sequence**

A commonly used sequence for LGE is the prospectively ECG-gated, segmented inversion recovery 2D fast gradient echo (segmented turboFLASH according to the vendor, but here abbreviated IR_FGRE). A gradient echo is a rapid, saturation recovery sequence with a short TR (TR < 200 ms) a low flip angle (FA) (< 90°), and a gradient echo for refocusing. The segmented acquisition requires about 12 heart beats per breath hold, and it takes one breath hold per slice. Spatial coverage of the whole heart requires about 10-12 slices. The sequence utilizes an ECG trigger and acquires 25 phase encoding lines every other heart beat. A 300 ms time delay forces the acquisition to the diastolic phase where the movement of the heart is minimal\(^73\). The sequence is often referred to as the reference for scar imaging\(^3, 62\).
Single shot inversion recovery 2D steady state free precession (single shot trueFISP, here abbreviated SS_SSFP) is a fast technique that acquires one slice during one heart beat. Single shot is an echo-planar imaging technique that utilizes a reduced sampling of K-space within one single acquisition, which takes about 0.1 s. The sequence, however, suffers from artefacts such as chemical-shift and susceptibility. Since the acquisition time is short, the sequence is independent of patient cooperation which reduces artefacts from arrhythmia and breathing at a cost of a lower spatial resolution. The steady-state free precession (SSFP) techniques in general offer high CNR between myocardium and blood at a high SNR\textsuperscript{74} which may facilitate volumetric measurements of the LV and reduce observer dependence\textsuperscript{75}. In a comparison of SSFP with fast gradient echo in the assessment of ventricular function, SSFP allows for better detection of the endocardial border\textsuperscript{76}. It has been shown that SS_SSFP provides adequate image quality compared with IR_FGRE\textsuperscript{77} and there is a close correlation between the two sequences in assessing infarct volume in patients with sinus rhythm\textsuperscript{78,79}.

### 4.5 Segmentation of myocardium and of scar

Segmentation is an image analysis technique. The term segmentation is used to describe the process of selecting a specific object from an image. It is usually followed by some further operation, for example to determine the volume of the object, figure 8.1. There are three approaches to segmentation; manual, semi-automatic and automatic. Manual segmentation of a scar is time consuming, subject to human error and has poor intra- as well as inter-observer reproducibility. A completely automatic segmentation is difficult to achieve in diagnostic imaging since the intrinsic contrast between tissues may be low. Additionally, a fully automatic segmentation frequently has difficulties in detecting edges correctly and to handle partial volume effects.

There is a need to develop methods that accurately quantify LGE images. Different approaches have been suggested; visual\textsuperscript{80}, semi quantitative visual\textsuperscript{81} as well as objective semi-automatic methods\textsuperscript{82-84}. Heiberg et al have compiled a semi-automatic computer software, Segment\textsuperscript{85,87}, that is available for scientific users. After manual delineation of the endo- and epicardial borders on the LGE images, the software suggests spatial limits for the scar. The algorithm can be summarized as follows: In each slice, the mean signal intensity and standard deviation (SD) is calculated in 5 sectors. The sector with the lowest
mean signal intensity is considered 'remote' myocardium. A slice specific threshold is calculated as the mean of the 'remote' sector + 2.4 SD from the mean signal intensity in the 'remote' region. The number of standard deviations from 'remote' is chosen after an optimization process to minimize the variability of the algorithm. A three dimensional image processing algorithm is applied to limit the heterogeneity of the hyperenhanced regions, and to exclude small regions that constitute noise rather than infarction. Manual correction is possible when the observer does not agree with the outcome of the scar analysis of the software.
5. CARDIAC ULTRASOUND

In 1954 the cardiologist Inge Edler and physicist Hellmuth Hertz at Lund University first introduced cardiac ultrasound. They established the characteristic motion pattern for the anterior leaflet of the mitral valve by M-mode ultrasound. However, since the image quality of the first recordings was low, many cardiologists did not think the method was worth pursuing. Today echocardiography is the most frequently used – and usually the initial – imaging test for all abnormalities of the heart or great vessels. Echocardiography is easily available, mobile, inexpensive, non-invasive and non-ionizing. The draw-backs are its dependency on the manual skills of the operator’s and the extended learning curve for the reading physician as well as for the technician.

5.1 General principles

Ultrasound is usually defined as sound with a frequency exceeding 20 kHz, usually above what can be perceived by the human ear. A sound wave is typically produced by a piezoelectric crystal encased in a probe. Strong, short electric pulses emitted from the ultrasound scanner causes motion of the crystal – “ringing” - at the desired frequency. The sound is focused by e.g. the shape of the transducer. The speed of ultrasound is 1.540 m/s in human soft tissue and the wave is focused at a desired depth. The sound wave is partially reflected in the interface between tissues depending on slight differences in the velocity of sound. Specifically, sound is reflected where there are definite changes in the density in the body for example between the blood pool and the mycardial wall. Some of the reflections return to the transducer. The scanner determines the time delay between transmit and receive from which the depth/distance to the structure may be calculated. The returning sound wave induces resonance in the piezoelectric crystal producing electric signals that are processed and transformed into a digital image.
5.2 Echocardiographic techniques

There are different techniques in clinical echocardiography that will be presented below. These expressions will later be used in this thesis.

M-mode: M stands for motion and was the first practical application of cardiac ultrasound. M-mode is produced by a sequence of multiple linear arrays directed towards the heart and can be viewed as a 2D image on the screen. It has a very high frame rate, approximately 500 Hz, and thus enables the evaluation of very rapid motion, such as the moving cardiac valve leaflets. In addition, long sequences covering several heart beats may be assessed, figure 5.1.

2D-echocardiography: In 2D-echocardiography ultrasound beams are emitted successively within a sector scan plane. 2D-echocardiography is the basic modality for visualizing cardiac structure and wall motion. Frame rate depends on the width and depth of the imaging sector, but is defined as 25 frames per second in the current DICOM standard. Some of the returning sound waves are “overtones”, the 2nd harmonic, with a frequency twice as high as the transmitted wave. This effect allows using low frequency transmit with better penetration and using received harmonics for reconstructing the object. This imaging technique is called Second Harmonic Imaging, figure 5.1.

Doppler Imaging: The Doppler effect characterizes sound reflected by moving structures. By calculating the frequency shift of a particular sample volume, for example a jet of blood from a leaking heart valve, its speed and direction can be determined and visualized. The Doppler information is displayed graphically using spectral flow Doppler or as gray scale image overlay using colour flow Doppler. Tissue Doppler Imaging (TDI) allows visualization of the motion of the myocardial walls. The ultrasound signal from moving myocardial tissue has higher amplitude but lower frequency (due to a low velocity) than signals from moving blood cells. Spectral tissue Doppler has inherently a high temporal resolution while colour tissue Doppler needs a frame rate in excess of 100 frames per second to correctly display peak velocities in wall motion. TDI is most often visualized as coloured 2D-echocardiography or in M-mode format where red denotes movement towards and blue movement away from the transducer, figure 5.2.
5.3 Myocardial deformation or “Strain”

Strain ($\varepsilon$) is here defined as the deformation of an object, normalized to its original length\(^8^9\). In a one-dimensional object, the only possible deformation of the object is lengthening or shortening. Elements of the myocardium can be deformed in a longitudinal, a radial or circumferential direction. In addition, shear strains add complexity to the analysis of myocardial deformation. Strain
can be written as: $\varepsilon = (L - L_0)/L_0$ and is thus a ratio, but often expressed as a percentage. By convention positive strain is expressed as lengthening and negative strain as shortening. Cardiac strain expresses the local deformation of contracting muscle\textsuperscript{90-92}. It is a complicated measure that requires 9 tensor values to adequately describe motion in all directions\textsuperscript{93}. Simplified solutions are those that determine strain along the tissue Doppler beam (1-dimensional) or from speckle in the gray scale image (2D-strain, 2-dimensional). Strain is supposed to be less influenced by tethering of neighbouring myocardium than myocardial velocities\textsuperscript{94}. It may quantify the severity of myocardial segmental dysfunction\textsuperscript{95, 96} as well as predict the recovery of regional wall motion in patients with acute myocardial infarction subjected to PCI\textsuperscript{97}. Global longitudinal strain is an effective method for quantifying global ventricular function\textsuperscript{98}, is closely related to infarct size in chronic ischemic heart disease\textsuperscript{99} and might be an important clinical tool for evaluating risk in patients with acute MI\textsuperscript{100}, figure 8.2.
6. MYOCARDIAL PERFUSION SPECT

The most common reason for performing MPS is CAD where the perfusion of the myocardium can be visualized by an intravenous injection of a radioactive tracer followed by tomographic imaging with a gamma camera\textsuperscript{101}. The advantages of MPS are the high sensitivity and specificity, as well as a high negative predictive value\textsuperscript{102}. The drawbacks are the use of radioactive agents and in some situations a lower specificity due to attenuation effects.

6.1 General principles

Following injection, the radioactive tracer will be extracted from the blood and binds to the target tissue. From the binding site, photons are emitted and absorbed in the scintillation detector crystal (a gamma camera) causing a pulse of light. Photomultiplier tubes amplify the incoming signal, which is in proportion to the tracer distribution/perfusion of the examined tissue. A collimator attached to the gamma camera allows only detection of parallel photons, and these photons are the basis for the creation of an image. In addition the choice of collimator type determines the spatial resolution and sensitivity of the system. Three electrical signals are registered from the gamma camera detector, two that indicate where the photon is absorbed in the crystal (x- and y- pulses) and one that indicates the energy of the photon (z-pulse). The z-pulse is used in the pulse-height analyzer for discrimination of scattered radiation with the use of energy window setting.

SPECT is a method that rotates the gamma camera around the object in order to obtain many angular projection images. Mathematical algorithms are used to reconstruct images of selected planes within the object from these projection data. The images are presented as cross-sectional slices through the patient or the examined organ, for example the heart. SPECT increases the contrast in the images compared to planar imaging.
6.2 Radioactive tracers

An attractive perfusion tracer for the myocardium should have the following characteristics: it should be extracted from the blood in proportion to flow, have a high extraction fraction but still remain in the myocardium long enough for imaging and have a rapid elimination. It should also cause a low over-all radiation exposure.

In the 1970s the first radiopharmaceutical tracer used for MPS was thallium-201 (201Tl). 201Tl is a potassium analogue and is therefore actively transported into the cell by the sodium-potassium pump. Since potassium is the major intracellular cat ion in muscle and is virtually absent in scar tissue, 201Tl is a tracer well suited for differentiating between normal/ischemic myocardium and scarred myocardium. 201Tl emits around 80 keV of photon energy and has a half-life of 73 hours. Following intravenous injection, approximately 88% is cleared from the blood after the first circulation103, but because the heart receives only 5% of the cardiac output, only 4% of the total dose is taken up by the myocardium, while the rest mainly goes to skeletal muscle. In the 1990s technetium 99m-labeled myocardial perfusion tracers were introduced104, sestamibi and tetrofosmin. Technetium 99m (99mTc) emits 140 keV of photon energy and has a half-life of 6 hours. 140 keV is more favourable for the absorption of the photons in the crystal of the gamma camera compared with 80 keV of 201Tl. In addition the short half-life of technetium also lowers the dose absorbed in tissue. 99mTc-tetrofosmin distributes to the myocardium in proportion to blood flow105 and is taken up by viable cells where it is bound to the mitochondria104.

6.3 Imaging protocols and perfusion defect size

For 99mTc-tetrofosmin separate injections are required for rest and stress imaging, either in a one-day or, preferably, in a two-day protocol. For stress images either physical exercise or pharmacological stress can be used. Exercise remains the technique of choice because it provides extra information such as physical work capacity, symptoms and extent and duration of the ECG-changes. However, there are a large number of patients where exercise tolerance is suboptimal, preventing the patient from reaching 85% of age-predicted peak heart rate. In these cases, the stress agent of choice is adenosine, which is a naturally occurring purine that causes vasodilatation by increasing intracellular cyclic AMP. Near maximal coronary vasodilatation is
achieved in 85% of patients with an intravenous dose of 140μg/kg/min. The increase in coronary flow in healthy humans at this dose is greater than 4 times the value at baseline. Adenosine dilates the healthy-, but not the sclerotic segments of the coronary arteries and thus a coronary steal syndrome will arise106.

To assess LV end diastolic and end systolic volume, EF and wall motion, gated cardiac MPS can be used101. It is achieved by dividing the R-R interval of the ECG in intervals, collecting data for each unique interval. The average value is assessed for each interval and a separate sub-image is created for each interval. When viewing the function of the LV the sub-images are played in subsequent order. This presupposes regular R-R intervals. Gated MPS increases the ability of MPS to detect CAD107, 108.

Acute infarct size estimated from 201Tl MPS has a close correlation with true infarct size obtained from pathologic specimens109. Medrano et al showed that the perfusion defect size assessed with MPS compared well with the histological evaluation of infarct size in 15 explanted hearts with ischemic cardiomyopathy110. In humans, defect size with 201Tl MPS correlates well with biochemical markers of myocardial damage111, 112 and with EF112, as well as with infarct size from 99mTc-sestamibi113, 114. The perfusion defects caused by infarcts are fixed defects, and the assessment of fixed perfusion defects by MPS is today an accepted and validated tool for the quantification of infarct size34. Several studies have shown a good agreement between perfusion defect and LGE uptake in acute myocardial infarction66, 115 as well as in chronic infarction66, 116. MPS can be used to predict clinical outcome according to infarct size25, figure 6.1.

In stress induced ischemia there will be a defect only on the stress images. On the rest images the perfusion defect will disappear since the myocardial perfusion is restored at rest. By comparing stress- and rest MPS images, myocardium with stress induced ischemia can be recognized117.

MPS has often been used as a reference method to estimate infarct size 34, based on visual qualitative evaluation of the perfusion defect. Objective measurement and standardized evaluation is desirable in the application of all cardiac imaging methods. Computer-assisted assessment of infarct size in MPS imaging may reduce the variability between different observers 118, 119 and there are several brands on the market. We studied PERFIT® (HERMES Medical Solutions, Stockholm, Sweden), which is an automatic software for
the quantitative analysis of infarct size and severity. The reference is a three-dimensional, gender specific, averaged heart, generated from a defined reference population\textsuperscript{120, 121}.

Figure 6.1 Left ventricle in short axis view. Left: Normal perfusion. Right: Perfusion defect indicating scar.
7. AIMS OF THE STUDY

The general aim of this thesis was to study methods to assess scar size in chronic MI, primarily with the use of LGE MRI. In addition, the effect of scar on LV function was investigated and an attempt was launched at demonstrating myocardial salvage in acute ST-elevation myocardial infarct (STEMI).

The specific aim of each study was to:

I. compare the scar size at rest by MPS, as determined with an automated computer software, PERFIT®, with scar size manually delineated on LGE images.

II. compare the scar size and evaluation time using a semi-automatic computer software, Segment, with manual delineation.

III. determine image quality and infarct size with the two MRI scar sequences, IR_FGRE and SS_SSFP, in patients with permanent atrial fibrillation and chronic myocardial infarction.

IV. determine myocardial area-at-risk in acute MI with the use of tissue Doppler imaging and visual wall motion assessment, and to determine whether these measurements correlated on a global, regional and segmental level with the size of the final scar.
8. MATERIAL AND METHODS

All studies complied with the Declaration of Helsinki. Studies were approved by the Ethics committee at Linköping University (paper I, II, III) or (later) by the Regional ethical review board in Linköping (paper IV). All patients gave informed consent.

8.1 Study population

Paper I and II: Forty patients, 33 men and 7 women, average age 65 ± 10 years (range 36 - 84) were consecutively enrolled between June 2002 and March 2004. Thirty-two of these patients had been diagnosed with MI and the remaining 8 had symptoms suggestive of CAD. Patients referred for MPS with suspicion of CAD were included in the study if they had an irreversible uptake reduction suggesting a MI.

Paper III: Twenty patients, all men, average age 75 ± 6 years (range 59 - 83) were enrolled in the study. All 20 patients had MI determined from chest pain, ECG abnormalities and/or elevated levels of either Troponin T >0.05 μg/l or CKMB >5.0 μg/L, in at least two blood samples while hospitalized. The diagnosis had to be confirmed more than 6 weeks prior to the MRI examination. At the time of the MRI study, all patients were in atrial fibrillation.

Paper IV: Twenty-six patients (23 men) average age 65 ± 8 years (range 50 - 78) were selected for this analysis from among 99 patients included in a study of primary PCI for STEMI. In the main study, 159 patients were included and 99 finally completed the investigations. Acute echocardiography was possible only during office hours, enabling the inclusion of 26 patients for this echo sub-study. The culprit lesion was located in the left anterior descending coronary artery system (LAD) in 15 patients, in the right coronary artery (RCA) in 9 and in the left circumflex artery (LCx) in 2 patients.
8.2 Magnetic Resonance Imaging

Three magnets were used: A 1.5 T Magnetom Vision, (paper I and II), a 1.5 T Symphony (paper III) both from Siemens, Erlangen, Germany, and in paper IV a 1.5 T Achieva (Philips Healthcare, Best, The Netherlands). A circular polarized body-array surface coil was used in all measurements. ECG-triggered MR images were obtained.

In all studies cine-MR imaging covered the entire left ventricle with short axis slices and three long axis planes (2-, 3- and 4-chamber views). A fast gradient echo (FGRE) sequence (paper I and II), a SSFP sequence (paper III) and a balanced steady state free precession turbo field echo (b-SSFP TFE) (paper IV) were used for the cine-images.

The contrast-enhanced images were acquired at the same slice positions as the cine-images. Gadopentetate dimeglumine (Gd-DTPA) 0.2 mmol/kg bodyweight (Schering Nordiska AB, Järfalla, Sweden) was administrated intravenously and LGE sequences were used. A segmented IR_FGRE sequence was used in papers I-III. In addition, a SS_SSFP was recorded in paper III. In paper IV the IR turbo field echo (IR-TFE) sequence was a segmented 3D spoiled gradient echo.

In paper III a comparison was made between two different LGE sequences. For the single shot sequence, SS_SSFP, the following settings were used: TR = 10.8ms, echo time (TE) = 1.26ms, FA = 50°, bandwidth (BW) = 1180 Hz, slice thickness = 8mm, image matrix = 192 x 108, number of excitations (NEX) = 1, field-of-view (FOV) = 380mm. Corresponding settings for the segmented sequence, IR_FGRE, were: TR = 12ms, TE = 5.4ms, FA = 30°, BW = 140 Hz, slice thickness = 8mm, image matrix = 256 x 160, NEX =1, and FOV = 380mm. A 300ms time delay was added to force the acquisition to the diastolic phase, where the movement of the heart is minimal. However, since the patients had irregular R-R-intervals, the actual timing of the acquisition differed between beats. In the single shot acquisition, breath holding was not required. Instead, the acquisition was initiated by the technician from end-expiration in the respiratory trace. In the segmented cine imaging, the patients were instructed to hold their breath in end-expiration. For all LGE sequences the optimal inversion time was chosen from a midventricular short-axis slice where the signal from healthy, normal myocardium was nulled 62, 63.
8.3 Magnetic Resonance Imaging Analysis

Left ventricular volume and scar measurements: In all studies, LV myocardial volume (end diastolic volume and end systolic volume) was measured from the short axis cine slices. Infarct size was measured on short axis slices in paper I – IV. The papillary muscles were included in the LV size/infarction size if they were attached to the myocardium at that particular site. Scar transmurality was assessed in the long axis views of paper IV to facilitate the comparison with tissue Doppler measurements and visual assessment of wall motion.

In paper I and II, segmentation was performed manually for the myocardium as well as for scar using ImageJ 1.29X (Wayne Rasband, NIH USA, http://rsb.info.nih.gov/ij/). The time required for performing the measurements was recorded. Problems with partial volume effects were resolved with consensus (6% of all slices).

In paper II we compared the above mentioned manual infarct segmentation with a semi-automatic infarct segmentation using an automated infarct delineation algorithm in the software “Segment” (http://segment.heiberg.se) as described by Heiberg et al.85-87. The result was displayed in two steps, “semi-automatic infarct sizing” and “semi-automatic corrected infarct sizing”, i.e. if a manual correction was performed. Long axis views aided in the visual determination of infarcted myocardium. Myocardial segmentation was performed manually, by using “Segment” by two observers. Both observers recorded the time needed for the myocardial segmentation and for manual corrections of the scar analysis when needed, figure 8.1. The automatic scar analysis took only a few seconds.

In paper III and IV infarct size was measured by two observers using the software “Segment”85-87. Myocardial segmentation was performed manually by using “Segment” by two observers in paper III and by one observer in paper IV.
Wall motion score index (paper I): WMSI was assigned in the same manner as with echocardiography (see section 8.4).

Coronary artery supply area (paper I): In the 33 patients where an infarct scar was seen on both MPS and LGE, the major coronary artery supply for the infarcted segments in LGE was manually determined according to a 16 myocardial segmental model that closely resembles the presently recommended 17-segment model\textsuperscript{122, 123}. The LV was divided into equal thirds perpendicular to the long axis. A mid-slice in each third was selected and the segmental scar area calculated after manually outlining the epicardial and endocardial borders \textsuperscript{85}. The LGE positive fraction in each coronary artery perfusion area was calculated provided the percentage involvement of any segment exceeded 5%. All segments were assumed to be of equal size. The coronary perfusion area with the highest infarct fraction was assumed to be perfused by the infarct related artery.

Visual determination of image quality (paper III): Visual assessment of image quality of the LGE images (IR_FGRE and SS_SSFP) was performed in view of the following four aspects: delineation of 1) noninfarcted and 2) infarcted myocardium, 3) the occurrence of motion- and other artefacts and 4) an overall evaluation of the image quality of the LV. A five-point rating scale was used for all groups with five as the highest and one as the lowest grade\textsuperscript{124}. A score of 5 was given when the parameters were considered “very good”. A score of
4-3-2- and 1 was given when the parameter (segmentation of noninfarcted- and infarcted myocardium, artefacts and overall impression) was assessed as “good”, “moderate”, “poor” and “very poor” respectively. For visual assessment of the quality of the cine-images, each short-axis slice of the LV was evaluated in two aspects: 1) the occurrence of artefacts and 2) overall evaluation of the motion (ghosting, blurring, irregularity) of the left ventricular wall, using “5” as the highest grade and “1” as the lowest grade. The quality of the LGE- and cine images was evaluated by two observers and averaged. The two observers were blinded as to the sequence information except for cine.

Signal Intensity, Signal-to-Noise and Contrast-to-Noise (paper III): The SI, SNR and the CNR values were determined on images from both LGE sequences (IR_FGRE and SS_SSFP). To calculate the SI, regions of interest (ROIs), 25 to 50 mm², were placed in the normal myocardium (myo) and in the infarcted myocardium (inf). In the blood pool (bp), a larger ROI of at least 300 mm² was drawn. Noise was defined as the SD of the SI measurement in the air outside the patient. The SNR for different cardiac regions was calculated by dividing each SI by the noise. The CNR value for the infarcted myocardium in comparison to the normal myocardium was calculated as follows: CNR: \( \frac{SI_{\text{inf}} - SI_{\text{myo}}}{\text{Noise}} \). The CNR value for the infarcted myocardium in comparison with the blood in the ventricular cavity was calculated as follows: CNR: \( \frac{SI_{\text{inf}} - SI_{\text{bp}}}{\text{Noise}} \).

8.4 Echocardiography

Equipment: Siemens Sequoia 256 or 512; Siemens Healthcare Inc, Mountainview, CA, USA was used in paper I and III. In paper IV, a GE V7 or GE V5 equipped with 3MHz transducers utilizing harmonic imaging technology was used.

Wall motion scoring and ejection fraction: The LV was divided into 16 segments (6 basal, 6 mid, and 4 apical)\(^{122, 125}\). Wall motion was determined by at least two independent observers and the mean value of each segment was used. Wall motion scoring used conventional steps such as: normal = 1, hypokinetic = 2, akinetic = 3, dyskinetic = 4, aneurysm = 5\(^{122, 125}\). Scores were summed and divided by the 16 segments to obtain a global wall motion score.
index (WMSI) for the LV for each patient. Left ventricular EF was calculated using the biplane method of discs (Simpson).

**Tissue Doppler measurements (paper IV):** In the acute setting at least three apical views were obtained with colour tissue Doppler (two-beat loops) while the patient was draped and prepared for acute PCI. At follow-up, a minimum of three apical loops were recorded, preferably in end-expiration to minimize translational movement of the heart. Colour Tissue Doppler images were acquired with a frame-rate exceeding 90/s. Off-line analysis was performed using Echopac software (Echopac BT08, GE Vingmed Ultrasound, Norway). In each of the three apical views, six segments were defined and ROI using sample volumes of 6 x 12 mm were applied. Tissue Doppler values in the apical anteroseptal and inferoseptal segments were averaged into an apical septal segment and in the anterolateral and inferolateral averaged into an apical lateral segment thus allowing conversion from 18 segments into a 16 segment model. After checking for aliasing in the velocity mode, myocardial strain and displacement curves were drawn and the peak values were measured on two consecutive beats, if possible, figure 8.2. Peak systolic strain was calculated from the velocity determination in the longitudinal direction. Long axis LV function was assessed from mitral annular motion (MAM) which was measured in four positions on the mitral annular ring. Values for strain, displacement of the myocardial segments and MAM from the mitral annular ring were obtained by two observers and their average was calculated. The reference values for longitudinal strain by Kowalski et al (-16% ± 5%) were used as a cut-off\textsuperscript{126}. To obtain global measurements of strain, measurements from each segment were added and the sum divided by the total numbers of segments. To assess regional measurements of wall motion and strain in relation to infarct transmurality, numbers for the three segments of each wall (anterior, lateral, posterior and septal) were averaged.
Figure 8.2 Strain Doppler curves at follow up. Blue: normal longitudinal strain curve recorded from healthy myocardium in the middle septal segment. Red: reduced longitudinal strain in thinned, infarcted myocardium of the apical septal segment.

8.5 Myocardial Perfusion SPECT

Imaging (paper I): The rest images from a two-day stress/rest protocol were used. Imaging at rest was performed 2 - 3 days after stress imaging using 8.6 MBq $^{99m}$Tc tetrofosmin/kg bodyweight (max 860 MBq) (Amersham Health, Buckinghamshire, UK).

A dual-detector gamma camera (E.CAM, Siemens Medical Systems Inc, Hoffman Estates, Il, USA) equipped with a high resolution collimator was used. Thirty-two views were acquired in steps of 2.8 degrees per detector and the acquisition time/angle was 25 s. In the first nine patients, 16 views per detector were used with an acquisition time/angle of 50s. A 19% window was “asymmetrically placed” (129 – 155 keV) on the 140 keV peak. A 64*64 word matrix with a pixel size of 6.6 mm was used. The acquisition files were reconstructed by the nuclear technicians using filtered back-projection prefiltered with a Butterworth filter (cut off 0.8/cm, order 10) (Hermes Medical Solutions, Stockholm, Sweden). The result of the reconstruction procedure was controlled and the images were initially analyzed and reported for clinical patient care by four experienced nuclear physicians, whose individual
evaluations were the basis for inclusion in the study. After inclusion, images at rest were reanalyzed with PERFIT by one expert reader without knowledge of the LGE results.

Analysis with PERFIT (paper I): PERFIT assesses the size of the myocardial scar (ml), the infarct extent (% of myocardial volume) and analyzes the percentage of each coronary artery perfusion area involved. The threshold for MPS scar is set to an absolute level of < 2 SD of the highest perfusion tracer uptake in a remote area of the myocardium. In the PERFIT analysis, the image alignment by the software was visually checked but no manual correction of the automatic fit was necessary, figure 8.3.

![Figure 8.3 Left: Evaluation of the scar by PERFIT in short-axis view. Right: Corresponding image without automatic scar determination.](image)

8.6 Statistics

The myocardial and scar volume measures were analysed by two-sided t-test for paired observations. Correlation coefficients and related p values were reported, Bland-Altman plots used and slope differences analysed by t-test (paper III). The methodological error of the two raters in paper III and of the functional measures (paper IV) were expressed as standard error of a single determination (S\text{method}) using the formula, proposed by Dahlberg, \[ S_{\text{method}} = \sqrt{\frac{\sum d^2}{2n}}, \] where \( d_i \) is the difference between the i:th paired measurement.
and n is the number of differences. F-test was used to compare $S_{\text{method}}$ (comparison of variance) between IR_FGRE and SS_SSFP (paper III).

Kappa measurements were used to determine the correspondence between MPS and LGE in the determination of the major vascular supply of the scar region (paper I) and to evaluate interobserver agreement (paper III).

Mean coefficient of variation (COV, %) calculated as $\text{COV} = 100 \times \frac{(O1-O2)}{(O1+O2)/2}$ where $O1$ and $O2$ are the measurements of each observer, was calculated between myocardial and infarct volume measurements (paper II).

For image quality, Wilcoxon pairwise signed rank test was used to compare modality performance based on the ordinal-scaled criteria (paper III).

In paper IV the difference on a global level between pre- and post PCI exams was analysed by two-sided t-test for paired observations. Spearman’s rank correlation was used for global-, regional-, and segmental functional parameters vs. infarct size and infarct transmurality. The difference between normal segments (transmurality < 1%) and segments with transmurality ≥ 50% on a regional level was analyzed with Mann-Whitney’s U-test. Receiver-operating-characteristics (ROC) curve analyses were performed using the statistical software MedCalc® Version 6.10 (MedCalc Software, Mariakerke, Belgium). The interaction between WMSI and strain on the detection of segments with a transmurality ≥50% was analysed with logistic regression.

Analyses were performed using SPSS 13.0 (SPSS Inc, Chicago, Illinois). Two-tailed $P$ values were used with $p \leq 0.05$ considered to indicate statistical significance.
9. RESULTS

9.1. Infarct size is comparable when determined with LGE and MPS (Paper I)

The myocardial scar volume assessed with MPS was 29.6 ± 23.2 ml (range 0 – 87) compared with LGE 22.1 ± 16.9 ml (range 0 – 69), p = 0.01, with a correlation coefficient of $r = 0.71$ and a mean difference of -7.5 ml. Infarct extent was $11.7 ± 9.4\%$ (range 0 – 38) using MPS and $13.0 ± 9.6\%$ (range 0 – 35) with LGE, p = 0.32, (difference 1.3 percentage points) with a correlation coefficient of $r = 0.63$, figure 9.1. The intraobserver variability for LGE infarct volume was $0.3 ± 8.0$ ml and $0.2 ± 6.4$ ml respectively for the two observers and for LGE infarct extent $0.1 ± 4.3\%$ and $0.2 ± 3.8$ respectively. Interobserver variability for LGE infarct volume was $1.0 ± 3.0$ ml ($p = 0.05$) and for infarct extent $0.3 ± 2.4\%$ ($p = 0.4$).

PERFIT and LGE were concordant in 34 patients, while differences were seen in six patients. In five patients with normal LGE results, PERFIT and clinical evaluation reported myocardial perfusion defects. A retrospective review of these MPS studies showed that attenuation defects were possible. In one patient, PERFIT did not detect a scar that was reported from clinical MPS evaluation and with LGE. Additionally, clinical MPS erroneously reported a scar in one patient that was cleared with PERFIT as well as LGE, table 9.1. If these 7 patients were removed from the analysis, infarct volume assessed with MPS was $33.2 ± 23.5$ ml and with LGE $26.7 ± 14.9$ ml, ($p = 0.04$). Infarct extent was $13.2 ± 9.6\%$ with MPS and $15.7 ± 8.3\%$ with LGE, ($p = 0.08$). The correlation coefficient between the two methods was in this subset 0.70 for infarct volume and 0.59 for infarct extent.

In three patients, the LGE analysis suggested a larger infarct volume and/or extent than MPS (> 1 SD of their difference). In two of these cases, the scar area included the apex which made delineation of the endocardium on LGE difficult due to low contrast between the infarct area and the SI in the blood pool. In the third patient, bowel uptake on MPS-images interfered with the interpretation of the perfusion reduction in the inferior wall. In six studies MPS showed a larger scar volume and/or extent compared with LGE (>1 SD). In two of these studies MPS showed a reduced uptake where LGE showed thin walls and in four patients MPS showed reduced inferior uptake where
LGE showed a small inferior infarct or no scar at all. In three of these four patients both MPS and LGE displayed dilated LV.

WMSI determined with cine-MRI correlated moderately with infarct volume and infarct extent. The correlation WMSI(cine-MRI) versus infarct volume(MPS) was $r = 0.71$ and infarct extent(MPS) $r = 0.71$. WMSI(echo) vs infarct volume(MPS) was $r = 0.64$ and for infarct extent $r = 0.65$, respectively. WMSI (cine-MRI) vs. infarct volume(LGE) was $r = 0.62$ and infarct extent(LGE) $r = 0.60$. WMSI(echo) versus infarct volume (LGE) was $r = 0.57$ and infarct extent $r = 0.56$ respectively.

In the 33 scans where MPS and LGE both showed myocardial scar, PERFIT determined that LAD was the main coronary artery supply of the infarcted segments in 21 scans (LAD territory involvement in a total of 25 exams), whereas LCx and RCA were the supply arteries in 6 scans each (LCx and RCA territory involvement in a total of 19 and 16 exams respectively). Corresponding figures with LGE were for LAD 20 scans (LGE uptake in a total of 107 segments) and for LCx and RCA 5 and 8 scans respectively (LGE uptake in a total of 63 segments and 71 segments respectively). Hence, there was a good agreement in 30 of the 33 scans with myocardial damage, (Kappa = 0.84).

![Figure 9.1 Bland-Altman plots showing the agreement between perfusion defect size by MPS, assessed with PERFIT, and LGE images assessed with manual segmentation.](image)
Results

<table>
<thead>
<tr>
<th>MPS(Perfit)</th>
<th>LGE normal</th>
<th>LGE pathologic</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>pathologic</td>
<td>5</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Sum</td>
<td>6</td>
<td>34</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 9.1 Concordance between MPS and LGE. Normal and pathologic results reported with the two methods.

9.2. The semi-automatic method shortens evaluation time with maintained clinical accuracy (Paper II)

The time for evaluating a cardiac MRI study was 9.2 ± 1.8 minutes (range 6-14) with the semi-automatic corrected method, of which 1.2 ± 0.6 (range 0.5–3.0) minutes was devoted to minor adjustments. Manual infarct sizing required 21.6 ± 4.5 minutes (range 15-31), figure 9.2.

The myocardial volume assessed with the semi-automatic method was 168.1 ± 51.0 ml and with manual evaluation 172.4 ± 53.0 ml (r = 0.95, p = 0.09), figure 9.3. Corresponding figures for infarct volume and infarct percentage were 25.9 ± 20.2 ml vs. 22.1 ± 16.9 ml (r = 0.92, p = 0.005) and 15.1 ± 10.8% vs. 13.0 ± 9.6% (r = 0.91, p = 0.005), figure 9.4. Semi-automatic corrected infarct sizing showed slightly larger infarct size, 3.8 ± 8.1 ml, and infarct percentage 2.1 ± 4.4 % than the manual method.

Generally, the manual adjustments of infarct volume in the semi-automatic corrected method were small. The infarct volume assessed with semi-automatic method was 26.4 ± 19.2 ml and with semi-automatic corrected method 25.9 ± 20.2 ml (r = 0.99, p = ns). Corresponding figures for infarct percentage were 15.5 ± 10.3% and 15.1 ± 10.8% (r = 0.99, p = ns). The applied corrections were of two types. Corrections were performed if the delineation of the myocardium erroneously included parts extrinsic to the myocardium. Also, corrections were frequent if the scar area was considered to be due to partial volume effects. There were, on average, 13 corrections of the first type and 20 corrections of the second type. For corrections of the first type, 70 % were deletions and 30 % were additions. For corrections of the second type, deletions and additions were 50 % each.
With manual infarct sizing, the intraobserver variability of the two observers for myocardial volume was $5.2 \pm 13.6$ ml and $2.4 \pm 18.6$ ml respectively, for infarct volume $0.3 \pm 8.0$ ml and $0.2 \pm 6.4$ ml, and for infarct percentage $0.1 \pm 4.3\%$ and $0.2 \pm 3.8\%$. Interobserver variability for myocardial volume was $1.7 \pm 14.7$ ml ($r = 0.96$, $p = 0.5$), infarct volume $1.0 \pm 3.0$ ml ($r = 0.98$, $p = 0.05$) and infarct percentage $0.3 \pm 2.4\%$ ($r = 0.97$, $p = 0.4$). In the semi-automatic method, each observer used the same segmentation of the left ventricle for both semi-automatic and semi-automatic corrected infarct sizing and only adjusted the scar area. Due to different approaches to the segmentation process the interobserver variability for myocardial volume was $32.3 \pm 20.6$ ml ($r = 0.95$, $p = 0.000$), infarct volume $11.0 \pm 12.3$ ml ($r = 0.87$, $p = 0.000$) and infarct percentage $3.4 \pm 5.9\%$ ($r = 0.87$, $p = 0.001$).

![Flow chart showing the number of exams and the average evaluation time for the semi-automatic and the manual infarct sizing methods. After running the software for the determination of infarct size the observers on average corrected 25 exams.](image)

**Figure 9.2** Flow chart showing the number of exams and the average evaluation time for the semi-automatic and the manual infarct sizing methods. After running the software for the determination of infarct size the observers on average corrected 25 exams.
Results

Figure 9.3 Bland-Altman plot showing the agreement between determinations of myocardial volume with the semi-automatic corrected method vs. the manual method.

Figure 9.4 Bland-Altman plot showing the agreement between determinations of infarct volume and infarct percentage with the semi-automatic corrected method vs. the manual method.
9.3. SS_SSFP displays better image quality and equal infarct size compared to IR_FGRE, in patients with ongoing atrial fibrillation (Paper III)

On the still images SS_SSFP displayed significantly better image quality than IR_FGRE in all four aspects assessed, table 9.2. On the cine images artefacts were more frequent in LGE imaging, as shown from score 3.5 ± 0.5 for cine compared with 4.0 ± 0.8 for IR_FGRE and 4.5 ± 0.4 for SS_SSFP. “Overall image quality” in cine was 3.8 ± 0.5, in IR_FGRE 3.3 ± 0.7 and in SS_SSFP 3.8 ± 0.4. With cine-MRI in general there were more artefacts in the base of the left ventricle compared to the middle part and the apex of left ventricle, figure 9.5. The two observers achieved fair agreement of the quality assessment in three of the four parameters (kappa 0.41-0.60) for IR_FGRE whilst in SS_SSFP the parameters showed generally lower agreement according to the kappa statistics.

Myocardial volume was 7% higher using SS_SSFP (170.7 ml) compared with IR_FGRE (159.2 ml, r = 0.93, p < 0.001). No differences were found for infarct size (IR_FGRE 20.4 ml, SS_SSFP 19.3 ml, r = 0.84, p = 0.6) or extent (IR_FGRE 12.4%, SS_SSFP 11.0%, r = 0.80, p = 0.3). The methodological error (S_method) of myocardial volume (IR_FGRE 36.1 ml, SS_SSFP 31.3 ml, p = 0.73), infarct volume (IR_FGRE 7.4 ml, SS_SSFP 7.8 ml, p = 0.42) and infarct extent (IR_FGRE 3.4%, SS_SSFP 3.1%, p = 0.64) revealed no difference between the two methods, but in the determination of LV end diastolic volume, single shot displayed a larger variation (IR_FGRE 12.5 ml, SS_SSFP 24.5 ml, p = 0.003).

Interobserver variability for infarct volume was for IR_FGRE 4.2 ± 9.8 ml (r = 0.8, p = 0.07) and for SS_SSFP 5.6 ± 9.6 ml (r = 0.8, p = 0.01). Corresponding figures for infarct extent were 1.0 ± 4.8% (r = 0.9, p = 0.39) and 0.6 ± 4.5% (r = 0.8, p = 0.55). The correlations of WMSI on infarct volume (all segments were successfully visualized) was not significantly different for the two methods and the regression coefficients (slopes) were almost identical (WMSI = 1.27 ± 0.020x IR_FGRE_inf(%) r = 0.52; p = 0.02 and WMSI= 1.25 + 0.024x SS_SSFP_inf(%); r = 0.54; p = 0.01; i.e. the slope difference between the two methods was not statistically significant, (p > 0.9).

The segmented reference sequence took on average 8.8 ± 2.0 minutes to acquire short and long axis images, while the corresponding single shot acquisition took 4.4 ± 1.6 min, (p < 0.001). Patient heart rate was 71 ± 19 b/min
during scanning with the IR_FGRE sequence and 73 ± 17 b/min during the SS_SSFP sequence, p = n.s.

SNR was higher (better) in IR_FGRE (SNR\textsubscript{myo} = 6.7, SNR\textsubscript{infarct} = 32.4, SNR\textsubscript{blood} = 22.6) compared to SS_SSFP (SNR\textsubscript{myo} = 4.3, SNR\textsubscript{infarct} = 26.1, SNR\textsubscript{blood} = 16.6), but this difference was statistically significant only for scar and for the blood pool (SNR\textsubscript{myo} p = 0.07, SNR\textsubscript{infarct} p = 0.048, SNR\textsubscript{blood} p = 0.02). No significant difference was found between the two methods regarding CNR, (CNR\textsubscript{inf-myco: IR_FGRE} 25.6, SS_SSFP 21.9, p = 0.09, CNR\textsubscript{inf-blood: IR_FGRE} 9.7, SS_SSFP 9.5, p = 0.87).

Figure 9.5 Examples of improved myocardial delineation and artefact reduction using the fast sequence. Left panel: LGE image, upper and lower from two different patients, acquired with the segmented IR_FGRE sequence. White myocardium is scar, black is healthy myocardium. Right panel: LGE image, corresponding slice acquired with the SS_SSFP sequence. Note the improved delineation of the myocardium and infarct (upper row) and the reduction of artefacts (lower row) on the SS_SSFP slices.
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Mean (SD)</th>
<th>Median (quartile range)</th>
<th>Mean (SD)</th>
<th>Median (quartile range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninfarcted myocardium delineation</td>
<td>3.6 (0.7)</td>
<td>3.4 (3.1-4.2)</td>
<td>3.9 (0.4)</td>
<td>4.0 (3.6-4.2)</td>
<td>0.037</td>
</tr>
<tr>
<td>Infarcted myocardium delineation</td>
<td>2.7 (0.8)</td>
<td>2.7 (2.1-3.3)</td>
<td>3.2 (0.6)</td>
<td>3.1 (2.8-3.6)</td>
<td>0.041</td>
</tr>
<tr>
<td>Occurrence of artifacts</td>
<td>4.0 (0.8)</td>
<td>4.1 (3.6-4.8)</td>
<td>4.5 (0.4)</td>
<td>4.6 (4.4-4.9)</td>
<td>0.021</td>
</tr>
<tr>
<td>Overall assessment of left ventricle/left ventricle motion</td>
<td>3.3 (0.7)</td>
<td>3.3 (2.9-3.9)</td>
<td>3.8 (0.4)</td>
<td>3.8 (3.5-4.1)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 9.2 Image quality, 5 levels are used in the assessment of quality. Mean values from two interpreters. Statistically significant differences are bolded.
9.4. WMSI is more sensitive than strain in detecting area-at-risk (Paper IV)

WMSI and strain were compared in a ROC-analysis as for the prediction of segments that were to develop scar with a transmurality \( \geq 50\% \), figure 9.6. Area-under-curve (AUC) was significantly higher for WMSI (0.92) than for strain (0.78), \( p < 0.0001 \). Sensitivity at 80\% specificity was for strain 64\% and for WMSI close to 90\%. In a logistic regression analysis incorporating WMSI and strain, both parameters were significant for the prediction of transmurality \( \geq 50\% \) but strain did not add significant information beyond what was carried by WMSI.

Global left ventricular measures: LV myocardial volume was 167.8 ± 36.9 ml (range 88 – 254 ml). Infarct size, determined at follow-up 4 - 8 weeks after PCI, was on average (± SD) 14.9 ± 5.6 ml (8.7 ± 7.4\% of the volume of the LV myocardium). Mean transmurality of affected segments was calculated for each of the 24 patients with follow-up scars \( \geq 1\% \) giving a patient average of 44.3 ± 18.0\% (range 8.5 - 76). At follow-up, WMSI improved from an average (± SD) of 1.6 ± 0.3 to 1.4 ± 0.3 (n = 26; \( p = 0.001 \)). Corresponding numbers for ejection fraction were 38.5 ± 8.5\% to 46.8 ± 8.5\% (n = 17; \( p = 0.001 \)) and for global strain -13.2 ± 3.3\% to -15.7 ± 3.5\% (n = 26; \( p < 0.001 \)). Displacement changed from -5.4 ± 1.8 mm to -6.1 ± 1.4 mm (n = 26; \( p = 0.030 \)). The change in MAM did not reach statistical significance (mean 10.5 ± 2.7 mm to 11.1 ± 2.3 mm; n = 26; \( p = 0.167 \)).

There were statistically significant correlations between infarct size and percent transmurality post-PCI (assessed by MRI) on the one hand and systolic ultrasonic measures pre- and post-PCI on the other, table 9.3. The highest correlation was for WMSI post-PCI vs. infarct size (\( r = 0.83 \)) and for WMSI post-PCI and transmurality (\( p = 0.88 \)), but also global strain post-PCI correlated with infarct size (\( r = 0.51 \)) and with transmurality (\( r = 0.64 \)).

Regional ventricular measurements: Wall motion score correlated moderately with transmurality acutely and at follow-up (\( r = 0.67, p < 0.001 \) and \( r = 0.63, p < 0.001 \)) while the correlation for longitudinal strain vs. transmurality was lower at both time points (\( r = 0.51, p < 0.001 \) and \( r = 0.44, p < 0.001 \)) and for MAM still lower (\( r = -0.25, p = 0.01 \) and \( r = -0.41, p < 0.001 \)).

Segmental ventricular measurements: In the initial study, 390 out of 416 segments (94\%) were successfully visualized and at follow up 410 of the 416
segments (99%). Wall motion score correlated moderately with transmurality acutely and at follow-up (r = 0.58, p < 0.01 and r = 0.53, p < 0.01) while longitudinal strain correlated weakly with transmurality at both time points (r = 0.38, p < 0.01 and r = 0.31 p < 0.01). Displacement, regardless of the position of the segment (apical-middle-basal) also correlated weakly with transmurality (r = 0.28, p < 0.001 and r = 0.34, p < 0.001).

The methodological error (S\text{method}) between three observers were for WMSI 0.50 (COV =32\%) and 0.42 (COV=30\%) calculated for the pre- and post-PCI investigations. Corresponding methodological errors for two observers of the MAM were 1.30 mm (12.4\%) and 1.04 (9.3\%), respectively. The methodological error in absolute numbers was for strain pre-PCI 5.4 and for post-PCI 4.5. Corresponding values for displacement were 1.59 and 1.43, respectively. COV for these measurements is of no interest since the values includes zero. No significant differences were found, in regard to these measurements, between pre- and post- PCI examinations. S\text{method} for scar assessed by MR post-PCI was 1.6 ml (11\%) or related to myocardial volume 1.1\% (12\%). Interobserver variability for infarct volume was 0.1 ± 2.3 ml (p = 0.9, r = 0.99) and infarct extent 0.0 ± 1.5\% (p = 0.9, r = 0.98).

![Figure 9.6 ROC-curves displaying the interrelationship between sensitivity and specificity for wall motion score index and strain vs. the detection of segments with a transmurality ≥50\%. Area-under-curve for WMSI is 0.92 and for strain 0.78, p<0.0001.](image-url)
### Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Infarct size</th>
<th>Transmurality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scar%</td>
<td>All segments</td>
</tr>
<tr>
<td>Strain (ε)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre_PCI</td>
<td>n=26; r=0.48; p=0.014</td>
<td>n=26; r=0.61; p=0.001</td>
</tr>
<tr>
<td>Post_PCI</td>
<td>n=26; r=0.51; p=0.008</td>
<td>n=26; r=0.64; p=&lt;0.001</td>
</tr>
<tr>
<td>MAM</td>
<td>n=26; r=-0.24; p=0.245</td>
<td>n=26; r=-0.39; p=0.051</td>
</tr>
<tr>
<td>Pre_PCI</td>
<td>n=26; r=-0.56; p=0.003</td>
<td>n=26; r=-0.61; p=&lt;0.001</td>
</tr>
<tr>
<td>Post_PCI</td>
<td>n=18; r=-0.29; p=0.238</td>
<td>n=18; r=-0.52; p=0.029</td>
</tr>
<tr>
<td>EF%</td>
<td>n=24; r=-0.06; p=0.790</td>
<td>n=24; r=-0.18; p=0.411</td>
</tr>
<tr>
<td>WMSI</td>
<td>n=26; r=0.55; p=0.003</td>
<td>n=26; r=0.75; p=&lt;0.001</td>
</tr>
<tr>
<td>Pre_PCI</td>
<td>n=26; r=0.83; p=&lt;0.001</td>
<td>n=26; r=0.88; p=&lt;0.001</td>
</tr>
</tbody>
</table>

Table 9.3 Spearman’s rank correlations (n; r; p) between global ultrasonic systolic measures pre and post PCI on the one hand and infarct size and transmurality post PCI on the other. Significant correlations are bolded.

57
A common definition of myocardial infarction is “myocardial cell death due to prolonged ischemia”. This has been proposed by the European Society of Cardiology in a joint statement with the American College of Cardiology. It is important to assess scar size since it determines the treatment and the prognosis. Different modalities have their own peculiarities of visualizing myocardial scar and the effect of the scar on the function of the LV. Cardiac MRI is a relatively new modality with high spatial and temporal resolution and is able to visualize scar with high diagnostic accuracy. This allows for LV function to be correlated to scar size.

10.1 Infarct size

MPS indirectly estimates myocardial scar size as an irreversible perfusion defect while LGE visualizes an increase in the extracellular concentration of Gd which, in a chronic scar situation, very closely corresponds to the area of fibrotic tissue. Echocardiography, as earlier described, visualizes the effect of the scar on wall motion. The validation of each method is the central issue. How do the modalities compare to each other in assessing scar size? What factors explain the differences between methods? How difficult is the evaluation and how exact is the data it delivers?

In this study, we found that infarct size was slightly larger when determined with MPS compared with LGE. This is in line with Hedström et al comparing MPS and LGE in acute as well as chronic coronary conditions. Using $^{201}$Tl, a similar result was found by Lund et al in 60 patients with acute MI. Medrano et al compared the sestamibi perfusion defect in vivo with the histological evaluation of infarct size in 15 explanted hearts with ischemic cardiomyopathy. They found a good agreement between the two techniques ($r = 0.89$) although there was a slight overestimation with MPS.

The threshold for MPS scar by PERFIT is set to an absolute level of $<2$ SD of the highest perfusion uptake in a remote area of the myocardium. To compare the patient image with the reference template, the numbers of scintillation events (“counts”) in a voxel are compared with values in a voxel of the same size and location in the template. Some restrictions apply: the
maximal count position should not be in the inferior wall and it must be located at a point where the corresponding area in the template displays at least 60% of the maximal count value. The clinical cut-off for scar volume is set to 2% of the myocardial volume.

The mechanism behind LGE is an increased extra-cellular distribution of Gd-DTPA due to loss of cellular membrane integrity. In normal myocardium, only extracellular distribution of Gd-DTPA is seen\(^6\). Also the time constants for wash-in as well as for wash-out differ between normal and injured myocardium\(^6\). Bondarenko et al have worked out a standardized definition of delayed hyperenhancement in the analysis of LGE-imaging. By thresholding the window setting of the images in patients with chronic CAD at 2, 3, 4, 5, and 6 SD above the mean signal intensity of remote, healthy myocardium in the same slice, they found that the usual cut-off of 2 SD would result in a considerable overestimation of infarct size compared to visual assessment. A window setting of 5 SD above the mean SI of remote, nonenhanced myocardium was found optimal\(^2\). A high window setting has also been suggested by other authors\(^3, 130\). However, “Segment”, as used in all four papers, has been extensively validated\(^85-87\) and utilizes more information than just thresholding to determine scar area, since it also accounts for partial volume effect by weighting the pixels according to their SI.

In acute MI, the injured area may not become completely enhanced\(^131\), which has been attributed in part to microvascular obstruction. This less enhanced area is typically located in the center and not at the edges of the scar, and is believed to contain intramyocardial blood products\(^131\). The presence of microvascular obstruction is more common in larger infarcts\(^132\) and predicts more frequent cardiovascular complications even after taking infarct size into account\(^2\). We did not see any microvascular obstruction in our studies since we investigated only chronic MI with MRI.

The time span between contrast administration and imaging is found to affect infarct size. Petersen et al found that infarct size measurements are a function of time postcontrast when TI is held constant\(^133\). However, if TI is continually optimized, scar imaging is successful in a time window of 5 to 30 minutes after contrast administration independent of two commonly used contrast dose levels, 0.1 or 0.2 mmol/kg\(^134\). In our studies, all imaging was within this time span.

A major difficulty with MPS is soft tissue attenuation, which often is located in the inferior/posterior wall of the heart. In this region, LGE is known
to have higher sensitivity for myocardial scar compared to MPS\textsuperscript{135}, especially in the setting of a nontransmural infarction\textsuperscript{136}. McCrohon et al found that only approximately 25\% of patients with presumed inferior attenuation defect on MPS have abnormalities on LGE\textsuperscript{137}. These features were also present in our patients in study I: in four of the six patients where MPS showed infarct size exceeding $+1$ SD compared with LGE, MPS displayed hypoperfused myocardium in the inferior wall and in three of the five patients where MPS suggested MI but LGE did not, there was reduced perfusion in the inferior wall, determined with MPS. To reduce the impact of attenuation, a variety of techniques have been used such as imaging the patient in the prone position\textsuperscript{138,139} and ECG-gated MPS imaging\textsuperscript{107}. Both techniques increase the ability of MPS to detect CAD. Attenuation correction has been shown to improve the accuracy of $^{201}$Tl MPS\textsuperscript{140} and it is suggested that attenuation correction should be regarded as standard for MPS imaging\textsuperscript{141}. Another possible explanation for a falsely reduced isotope uptake could be a reduced wall thickness\textsuperscript{142}, as also was found in our study.

Spatial resolution is known to be higher with LGE compared to MPS, causing larger problems with partial volume effects for MPS, which lowers the potential for the detection of subendocardial scar but does not impair the detection of transmural scar\textsuperscript{143}. Notwithstanding, partial volume effects\textsuperscript{1} are still evident when the heart is investigated with LGE, especially in the left ventricular outflow tract and in the apex area, where the curvature of the LV is largest. Such effects are also seen in scarred myocardium and accentuated when the difference in SI between infarcted myocardium and the blood pool is low. This was also the impression of both investigators who outlined the myocardium and scar in our studies.

Higher reproducibility and lower intra- and interobserver variability for a modality give better diagnostic certainty. The reproducibility of LGE has been studied by recording images at 10 and 25 minutes post contrast (two different technicians). In this setting, repeatability was $\pm 2.4$ scar percentage points but the quantifying method was only described as being “automatic”\textsuperscript{65}. In MPS, repeatability has been determined to be in the range of $\pm 4.0$ scar percentage points\textsuperscript{65}. In our studies we did not perform any reproducibility measurements for the acquisition phase, but the intra- and interobserver variability for the evaluation of infarct volume and infarct extent on LGE images was generally low, ranging from $0.0 \pm 1.5\%$ (infarct extent, paper IV) to $5.6 \pm 9.6$ ml (infarct volume assessed by SS_SSFP, paper III). However, the interobserver
variability of infarct volume assessed with the semi-automatic method, study II, was somewhat higher at 11.0 ± 12.3 ml.

Interobserver variability in general is a well recognized problem in all types of imaging. Hoffmann et al.\textsuperscript{88} showed that physicians employed in the same echo lab agreed in wall motion assessment but there was lower agreement when compared with physicians trained in other hospitals. Knitting et al.\textsuperscript{144} showed that the agreement for detecting regional delay in myocardial motion is low, probably due to limits of the human eye in perceiving temporal differences. The author also noticed individual differences in the ability to assess cardiac motion. To reduce interobserver variability, we and others suggest that computer-assisted interpretation may be helpful. Lindahl et al.\textsuperscript{8} showed that physicians classifying MPS in a bull’s eye presentation benefitted from the advice of an artificial neural network. This effect could be quantified in terms of an increased area under the ROC-curve\textsuperscript{119}. The same author also suggested that the network can assist physicians in achieving correct interpretation and thereby improving the diagnostic accuracy\textsuperscript{118}. The problem of segmentation is central to all quantitative cardiac measurements and computed-assisted segmentation of the LV has been applied to different image types. Computed-assisted segmentation should perform best when image contrast is high such as it is in SSFP cine MRI, however, manual tracing has in that situation been found to be superior\textsuperscript{145}. Several objective semi-automatic methods for the analysis of myocardial scar have also been described\textsuperscript{82,84}. A major drawback is their sensitivity to partial volume effects but the weighting by pixel SI used by Heiberg, as described above, provides automatic scar quantification with higher accuracy and lower variability than a dichotomous algorithm\textsuperscript{86}.

In the busy daily clinical practice, a rational workflow with short evaluation time is necessary. Substantial time savings have been suggested in the segmentation of the LV\textsuperscript{145} as well as of the myocardial scar\textsuperscript{84}. This was also found in our study where we reduced the evaluation time by more than 50\% compared with manual assessment, with maintained clinical accuracy.

In all imaging techniques, and also in MRI, there is a trade-off between spatial and temporal resolution. Important physical constraints on the reduction in imaging time are relaxation time, SNR and spatial resolution. It is worth noting, that for any given spatial resolution and contrast, SNR needs only to be sufficient for lesion detection. Above that level, an increase in SNR
Discussion

makes the image more pleasant for the viewer, but does not necessarily impart a higher accuracy in the diagnosis. The single shot sequence used in study III limited read-out to central K-space and displayed images with fewer artefacts compared to the segmented sequence. Segmentation of the myocardium as well as of the infarct area was facilitated. Overall the fast sequence was favourably rated in regard to quality compared with the segmented sequence. The infarct size and the error in its determination were, however, equal for both sequences.

To determine myocardial salvage, an initial measure of myocardial area-at-risk is required. Myocardial oedema, determined with MRI, and myocardial perfusion, determined with MPS have been used, mainly because imaging then does not have to be performed acutely. In study IV, we selected wall motion assessment, either visual or by tissue Doppler, because of its low cost, availability at the bedside, and the possibility to perform assessment in immediate relation to the intervention. We found that both methods identified segments that were to develop scar transmurality in excess of 50%. However, WMSI was superior to strain in regard to sensitivity as well as specificity. Thus, in the situation of acute MI, strain measurement was of no added benefit.

10.2 Functional measurements of the left ventricle

In the echocardiographic laboratory, visual assessment of wall motion is by far the most common method to evaluate LV systolic function. The correlation between echocardiographic wall motion abnormality and histologically determined infarct size has been evaluated in experimental animal studies\textsuperscript{33,146}. A few studies have been performed in humans. Shen et al found that WMSI was positively correlated ($r = 0.52$) with global infarct size determined at autopsy\textsuperscript{32}. This is in line with all our results comparing WMSI and scar size determined by LGE in paper I, III and IV, although the correlation was somewhat higher between WMSI and scar size post-PCI, $r = 0.83$ (paper IV). However, visual assessment is highly subjective\textsuperscript{144} and has limited ability to perceive temporal differences\textsuperscript{144}.

TDI is considered objective and quantitative in assessing both regional and global LV function compared to WMSI. LV systolic function is, as mentioned, complex in itself and also when assessed with different techniques for
measuring strain. Simplified solutions are those that determine strain along the tissue Doppler beam (1-dimensional) or from speckle in the gray scale image (2D-strain, 2-dimensional).

Global strain reflects the averaged segmental myocardial long-axis relative shortening and is a global functional measure\textsuperscript{147}. We found that global strain determined with tissue Doppler showed a moderate correlation with total infarct size ($\text{strain}_{\text{pre\_PCI}} r = 0.48$, $\text{strain}_{\text{post\_PCI}} r = 0.51$), lower than that for WMSI ($\text{WMSI}_{\text{pre\_PCI}} r = 0.55$, $\text{WMSI}_{\text{post\_PCI}} r = 0.83$). On the contrary, global strain has by other authors been shown to have a higher correlation to infarct size than WMSI. In chronic infarction, Gjesdal et al showed a correlation of 0.84 between global strain and scar compared to WMSI and scar (0.70)\textsuperscript{99}. Vartdal et al found the corresponding figure of 0.77 between strain and scar and 0.45 between WMSI and scar in patients with acute STEMI\textsuperscript{100}. In both studies speckle tracking was used which might have improved the quantification of strain. In the fourth paper we selected tissue Doppler strain since we anticipated difficult scanning conditions and hoped that the strong tissue Doppler signal would allow analysis also of images with low contrast and with pulmonary shadowing. A negative aspect of tissue Doppler strain in contrast to speckle tracking is, however, the angle dependency\textsuperscript{148} in addition to being 1-dimensional.

How can the widely different results of using technologically advanced strain methods be understood? The learning curve is obvious, but it is also interesting to note that results and reference values differ when strain is calculated from different and simplified methods. Also, fibre organization in terms of sheet and fibre directions has been shown to be important\textsuperscript{149}.

Strain, whether 1- or 2 dimensional, is load dependent, evident in paper IV when the patients at times were hypotensive and in pain. However, the results at follow-up, when imaging conditions were more favourable, were in the same range as those obtained acutely. The aspect of load dependency has not been further analysed in the present studies\textsuperscript{94, 150}.

Despite theoretical advantages, strain was inferior to visual assessment in predicting scar transmurality not only on global level, but also on regional and segmental levels. MAM and displacement correlated even more weakly than strain. This is in line with Skulstad et al who studied the relationship of strain and displacement for quantification of regional myocardial function\textsuperscript{151}. 

Chapter 10

Infarct Size and Myocardial Function
10.3 Future developments and clinical implications

In daily patient care the crucial part is to determine in which what patients to intervene in order to restore LV function. It is essential to rule out hibernation as a reversible cause for myocardial dysfunction. The LGE technique is unique in its ability to visualize scar. LGE imaging, combined with cine imaging, could possibly detect hibernated myocardium and facilitate the visualization of LV dysfunction. Setser et al evaluated a cine LGE sequence based on IR SS_SSFP. Overall they found that wall motion was correctly scored in 71% of the myocardial wall segments compared to cine-loops assessed with SSFP, and scar extent in 76% of the segments compared to standard LGE images. However, the temporal resolution was too low, but could be improved by parallel imaging and/or segmental K-space schemes.

Cine-MRI imaging is considered to be the most accurate clinical method for assessing ventricular volumes since it can acquire a 3D volume independent of geometric assumptions. Segmented SSFP is an excellent technique for rapid cine-imaging of the heart, however, repeated breath-holds require patient cooperation and image quality is sensitive to effects of arrhythmia. The SSFP sequence can also be applied to real-time imaging at a lower spatial resolution and hence facilitate imaging in patients with breath-holding problems or arrhythmia. Several authors have shown that cardiodynamic measurements obtained with real-time SSFP cine under free breathing correlate sufficiently with segmented SSFP. In the future, further reduction in TR or the use of parallel imaging techniques such as SENSE might improve temporal resolution.

Although MPS is widely used in current clinical practice, it suffers from limitations such as long duration of image acquisition, low image resolution and radiation dose. Lately a new non-invasive technique, cardiac computed tomographic angiography (CCTA), has emerged as a serious competitor, although it needs much more clinical evaluation. In hybrid systems, MPS can be combined with CCTA, resulting in a display of the functional effect on perfusion of coronary stenoses. New MPS hardware with novel detector and collimator design has been introduced, as well as new reconstruction software. These new scanners increase the sampling of the myocardium which can be used either for shortening the time required for the exam or to improve the sensitivity in detecting a reduced perfusion. In general, these new systems offer both an improvement in spatial resolution and an increased
sensitivity. A decrease in scan time to as low as 2 minutes has been reported\textsuperscript{157,158}.

Myocardial contrast echocardiography (MCE) is an ultrasound technique that has the potential to display and quantify myocardial perfusion. Following intravenous contrast injection, micro bubbles opacify the LV cavity and the myocardium. When the bubbles are destroyed by applying ultrasound with a high mechanical index, the wash-in of fresh bubbles may be detected as an increase in SI. Peak intensity and micro bubble replenishment can be assessed, which in turn reflects the microcirculatory flow in the myocardium\textsuperscript{160}. Lafitte et al have shown in dogs that real-time MCE defect size and quantitative refilling parameters compare well with infarct size and area-at-risk determined by histology\textsuperscript{161}. It has also been shown that MCE markers of infarct size are useful in predicting the risk of LV remodelling following acute MI\textsuperscript{162}. Today MCE still has serious limitations preventing widespread clinical use: tissue signal, artifacts from motion and increased bubble destruction are major problems. It should also be remembered that the shape of the filling curve is influenced by several imaging variables such as depth, angle and instrument setting. However, MCE is a technique with a potential to provide essential information, extremely valuable at the bedside, regarding the presence and extent of ischemic coronary heart disease and scar size.

To achieve a true understanding of the anatomy and pathology by 2D-echocardiography, a complex mental integration of multiple image planes is required. 3D-echocardiographic images are presented in a more reality-like fashion that could facilitate their interpretation. In addition, 3D-echocardiography improves the calculation of LV volume and mass by avoiding geometric assumptions. Compared with MRI data, 3D-echocardiography has a better correlation for end-diastolic volume and end-systolic volume than 2D-echocardiography\textsuperscript{163}. In an experimental study in dogs, Yao et al showed that there is a good correlation (r=0.93) between dysfunctional mass of the LV and infarct mass determined by histology\textsuperscript{164}, and De Castro et al showed the same for dysfunctional mass derived from 3D-echocardiography and LGE uptake on MRI images in patients with chronic MI\textsuperscript{165}. High-resolution real-time 3D-echocardiography is a technique that enables the observation of surface structures and the movements of the beating heart in real time. In a healed MI there is reduced or absent endocardial contraction; the area is smooth, without rough muscle folds that shrink during systole and the scar area has an increased acoustic intensity
compared to healthy myocardium. Thus indirect assessment of scar size is possible also with 3D-echocardiography. With the state of current technologies, real-time 3D-echocardiography has limitations in temporal and spatial resolution and in visualizing the apical region of the LV. Improvement in image resolution from the use of high frequency transducers, wider sector angles and higher frame rate might reduce these problems.

To summarize, the foremost advantages of MR in cardiac imaging are the spatial resolution and the ability to visualize myocardial scar. However, it is important for patients as well as for the entire health care system, that each patient receives adequate investigations and individualized treatment. As shown above, each modality, whether MRI, echocardiography or MPS, has strengths and weaknesses, and should be used accordingly. No single modality is considered “the golden standard” for all purposes. MRI has the ability to capture slices of the body in all imaginable planes, does not use ionizing radiation, displays excellent image contrast and visualizes scar and transmurality, but has drawbacks such as high costs and limited availability. Echocardiography is inexpensive, easily available, mobile, does not use ionizing radiation but is highly operator dependent. Finally, MPS has high sensitivity and specificity as well as a high negative predictive value for CAD, but is time consuming and uses radioactive agents.
CONCLUSIONS

• MPS and LGE agreed fairly well in the determination of infarct scar size although infarct size was slightly larger with MPS.

• WMSI, determined with both MRI and echocardiography, correlated moderately with both infarct size and infarct extent determined with LGE.

• Infarct evaluation time was halved when using a semi-automatic computer software, Segment, compared with manual assessment, with maintained clinical accuracy.

• In patients with chronic atrial fibrillation and chronic MI, the fast single shot sequence, SS_SSFP, acquired under free breathing, displayed significantly better image quality than the segmented sequence IR_FGRE, acquired during breath holding. Infarct size and the error in its determination were equal for both sequences and the examination time was shorter with SS_SSFP.

• Visual assessment is superior to measuring Doppler strain for the detection of scar with transmurality ≥50% in patients with acute MI.

• WMSI shows a higher correlation than strain on a global-, regional- and segmental level in relation to the size of the final myocardial scar determined with LGE.
ACKNOWLEDGEMENTS

Now, when I have almost finished this long journey, I can look back and state that this work would never have been possible without the generous help and support from many people in various areas of life - research, clinical work, friendship and family life. I am grateful and thankful to all of you. Special thanks are due to:

Jan Engvall, associate professor and tutor. It has been a pleasure working together with you during these years and I am really grateful for your time, support and trust in my work. You have guided me over the highest hills and lifted me out of gloomy, depressive valleys of research. Your never ending enthusiasm and patience is admirable and, luckily for me, also contagious. You have taught that nothing (almost) is impossible; you only have to look at it differently!

Peter Blomstrand, co-supervisor, co-author and head of the Department of Clinical Physiology, Ryhov County Hospital. Thank you for fruitful discussions and wise counselling. Thank you also for always trusting me and for allowing time-off from my clinical duties thus giving me the opportunity for research.

Lars Brudin, professor and co-author. Working together with you on statistics is a truly educational experience! No one but you can explore the field of statistics so thoroughly, forget time and place answering e-mail at 00:57 Saturday morning! Thank you!

Britt-Marie Ahlander, Per-Gunnar Björklund, Einar Heiberg, Jan Ohlsson, Sven-Åke Starck, and Tim Tödt, all co-authors. Thank you for your contribution to the progress of these studies; patient exams and invaluable advice during the writing of the manuscripts.

Pearl & Jan Ohlsson, for excellent help revising my English in all papers, and Magnus Areskog and Monica Liehl, for proof reading of the manuscripts.

The staff at Eksjö and Värnamo County Hospitals and at Linköping University Hospital. Thank you for assistance in the recruitment of patients and in performing the patient exams. Your willingness to perform this work has been very valuable to me.
The staff at Ryhov County Hospital Medical Library for excellent help in obtaining literature.

My colleagues at the Department of Clinical Physiology and Olof Svensson for managing the daily work when I was absent.

Oskar Löfgren, head of the Department of Radiology, Ryhov County Hospital, for allowing me access to cardiac MRI.

What would life be without spare time and hobbies? Thank you all members of Åke Perssons Sängarförening and especially Åke Persson - thank you for the music! Singing brings a new dimension into life! I cherish you and your choir!

My parents, Gerd - for being my mother, always loving and believing in me and having time for me. Stig – for being my father, always supporting and encouraging me and, above all, loving me. My sister Anne – for being the best sister one can get, always being friendly, helpful and kind.

Last, but most important, my daughters Malin – for being cheerful, happy and humoristic; Sara - for being kind, sweet and thoughtful; Anna – for being cosy, understanding and full of life. You are the delights of my life! Jan – Thank you for sharing your life with me, loving me and never complaining about long hours!

The studies which constitute the basis of this thesis were supported by most valuable and generous grants from FUTURUM – the Academy of Healthcare, Jönköping County Council, FORSS – the Medical Research Council of Southeast Sweden, CMIV – the Center for Medical Image Science and Visualization, Linköping University, the Swedish Heart Lung Foundation, the Swedish Research Council, Linköping Heart Centre and Schering AB.
References

Infarct Size and Myocardial Function


References


40. van ‘t Hof AW, Liem A, Suryapranata H, Hoornjte JC, de Boer MJ, Zijlstra F. Clinical presentation and outcome of patients with early, intermediate


50. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987;59(7):23C-30C.


Infarct Size and Myocardial Function


81. Azevedo Filho CF, Hadlich M, Petriz JL, Mendonca LA, Moll Filho JN, Rochitte CE. Quantification of left ventricular infarcted mass on cardiac...


References


Infarct Size and Myocardial Function


132. Nijveldt R, Beek AM, Hofman MB, Umans VA, Algra PR, Spreeuwember MD, et al. Late gadolinium-enhanced cardiovascular magnetic resonance
evaluation of infarct size and microvascular obstruction in optimally
treated patients after acute myocardial infarction. J Cardiovasc Magn Reson

133. Petersen SE, Mohrs OK, Horstick G, Oberholzer K, Abegunewardene N,
Ruetzel K, et al. Influence of contrast agent dose and image acquisition
timing on the quantitative determination of nonviable myocardial tissue

134. Wagner A, Mahrholdt H, Thomson L, Hager S, Meinhardt G, Rehwald W,
et al. Effects of time, dose, and inversion time for acute myocardial infarct
size measurements based on magnetic resonance imaging-delayed contrast

Comparison of late enhancement cardiovascular magnetic resonance and
thallium SPECT in patients with coronary disease and left ventricular

imaging evaluation of myocardial viability in the setting of equivocal

137. McCrohon JA, Lyne JC, Rahman SL, Lorenz CH, Underwood SR, Pennell
DJ. Adjunctive role of cardiovascular magnetic resonance in the assessment
of patients with inferior attenuation on myocardial perfusion SPECT. J

myocardial perfusion defects on prone SPECT imaging: comparison with
cardiac magnetic resonance imaging in patients without established

Combined quantitative supine-prone myocardial perfusion SPECT
improves detection of coronary artery disease and normalcy rates in

140. Chouraqui P, Livschitz S, Baron J, Moalem I, Shechter M. The assessment of
infarct size in postmyocardial infarction patients undergoing thallium-201
tomographic imaging is improved using attenuation correction. Clin Nucl

141. Hendel RC, Corbett JR, Cullom SJ, DePuey EG, Garcia EV, Bateman TM.
The value and practice of attenuation correction for myocardial perfusion
SPECT imaging: a joint position statement from the American Society of
Nuclear Cardiology and the Society of Nuclear Medicine. J Nucl Cardiol

A, et al. Left ventricular wall motion abnormalities as well as reduced wall
thickness can cause false positive results of routine SPECT perfusion

Contrast-enhancement MRI and routine single photon emission
Infarct Size and Myocardial Function


References


