CARDIOVASCULAR MAGNETIC RESONANCE OF
ACUTE AND CHRONIC MYOCARDIAL ISCHAEMIA

PhD Thesis

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“It is your attitude
Along with your aptitude
That will decide your altitude”
to

my family in Italy

my friends in London

my friend in Spain

for their support and inspiration
ABSTRACT

BACKGROUND
Ischaemic heart disease is the leading cause of mortality and morbidity in the developed world. Cardiovascular magnetic resonance (CMR) is a non-invasive imaging modality providing in vivo myocardial tissue characterisation and quantification. We aimed to validate CMR in the field of interventional cardiology as a tool for guiding patient selection and management to the assessment of the results of interventions both in the acute and chronic settings.

METHODS AND RESULTS
We investigated the impact of primary angioplasty delay on the presence and extent of myocardial salvage, microvascular obstruction and infarct size. We found that “time is muscle”, and that shorter time to reperfusion was associated with smaller infarct size (p=0.05), less microvascular obstruction (p=0.04) and a greater amount of salvaged myocardium (p=0.003). Microvascular obstruction was then used as an endpoint in a prospective randomised trial assessing the impact of a thrombectomy device as adjunctive therapy in primary PCI. The incidence and extent of microvascular damage was significantly reduced in the thrombectomy group compared to standard primary PCI (p=0.0005). CMR can identify 2 degrees of microvascular damage: early or persistent microvascular dysfunction. The latter was the strongest predictor of LV remodelling (p=0.03), it was predicted by infarct size (p=0.002), and infarct healing (shrinkage) occurred to a greater extent (p<0.006). We validated the clinical use of CMR perfusion in a cohort of patients with chronic coronary occlusion whose management is currently controversial. CMR identified myocardial viability and inducible myocardial ischaemia in a significant percentage of patients, guided revascularisation that reduced ischaemic burden (p<0.0001) with improvements in left ventricular function (p<0.0001) and health outcome measures (p<0.0001). Finally, improved CMR perfusion image quality was pursued with a new imaging protocol but this demonstrated increased incidence of artefacts (p<0.001) and lower diagnostic accuracy compared to the standard technique.

CONCLUSIONS
Cardiovascular magnetic resonance provides in vivo myocardial tissue characterisation that can potentially not only guide treatment but also assess its effects. The result of this work suggests that CMR could emerge as a clinical valuable technique in numerous interventional clinical settings within acute to chronic myocardial ischaemia, in addition to providing surrogate endpoints for clinical trials.
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CHAPTER 1
SUMMARY AND OBJECTIVES

Ischaemic heart disease is the leading cause of mortality and morbidity in the developed world. Cardiovascular magnetic resonance (CMR) is a non-invasive imaging technique providing in vivo myocardial tissue characterisation and quantification. The aim of this work is to define the diagnostic role of CMR in the field of interventional cardiology from patient selection to assessing the result of intervention, both in the acute and chronic settings.

The research questions in this thesis are:

- Is time to reperfusion an important determinant of infarct size and microvascular obstruction?

- Is salvaged myocardium reduced when reperfusion occurs late?

- Does the adjunct use of thrombectomy device in the setting of primary PCI reduce microvascular obstruction?

- Is microvascular obstruction related to infarct shrinkage?

- Can CMR detect myocardial viability and inducible perfusion defect in patient with chronic total occlusion?

- Can CMR detect the resolution of inducible perfusion defect following successful recanalisation of a chronic occluded vessel?

- Is a new stress perfusion protocol using SSFP sequence and half-dose of contrast less prone to artefacts compared to standard EPI with full contrast dose?
Prompt reperfusion in patients with ST-segment elevation myocardial infarction is associated with improved prognosis suggesting that “time is muscle”. Nevertheless, there are uncertainties regarding the effects of reperfusion strategies at myocardial level. In particular, it is unclear how much salvageable myocardium is present after reperfusion and to how to improve its identification in clinical practice. CMR has been validated against histology for the identification of infarct size, myocardial salvage and microvascular obstruction. In **Chapter 5**, we investigate the impact of time to reperfusion and delays in revascularisation on the presence and extent of myocardial damage. In **Chapter 6**, microvascular obstruction by CMR was then used as an endpoint in a prospective randomised trial assessing the impact of a thrombectomy device as adjunctive therapy in primary percutaneous coronary intervention. In **Chapter 7**, two degrees of microvascular damage are identified by CMR and their incidence, role on left ventricular remodelling and infarct healing are investigated.

Coronary chronic total occlusions (CTO) are identified in approximately one third of diagnostic coronary angiograms. Recanalisation of a CTO is still controversial due to inadequate patient selection. **Chapter 8** investigates the role of CMR in a selected cohort of patients with CTO in identifying those that could benefit from recanalization, and in predicting functional improvement after revascularisation and its impact on quality of life.

Myocardial perfusion imaging is not standardised and currently there is no consensus on the best sequence to use. Artefacts mimic genuine perfusion defects and improvement in image quality is desirable to improve the diagnostic confidence of the technique in the clinical setting. **Chapter 9** explores the utilisation of a novel perfusion protocol aiming to increase image quality while reducing the occurrence of artefacts.
CHAPTER 2
CMR IN ACUTE MYOCARDIAL ISCHAEMIA

2.1 MYOCARDIAL OEDEMA/MYOCARDIUM AT RISK

2.1.1 Pathophysiology
In normal myocardium intracellular water represents approximately 77% of the total tissue water, and the remaining 23% is intravascular. Although the physiological mechanisms regulating intracellular and interstitial fluid balance are complex and not completely understood, prominent aspects of these mechanisms include 1) the Starling filtration principle, regulating fluid exchange between the interstitial space and the capillaries, 2) cell membrane function and 3) lymphatic drainage (Figure 2.1).

![Diagram of hydrostatic forces affecting myocardial fluid balance](image)

Figure 2.1. The hydrostatic forces affecting myocardial fluid balance. A= arterial, V=venous, V1=veins leading to coronary sinus, V2=thebesian veins, I=interstitial pressure, C=capillaries, P=compressive force in ventricular wall owing to contraction, T=transmicrovascular flux, L=lymphatics. Reproduced from Laine
The increase in water content induced by ischaemia has been well documented in vitro\(^3\), in the isolated\(^5\) and *in-situ* heart.\(^6\) In particular, a 9.4% increase in the subendocardial water content was found after 2 hours of occlusion\(^7\), where in another study a 16.5% increase in tissue water was observed after 50 minutes of occlusion, increasing up to 45% after 75 minutes.\(^5\)

The mechanisms of myocardial oedema, cell swelling and inflammatory response (*Figure 2.2*) secondary to ischaemia are not completely elucidated. During ischaemia, the breakdown of large molecules leads to intracellular accumulation of metabolic end products of anaerobic glycolysis and ATP hydrolysis, increase in tissue osmolality resulting in cell swelling.\(^3\),\(^4\),\(^8\) During reperfusion, the hyperosmotic intravascular fluid is rapidly replaced by normo-osmotic blood, creating an osmotic gradient between the intravascular and extravascular spaces resulting in myocardial oedema.\(^4\) Viable reperfused myocytes may restore normal cell volume by recovering membrane function and reduction of osmotic load, and myocytes with disrupted sarcolemma equilibrate their osmotic pressure with the extracellular space and lose their excess in water.\(^9\) The hypoperfused, ischaemic, but reversibly damaged myocardium is defined as myocardium at risk.\(^10\)

*Figure 2.2* Myocardial oedema, cell swelling and inflammation secondary to ischaemia.

### 2.1.2 Other Imaging Modalities

**SPECT**

Currently, the gold standard for determining the area at risk (AAR) is Single Photon Emission Tomography (SPECT) with injection of Technitiium-99m (\(^{99Tc}\)) tracer prior to revascularisation.\(^11\) This technique has been validated extensively against microspheres.\(^12\),\(^13\),\(^14\)
Radiotracers need to be injected at the time of the occlusion but the imaging is performed subsequently, following revascularisation. $^{99}$Tc MIBI traces blood flow and does not redistribute significantly after reperfusion and it is preferably used for imaging AAR compared to thallium-201 which has a rapid redistribution that requires early scintigram during the occlusion. Myocardial salvage index is usually defined by the initial perfusion defect (tracer injected before reperfusion and patient imaged 6-8 hours after) minus the final infarct size (at follow-up SPECT scan, 7-14 days after) divided by the initial perfusion defect. Salvation index by SPECT has been correlated with TIMI flow grade\textsuperscript{15}, TIMI reperfusion grade\textsuperscript{16} and ST segment resolution\textsuperscript{17} after reperfusion therapy. SPECT is well clinically validated, widely available technique for assessing myocardial salvage. However, the requirement of radiotracer administration in the emergency room, the related radiation burden and the lower spatial resolution represent limitations of this technique.

AAR assessed by T2w CMR performed at 1 week after reperfusion has been validated against SPECT in patients with STEMI (\textit{Figure 2.3}).\textsuperscript{18}

\textit{Figure 2.3 Myocardium at risk by CMR and SPECT, from Carlsson\textsuperscript{18}.}
Echocardiography
Post-ischaemic oedematous myocardium is associated with both systolic dysfunction and increased stiffness, which might then result in higher LV filling pressures. An increased in myocardial thickness can be seen in routine 2D echocardiography which is the result of myocyte swelling and myofibrillar oedema, which also has some direct effects on myocardial contractility (strain) (Figure 2.4)\textsuperscript{19}.

\textbf{Figure 2.4} Relationship between myocardial water content (MWC) and mid wall myocardial strain $E_{cc}$ (A) and wall thickness (WT) (B). The open circles represent remote myocardium and the filled circles represent stunned myocardium. Adapted from Bragadeesh\textsuperscript{19}.

\textit{In vivo} determination of the AAR by myocardial contrast echocardiography has also been validated against SPECT but limited to the experimental setting.\textsuperscript{20}

Invasive Coronary Angiography
Invasive coronary angiography can also provide an estimate of myocardium at risk using the myocardial jeopardy index (Bypass Angioplasty Revascularization Investigation, BARI), as recently validated against CMR: salvaged provided in the early hours of reperfusion occurred by limiting the transmurality of irreversible myocardial damage.\textsuperscript{21} AAR by T2w CMR has been also directly compared and validated by conventional coronary angiography with the BARI risk score.\textsuperscript{22} However, the BARI score is simply an anatomical score based on an individualised assessment of the length and the calibre of the coronary arteries, and cannot distinguish between the benefit provided by residual or collateral flow and that provided by reperfusion.
2.1.3 CMR Technique and Tissue Validation

Changes in myocardial water content occurring in the early phase after ischaemia, and subsequent increased T2 signal intensity (SI) has been observed in the post-ischaemic oedematous myocardium and proposed as a sensitive marker of regional myocardial injury since the early 80s. Controversies arose on the extent of elevated T2 signal intensity in relation to “true” infarct size, and in particular whether myocardial oedema was matching or overestimating infarct size. Dymarkowski et al. clarified some of these aspects elegantly demonstrating that there was a strong correlation between the post-contrast T1-weighted MRI imaging and histologically determined infarct size, whilst T2-weighted imaging was overestimating infarct size by 10%. They also noted that the difference between the hyperintense areas on T2-weighted and enhanced T1-weighted images were likely to represent viable myocardium. Subsequent in vivo experimental studies in a dog model of acute myocardial ischaemia validated AAR with T2w against AAR with microspheres injected during ischaemia, and identified as myocardial salvage the proportion of myocardium at risk (which corresponded to the T2w area) which was not infarcted (the latter assessed by LGE imaging) (Figure 2.5).

Figure 2.5 Validation of AAR by T2w CMR against microspheres injected during ischaemia.

In human studies the increased T2 signal associated with oedema is observed very early in acute myocardial infarction (within 1 hour) and completely resolved few months later, allowing a window for the retrospective identification of ischaemia. The increased in the myocardial T2 signal is depicted with a T2-weighted sequence, among which the most commonly used is the STIR T2 sequence. Further studies confirmed the identification of AAR with T2w imaging, which systematically exceeded the infarcted area, and the difference between the two representing myocardial
salvage. T2w CMR can also accurately differentiate acute from chronic myocardial infarction. Finally, the prognostic importance of myocardial salvage index by CMR in patients with reperfused ST-elevation myocardial infarction (STEMI) has been recently demonstrated.

The advantage of CMR over the other imaging modalities is not only the increased spatial resolution, but the potential to assess the AAR retrospectively days after revascularisation overcoming the logistical complication in SPECT of injecting radiotracer at the time of coronary occlusion. However, the clinical implications on the presence and extend of myocardial oedema post-infarction are not entirely established. In particular, it remains uncertain whether myocardial oedema should be considered a surrogate endpoint in reperfusion trials.

2.2 MICROVASCULAR OBSTRUCTION

2.2.1 Pathophysiology

The extent of reversible and irreversible myocardial damage is temporally related to the duration of myocardial ischaemia. The ischaemic-necrotic wavefront of ischaemic cell death, which gradually moves from the subendocardium towards the subepicardium (Figure 2.6). The mechanism of this subendocardial to subepicardial progression of injury probably is multifactorial. It is mostly due to the additional resistance on the endocardial vessels due to compression (R3 coronary resistances, see Chapter 3, paragraph 3.1 pathophysiology of chronic ischaemia), as well as the length of the vessels. Transmural distribution of coronary collateral flow is a less well-accepted underlying cause. The no-reflow phenomenon, or microvascular obstruction (MVO), reflects severely compromised myocardial tissue perfusion (necrotic myocytes with gross microvascular damage) despite restoration of the epicardial artery patency.
Figure 2.6. Ischaemic-necrotic wavefront phenomenon, diagram and corresponding late gadolinium enhancement image.

No-reflow is a complex process that involves a number of different mechanisms including regional and diffuse endothelial swelling, endothelial gaps, fibrin tactoids, microemboli, rouleaux formation, neutrophil plugging, and compression of capillaries from adjacent swollen myocytes, spasm of the microvasculature at a precapillary level, and the formation of platelets plugs, as illustrated in Figure 2.7.

Figure 2.7. Mechanisms of the no-reflow phenomenon. Reproduced from Kloner.36
2.2.2 Other Imaging Modalities

Echocardiography

Technical developments coupled with new available contrast agents have contributed to establish myocardial contrast echocardiography (MCE) as another non-invasive imaging technique for assessing myocardial perfusion both visually and quantitatively, and in real time.\textsuperscript{37,38} In particular, myocardial blood flow velocity is measured by the rapid destruction of echo contrast microbubbles using ultrasound and then determining the rate at which they refill the myocardium. The extent of microvascular damage by MCE demonstrated to be superior to other known post-infarct reperfusion indexes (ST segment reduction, TIMI flow grade, TIMI blush grade) in predicting left ventricular remodelling.\textsuperscript{39} The advantages of the technique are easy access and affordability but it is limited by operator dependency, good echocardiographic windows and low spatial resolution.\textsuperscript{40}

Invasive Coronary Angiography

The Thrombolysis In Myocardial Infarction (TIMI) study group developed a grading scale for an invasive assessment on myocardial perfusion based on visual evaluation of the rate of contrast opacification of the infarct artery.\textsuperscript{41} Since then, TIMI flow grade (grading from 0: no perfusion to 3: complete perfusion) has become the standard for semiquantitative evaluation of myocardial perfusion before and after coronary reperfusion, as well as yielding important prognostic information in patients with AMI\textsuperscript{42}.

Just as TIMI flow grade is an important parameter to assess coronary artery flow, the Zwolle Myocardial Infarction Study Group suggested that a myocardial blush grade (MBG) (similar grading from 0-3) as seen on the coronary angiogram can be used to describe effectively myocardial perfusion, with similar prognostic importance.\textsuperscript{43} A TIMI myocardial perfusion (TMP) grading system (grading from 0 to 3) was then also established, and based on the contrast opacification of the myocardium (“blush”)\textsuperscript{44,45}

2.2.3 CMR Technique and Tissue Validation

CMR in the quantification of MVO has been validated against MCE and the histological standards of radioactive microspheres and thioflavin-S straining in an experimental model 3 days after coronary occlusion (Figure 3.8).\textsuperscript{46} Other groups confirmed the good correlation
between microvascular damage by CMR using a rest first-pass technique during contrast injection against the histological determination of endocardial damage.\textsuperscript{47}

\textbf{Figure 2.8.} Validation of MVO by first-pass CMR against microsphere. There is good correlation between the two techniques. Modified from Wu.\textsuperscript{46}

Studies have shown that the presence and extent of MVO following AMI as measured by early gadolinium enhancement CMR is associated with adverse ventricular remodelling\textsuperscript{48} and clinical outcome that is independent of the infarct size.\textsuperscript{49} It is only later that it appeared evident MVO could persist in the late gadolinium enhancement (LGE) images, suggesting the hypothesis of a more severe damage.\textsuperscript{50,51}

Currently, there is no consensus on the best technique to use and a number of clinical studies have used irrespectively one or the other\textsuperscript{52,53,54,55,56,57,58} or, in few cases, both techniques\textsuperscript{59,60,61,62,63} yielding conflicting results on the significance and extent of microvascular obstruction by CMR.

2.3 MYOCARDIAL INFARCTION

2.3.1 Other imaging modalities

Assessment of myocardial ischaemia and viability by SPECT offers invaluable diagnostic and prognostic information in patients with coronary artery disease.

Details on the technique are provided in Chapter 4, paragraph 4.3.2 “Single Photon Emission Tomography”.

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2.3.2 CMR Technique and Tissue Validation

After the contrast injection and the perfusion phase, the distribution of gadolinium in the heart is determined by the kinetics of access to different tissue types. Gd is an extracellular contrast agent that cannot penetrate in intact cell membrane; however, in the setting of acute infarction, the membrane ruptures allowing the penetration of contrast and its increased volumes of distribution; similar mechanisms are present in chronic scar, where damaged myocytes are replaced by collagen fibres (Figure 2.9).

![Figure 2.9. Mechanism of Gd distribution in normal and damaged myocardium. Adapted from Kim⁶⁴.](image)

Gd enhancement in infarction was initially noted in limited animal studies⁶⁵⁶⁶ and subsequently in small human studies.⁶⁷ Different curves of contrast wash-in and wash-out in normal and infarcted myocardium were identified, and the technique validated histologically with triphenyltetrazolium chloride (TTC) staining in dog model of myocardial infarction.⁶⁸ LGE correlated closely with the absence of TTC staining and electron microscopy changes indicating irreversible cell damage (Figure 2.10).
LGE occurs in both acute and chronic infarction, and correlates with fixed thallium defects. The absence of LGE correlates with viability as assessed by radionuclide and stress echocardiography.69

The presence/absence of LGE in dysfunctional segments predicts reversible myocardial dysfunction and recovery after revascularisation and thus viability with a good degree of confidence (sensitivity 98%, specificity 76%).70 In patients with left ventricular dysfunction, functional improvement after revascularisation is predicted by the transmural degree of LGE with a good of accuracy.71 In contrast with nuclear imaging, the detection of hibernation by CMR does not rely on the presence of myocardial ischaemia but on the mismatch between myocardial viability and contractile function.

CMR and has been also validated against SPECT for the detection of myocardial infarction and found to have an increased sensitivity in detecting subendocardial infarction, given the increased spatial resolution of the technique, whereas transmural myocardial infarction were detected at similar rate.72
References

1 Polimeni PI, Al-Sadir J. Expansion of the extracellular space in non-ischemic zone of the infarcted heart and concomitant changes in tissue electrolytes content in the rat. Circ Res 1975;37:735-752.


35 Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979;40:633-44.


Chapter 2

CMR in Acute Ischaemia


Kim RJ. Cardiovascular MRI and MRA. In Higgins and de Roos Ed. LWW 2003.


CHAPTER 3

CMR IN CHRONIC ISCHAEMIA: STRESS PERFUSION

3.1 INTRODUCTION

Cardiovascular disease is the main cause of death in most European countries, with a range of mortality rates between different countries (<3 per 1,000 inhabitants in the South-Western and Northern Europe and 9 per 1,000 inhabitants in Eastern Europe).\(^1\)

The cascade of events causing myocardial ischaemia and myocardial infarction is a complex temporal sequence of hemodynamic, electrocardiographic abnormalities and symptoms\(^2\), and subendocardial and transmural perfusion defects are the first expressions of the imbalance between myocardial oxygen supply and demand. Perfusion imaging therefore has a central role in investigation and management of patients with possible or actual coronary artery disease. In patients with stable angina or suspected coronary artery disease (CAD) exercise or pharmacological stress test are indicated for diagnostic work-up, as recommended by the recent European\(^3\) and American Guidelines\(^4\).

Exercise electrocardiography (ECG) is the test of choice to identify inducible myocardial ischaemia in the majority of patients with suspected stable angina for reasons of availability and costs. However, stress imaging techniques (with physical or pharmacological stress) have several advantages over the conventional exercise ECG\(^3\):

1. superior diagnostic performance for detection of obstructive CAD (Table 3.1);
2. ability to localize and quantify areas of ischaemia;
3. ability to provide information in the presence of resting ECG abnormalities (including left bundle branch block);
4. alternative test in patients unable to exercise;
5. alternative test when exercise testing is inconclusive;
6. preferred modality in patient with previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) (assess ischaemia after revascularisation);
7. preferred modality in women (in whom exercise ECG testing has a higher false-positive rate in women than in men).

As per the ESC guidelines, the use of exercise imaging is preferable where possible, as it allows for more physiological reproduction of ischaemia and assessment of symptoms.
However, pharmacological stress testing with either perfusion scintigraphy or echocardiography might also be used, and it is especially indicated in patients unable to exercise adequately.

### Table 3.1 Diagnostic performance of non invasive imaging testing.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ECG</td>
<td>68</td>
<td>77</td>
</tr>
<tr>
<td>Exercise echocardiography</td>
<td>80-85</td>
<td>84-86</td>
</tr>
<tr>
<td>Exercise myocardial perfusion</td>
<td>85-90</td>
<td>70-75</td>
</tr>
<tr>
<td>Dobutamine stress echocardiography</td>
<td>40-100</td>
<td>62-100</td>
</tr>
<tr>
<td>Vasodilator stress echocardiography</td>
<td>56-62</td>
<td>87-100</td>
</tr>
<tr>
<td>Vasodilators stress myocardial perfusion</td>
<td>83-94</td>
<td>64-90</td>
</tr>
</tbody>
</table>

Table modified from Fox et al, ESC Guidelines for Stable Angina.3
Different pre-test likelihoods and post-test referral bias might explain the wide range of results.

Although there is evidence to support superiority of stress imaging techniques over exercise ECG in terms of diagnostic performance, the cost of using a stress imaging test as a first line investigation in all comers should be considered.

The recently (March 2010) published guidelines on chest pain of recent onset jointly developed by National Institute for Health and Clinical Excellence (NICE) and the National Clinical Guidelines Centre for Acute and Chronic Condition in Great Britain represent a significant change in practise in some key areas of diagnosing acute coronary syndrome and angina.5 In particular, exercise ECG is no longer recommended for diagnosing chest pain, and it is replaced by imaging testing strategies with better diagnostic accuracy. The NICE guidelines on stable angina are illustrated in Figure 3.1. In patients with a low pre-test likelihood of CAD, calcium scoring is the recommended first line approach, followed by either 64-slice CT angiography or functional imaging test to assess inducible myocardial ischaemia (the latter as per the intermediate pre-test likelihood of CAD pathway), depending
on the calcium score result. The reason why calcium score is initially preferred to 64-slice CT angiography is because of the reduced radiation exposure of the former technique (~1mSv). Patients with high pre-test likelihood of CAD should undergo invasive coronary angiography, eventually followed by functional imaging testing in case of uncertain significance of coronary plaques.

However, the evidence from the NICE guidelines is not (yet) implemented in the ESC Guidelines (last and current edition was in 2006), and it is believed that until then in many European countries exercise ECG remains the first line modality to investigate patients with chest pain.
Figure 3.1. New (March 2010) NICE guidelines in stable chest pain.

Stable chest pain pathway

2. Diagnostic testing for people in whom stable angina cannot be diagnosed or excluded by clinical assessment alone

- **Estimated likelihood of CAD 10 to 28%**
  - Follow pathway for 10-28% CAD
  - **Estimated likelihood of CAD 30-60%**
    - Appropriate functional imaging test (see box 5 overleaf)
    - If reversible myocardial ischaemia found, treat as stable angina
    - If not, investigate other causes of chest pain**
  - Treat as stable angina

- **Estimated likelihood of CAD 61-100%**
  - Invasive coronary angiography if appropriate
  - Significant CAD: See box 4
  - Treat as stable angina

- Investigate other causes of chest pain**

*If coronary revascularisation is not being considered or invasive coronary angiography is not appropriate or acceptable to the person, offer non-invasive functional imaging*

**Consider investigating other causes of angina, such as hypertrophic cardiomyopathy or syndrome X in people with typical angina-like chest pain if investigation excludes flow-limiting disease in the epicardial coronary arteries.

Box 4 Definition of significant coronary artery disease

- Significant coronary artery disease (CAD) found during invasive coronary angiography is a 70% diameter stenosis of at least one major epicardial artery segment or ≥50% diameter stenosis in the left main coronary artery.

- Factors intensifying ischaemia. Such factors allow less severe lesions (for example ≥50%) to produce angina:
  - Reduced oxygen delivery: anaemia, coronary spasm
  - Increased oxygen demand: thyrotoxicosis, left ventricular hypertrophy
  - Large mass of ischaemic myocardium: proximally located lesions
  - Longer lesion length

- Factors reducing ischaemia. Such factors may render severe lesions (≥70%) asymptomatic:
  - Well developed collateral supply
  - Smallness of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply.

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3.2 PATHOPHYSIOLOGY

Myocardial ischaemia is created by the imbalance between oxygen supply and oxygen demand (Figure 3.2), where \( \text{MVO}_2 \) represents the metabolic needs and coronary blood flow (CBF) is determined by the driving pressure across the coronary vascular bed \( (\Delta P)/R \) (total coronary resistances). Changes in this pressure (within certain limits) are compensated by changes in coronary resistances, a mechanism known as coronary autoregulation.

![Figure 3.2 Balance between oxygen supply and demand. Modified from Klocke](image)

Coronary resistances are described in Figure 3.3 and include the basal viscous resistance \( (R_1, \text{impedence to flow offered during diastole when vascular bed is fully dilated}) \), autoregulatory resistance \( (R_2, \text{resulting from tonic contraction of vascular smooth muscle at the arteriolar level}) \), and compressive resistance \( (R_3, \text{compression of vascular structures by intramyocardial pressure}) \).

![Figure 3.3 Coronary resistances. Modified from Klocke](image)
In the normal artery, epicardial and microvascular dilatation occur during exercise. In the atherosclerotic artery, partial microvascular dilatation is present at rest to compensate the drop in pressure across the stenosed epicardial artery (Figure 3.4). During exercise, there is additional epicardial artery constriction that results in an increased pressure drop across the stenosis with limited additional microvascular vasodilatory capacity. As a result, myocardial blood flow is reduced and unable to meet the increased metabolic demands of exercise, activating the ischaemic cascade.

The reason why the subendocardium is more vulnerable to ischaemia than the epicardium is illustrated in Figure 3.3. In the presence of a coronary artery stenosis (which create a resistance, RS in Figure 3.3), the coronary autoregulatory system responds by reducing R2 to facilitate blood flow. R3 however remain the same, and it is greater in the subendocardium than in the epicardium. That explains the subendocardial vulnerability to ischaemia, and the progression of the ischaemic-necrotic wave front phenomenon from the subendocardium to the epicardium.

### 3.3 OTHER NON INVASIVE IMAGING MODALITIES

Different non-invasive imaging modalities can evaluate myocardial perfusion and assess the functional significance of epicardial coronary stenoses by demonstrating stress-induced ischaemia (perfusion abnormalities) in CAD. When luminal obstruction is <50%, maximal flow during exercise can be maintained. Coronary stenosis of >50% may be associated with ischaemia as coronary blood flow becomes inadequate to meet cardiac metabolic demand during stress.
There are two approaches for pharmacological testing: (i) infusion of dobutamine, a short-acting sympathomimetic drug which at incremental dose protocol increases myocardial oxygen consumption and mimics the effect of physical exercise; (ii) infusion of coronary vasodilators which cause maximal coronary hyperemia in normal coronary arteries and a reduction in flow in myocardial territories supplied by a stenosed coronary artery (steal phenomenon).

Adenosine is usually used as hyperaemic stimulus due to its potent vasodilator properties. An intravenous dose of 140 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$ causes maximal or near maximal hyperaemia in 92% of patients, with mean coronary flow increasing by 4.4 times the resting value.\textsuperscript{10} In humans, peak coronary flow occurs approximately after 4 minutes of infusion.\textsuperscript{11} The safety profile of adenosine is guaranteed by its short half life of adenosine (<10 seconds) and limited duration of side effects.

Dipyridamole causes coronary vasodilatation by increasing interstitial adenosine concentration, but its duration of action is quite long (>30 minutes) and consequent longer side effects.

Vasodilators can cause ischaemia through the following mechanisms:

1. increase flow across a stenosis leads to a fall in distal perfusion pressure with preferential shunting to the subepicardium, which is sufficient to cause subendocardial ischaemia\textsuperscript{12};
2. reduced flow in high-resistance collateral vessels serving an area of diseased artery by the generalised vasodilatation and fall in perfusion pressure (exacerbated by the small reduction in diastolic blood pressure);
3. reflex tachycardia from vasodilation raises myocardial oxygen demand.

Current clinically available techniques to evaluate myocardial perfusion are single photon emission computed tomography (SPECT), positron emission tomography (PET), echocardiography, and more recently cardiovascular magnetic resonance (CMR).

All these imaging modalities present some advantages and limitations. The most validated and established stress imaging techniques are echocardiography and perfusion scintigraphy (both may be used in combination with either exercise test or pharmacological stress). Indeed, a normal stress myocardial perfusion test is highly predictive of a benign prognosis since it is associated with a rate of cardiac death and myocardial infarction of <1% per year, which is nearly as low as that of the general population. Novel stress imaging techniques also include stress cardiac magnetic resonance (CMR). Among the most important limitations of SPECT and PET include radiation exposure (SPECT and PET), high cost and limited availability (PET) and vulnerability to soft tissue attenuation artefacts (SPECT), and lower spatial resolution (SPECT is ~10mm, which is inferior to PET (~4mm) and CMR (~2mm).

Overall, the potential advantages of CMR over the other imaging modalities are the increased spatial resolution with the ability to detect subendocardial ischaemia, and absent radiation exposure.

3.3.1 Echocardiography

In contrast to myocardial perfusion imaging using radiotracers, most of the echocardiographic methods of detection of myocardial ischaemia are based on identifying transient regional left ventricular dysfunction. Pharmacological echocardiographic stress testing has a diagnostic accuracy similar to SPECT with either coronary vasodilators or dobutamine. Dobutamine is a short-acting sympatho-mimetic drug that infused following an incremental dose protocol (from 5 to 40µg/kg/min) increases myocardial oxygen consumption mimicking the effect of physical exercise. Being a positive inotropic and chronotropic agent, dobutamine detects myocardial ischaemia (at high doses) as new regional wall motion abnormalities, as opposed to inducible perfusion defects with vasodilators stress.
The accuracy of dobutamine echocardiography is limited in patients with pre-excited wall motion abnormalities that make it difficult to detect new regional wall motion abnormalities, as in acute myocardial infarction and patients with left bundle branch block.\textsuperscript{14,15} 

Adenosine and dipyridamole are coronary vasodilators which create different in regional blood flow in regions supplied by haemodynamically significant stenotic coronary arteries (perfusion defect) versus regions supplied by non diseased coronary arteries (increase perfusion). This is the principle of steal phenomenon. Additional details on coronary vasodilators are discussed in paragraph 3.4.6.

Myocardial contrast echocardiography (MCE) can assess myocardial perfusion during maximal hyperemia, has the advantages of easier access and affordability but is significantly operator dependent, requires good echocardiographic windows and has a low spatial resolution.\textsuperscript{16} The combination of echocardiographic myocardial perfusion and wall motion abnormalities correlated well with SPECT.\textsuperscript{17}

Myocardial perfusion with three-dimensional echocardiography represents a promising new development in ultrasound imaging with the potential to overcome many of the limitations of 2D imaging.\textsuperscript{18}

### 3.3.2 Single Photon Emission Tomography

SPECT is a well validated and robust technique for myocardial viability and ischaemia with over 7 million scans per year performed in the US.

SPECT perfusion scintigraphy is performed to produce images of regional tracer uptake that reflects regional blood flow. With this technique, myocardial hypoperfusion is characterised by reduced tracer uptake during stress in comparison with uptake at rest.

The regional distribution of coronary myocardial perfusion can be visualised with radiopharmaceuticals (thallium-201 or technetium-99m) that accumulate proportional to regional myocardial blood flow.

Thallium-201 (\textsuperscript{201}Tl) is a potassium analogue and its uptake into cardiac and skeletal cells is both passive and active though an energy-dependent process involving the sodium-potassium ATPase enzyme system and intact cell membrane integrity. This compound became available in 1974 and has since been used successfully for 25 years.

However, some of the limitations of \textsuperscript{201}Tl perfusion imaging are:

1. Relative high radiation exposure to the patient due to its long half-life in the body (the dose of 80MBq delivers an effective dose of 14mSv)\textsuperscript{19};
2. Low injected dose (to limit radiation exposure) results in low count density of the myocardial images;
3. The low energy emission at 80KeV leads to low resolution images with significant attenuation by soft tissues.

New technetium-99m (\(^{99m}\)Tc)-labelled compounds with better imaging characteristics and novel biological properties do not suffer the first and the third of these problems and this has encouraged the introduction of such tracers for visualization of myocardial perfusion since the early 1990s. These compounds concentrate mainly in the cytosol (tetrofosmin) or the mitochondria (MIBI) of normally perfused and viable myocardium. Presently, \(^{99m}\)Tc-sestamibi and \(^{99m}\)Tc-tetrofosfim are widely used in identifying myocardial ischaemia with good agreement\(^ {20}\), although \(^{99m}\)Tc-sestamibi may have a better ability than \(^{99m}\)Tc-tetrofosfim to detect mild-to-moderate ischaemic defects.\(^ {21}\) In fact, tetrofosmin has a lower first-pass extraction fraction compared to sestamibi and therefore during vasodilator stress it is more difficult to detect reversibility of defect in the distribution of mild-to-moderate stenoses.

The advantages of \(^{99m}\)Tc-labelled compounds over thallium are:
1. lower radiation burden to the patient (8mSv for tetrofosmin, and 10mSv for MIBI);
2. higher energy photon produced (140 keV) that leads to higher resolution images;
3. higher energy tracers are less affected by attenuation.

AHA/ACC /ASNC guidelines for the use of cardiac nuclide imaging report an overall 87-89% sensitivity and 73-75% specificity for the detection of \(\geq 50\%\) CAD with exercise and vasodilator stress perfusion SPECT.\(^ {22}\) The ranges of sensitivities and specificities associated with various protocols and agents used in SPECT are summarised in Table 3.2.

### 3.3.3 Positron Emission Tomography

PET is emerging as a clinically valuable technique due to its unique ability to image and quantify metabolic processes, receptor occupancy, and blood flow.\(^ {18}\)F-FDG, a marker of glucose utilization, is the most commonly used metabolic radiotracer.

Viability assessment with FDG is based on the principle that viable myocardium is metabolically active and that ischaemic myocardium may in fact have enhanced glucose uptake. The most commonly used positron-emitting perfusion tracers include rubidium-82 (\(^{82}\)Rb), \(^{13}\)N-ammonia and \(^{15}\)O-water and they may be used to assess absolute blood flow, flow
reserve, or cell membrane integrity. \(^{15}\)O-water is freely diffusible and its extraction is dependent of the metabolic state, whereas uptake and retention of the other tracers are dependent on both perfusion and cell membrane integrity. \(^{82}\)Rb is a potassium analogue that, like thallium, requires the sodium-potassium pump for uptake.

**Table 3.2. Diagnostic performance of different SPECT protocols.**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise treadmill test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium-201</td>
<td>60-82</td>
<td>65-82</td>
</tr>
<tr>
<td>Tc-99m sestamibi</td>
<td>82-97</td>
<td>36-90</td>
</tr>
<tr>
<td>Tc-99m tetrofosmin</td>
<td>60-95</td>
<td>77-89</td>
</tr>
<tr>
<td><strong>Adenosine or dipyridamole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium-201</td>
<td>77-92</td>
<td>75-100</td>
</tr>
<tr>
<td>Tc-99m sestamibi</td>
<td>81-90</td>
<td>67-72</td>
</tr>
<tr>
<td>Tc-99m tetrofosmin</td>
<td>83-89</td>
<td>55-94</td>
</tr>
<tr>
<td><strong>Dobutamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium-201</td>
<td>86-100</td>
<td>36-100</td>
</tr>
<tr>
<td>Tc-99m sestamibi</td>
<td>76-100</td>
<td>64-100</td>
</tr>
<tr>
<td>Tc-99m tetrofosmin</td>
<td>80-95</td>
<td>72-80</td>
</tr>
</tbody>
</table>

Modified from Russell RR et al.\(^23\)

These published figures on sensitivity and specificity do not reflect how an expert centre might operate the various tests in a clinical setting. Also, different pre-test likelihood, post-test referral bias and retrospective analysis might explain the wide range of results.

PET perfusion imaging with \(^{82}\)Rubidium coupled with CT affords high sensitivity and overall accuracy for detecting CAD, including in patients with single-vessel disease, women, obese patients and patients with three-vessel CAD.\(^{24,25}\)

\(^{13}\)N-ammonia yields excellent image quality for visual and quantitative analysis of absolute myocardial blood flow and flow reserve, even at a subendocardial level.\(^26\)

Its sensitivity and specificity for the detection of CAD is 79% and 85%, respectively.\(^27\)

Clinical investigations have consistently demonstrated that preserved viability with PET is associated with improvement in regional wall motion after revascularisation, particularly in
regions demonstrating flow-metabolism mismatch (diminished flow, increased glucose uptake).\textsuperscript{28,29} This has been recently confirmed in a randomised controlled trail.\textsuperscript{30}

In contrast to SPECT, PET imaging has the ability to quantify flow in ml/min/g, which is particularly useful in identifying “balanced ischaemia” in patients with three-vessel disease by showing a failure of flow reserve in all three coronary territories.

Some limitations of this test include the fact that is not widely available, expensive, uses ionising-radiation exposure, and requires time consuming data analysis. Also, compared with CMR, PET lacks spatial resolution which is important for early detection of disease.

### 3.4 CMR PERfusion

After induction of vasodilator stress by adenosine (or dipyridamole), dynamic first-pass perfusion imaging is performed during intravenous injection of a gadolinium-based contrast agent, aiming to identify areas of inducible perfusion abnormalities (i.e. ischaemic). Following intravenous injection, the contrast will first appear in the right ventricular cavity, followed by the left ventricular cavity and finally leading to myocardial enhancement, where the contrast agent diffuses rapidly from the intravascular to the extravascular compartment.

This explains why perfusion defects persist very briefly after bolus injection, before disappearing due to redistribution in the extravascular space. The pharmacokinetics of gadolinium in the blood pool, normal and infarcted myocardium is described in Figure 3.5.

The corresponding increased image intensity is the result of the shortening of myocardial T1 relaxation time caused by the contrast agent, and the magnitude of the signal enhancement depends on the amount of contrast agent present.

Whilst Figure 3.5 shows curves of perfusion defect caused by microvascular obstruction and myocardial infarction, it does not contemplate a curve indicating inducible perfusion defects (as those seen during adenosine/dipyridamole infusion).
3.4.1 Contrast Agents
Gadolinium-based agents are the only clinically approved molecules for MRI imaging. Gadolinium is a metal belonging to the lanthanide group of the periodic chart. Due to its extreme toxicity, gadolinium is always chelated for in-vivo applications and it is one of the most effective paramagnetic agents, enabling to accentuate the difference in tissue relaxation characteristics. There are only a few licensed contrast agents for use in humans, and these are classified according to their molarity, osmolarity and viscosity (Table 3.3)\textsuperscript{32}.

![Figure 3.5 Kinetics and compartments of Gd-chelate contrast agent, from Pennell\textsuperscript{31}.](image)

### Table 3.3 Commonly administered contrast agents for CMR imaging.

<table>
<thead>
<tr>
<th>chemical name</th>
<th>generic name</th>
<th>brand name</th>
<th>company</th>
<th>classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Gd(DTPA)(H₂O)]⁻²</td>
<td>gadopentetate dimeglumine</td>
<td>Magnevist\textsuperscript{a}</td>
<td>Schering (Germany)</td>
<td>extracellular</td>
</tr>
<tr>
<td>[Gd(DOTA)(H₂O)]⁻²</td>
<td>gadoterate meglumine</td>
<td>Dotarem\textsuperscript{b}</td>
<td>Guerbet (France)</td>
<td>extracellular</td>
</tr>
<tr>
<td>[Gd(DTPA-BMA)(H₂O)]⁻²</td>
<td>gadodiamide</td>
<td>Omniscan\textsuperscript{c}</td>
<td>Nycomed-Amersham (U.K.)</td>
<td>extracellular</td>
</tr>
<tr>
<td>[Gd(HP-DTPA)(H₂O)]⁻²</td>
<td>gadotericol</td>
<td>ProHance\textsuperscript{d}</td>
<td>Bracco (Italy)</td>
<td>extracellular</td>
</tr>
<tr>
<td>[Gd(DOTA-butil)(H₂O)]⁻²</td>
<td>gadobutrol</td>
<td>Gadovist\textsuperscript{e}</td>
<td>Schering (Germany)</td>
<td>extracellular</td>
</tr>
<tr>
<td>[Gd(DTPA-EMI)(H₂O)]⁻²</td>
<td>gadoversetamide</td>
<td>OptiMARK\textsuperscript{f}</td>
<td>Mallinkrodt (U.S.)</td>
<td>extracellular</td>
</tr>
<tr>
<td>[Gd(BOPTA)(H₂O)]⁻²</td>
<td>gadobenate dimeglumine</td>
<td>MultiHance\textsuperscript{g}</td>
<td>Bracco (Italy)</td>
<td>hepatobiliary/ extracellular</td>
</tr>
<tr>
<td>[Gd(EOB-DTPA)(H₂O)]⁻²</td>
<td>gadoxetic acid disodium</td>
<td>Eovist\textsuperscript{h}</td>
<td>Schering (Germany)</td>
<td>hepatobiliary</td>
</tr>
<tr>
<td>MS-325</td>
<td>gadopentetamine trisodium</td>
<td>AngloMARK\textsuperscript{i}</td>
<td>EP IX/Mallinckrodt (U.S.)</td>
<td>blood pool</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Approved. \textsuperscript{b} In clinical trials.

Table reproduced from Caravan et al.\textsuperscript{32}
3.4.2 Contrast Dose

The optimal dose of contrast agent for perfusion CMR has not been determined, but a number of studies have helped identify the correct range which is considered to be between 0.05-0.1 mmol/Kg.

The best dose of gadodiamide for visual assessment of stress-induced regional perfusion abnormalities was found to be 0.1 mmol/kg bodyweight (as opposed to 0.05 and 0.15 mmol/kg bodyweight) using a GRE-EPI (Gradient Echo-Echo Planar Imaging) sequence. Superior image quality was found with an SSFP (Steady State Free Precession) sequence with both dosage regimes of 0.05 mmol/kg and 0.025 mmol/kg bodyweight for Gd-BOPTA, in comparison with T1-GRE or GRE-EPI sequences.

In a multicentre dose-ranging study it was established that the minimally efficacious dose of Gd-DTPA for detecting obstructive coronary artery disease was 0.05 mmol/kg (mean sensitivity 93±0%, mean specificity 75±7% and mean accuracy 85±3%) when compared to dose of 0.10 and 0.15 mmol/kg. In particular, higher doses yielded greater myocardial enhancement but did not result in higher diagnostic accuracy. This is most likely due to the fact that higher contrast doses are more likely to cause susceptibility artefacts that could be misinterpreted as genuine perfusion defects. The same images were assessed using upslope analysis and a higher sensitivity and specificity was found at 0.1 mmol/kg than at 0.05 mmol/Kg (but again, lower specificity at 0.15 mmol/kg).

3.4.3 Contrast Injection Rate

Another important parameter in perfusion imaging is the injection rate of the contrast agent bolus. This has not been standardized yet and it varies between centres from 3 ml/s to 7 ml/sec. In healthy myocardial segments, the myocardial enhancement (upslope) is mainly determined by the LV upslope and it is largely independent from the injection rate of the contrast agent bolus, as long as the injection speed is not below 3 ml/s. There are no publications of the effect of injection rate on perfusion defect visibility. Different opinions exist on this topic, but the fundamental tracer-kinetics behind the delayed perfusion of diseased segments implies that an abrupt increase of contrast agent concentration is desirable, even if this results in fewer MR images during the first-pass. If this aim is accepted, which is not always the case because of the reduced number of images, a fast injection rate is believed to assist. For example Elkington et al. demonstrated significantly increased peak Gd concentration in the ascending aorta with increased injection rate from 3 to 5 ml/s, with non-significant further increase at 7 ml/s injection rate (at rest). The peak myocardial enhancement, however, is dose dependent,
but the brief period of image contrast between regions of slower perfusion and normal myocardium contains unproven dependence on injection rate.

### 3.4.4 Pulse Sequences

Despite many comparison studies\(^{38,39,40,41,42,43}\), the perfusion protocol (pulse sequence, contrast agent dose and injection parameters) giving highest diagnostic confidence is not yet standardised.\(^{44,45}\) Most centres rely on T1-weighted sequences to create images that enhance with the passage of Gd contrast agents. The main sequences available are: 1) Fast Single Shot Gradient Echo (FLASH), 2) Echo-Planar or Hybrid Echo-Planar (EPI) and 3) Steady-State Free Precession (SSFP). The ideal sequence for perfusion imaging should be very rapid, be able to “freeze” cardiac motion, have a high SNR, high spatiotemporal resolution and should be robust to artefacts. The current available pulse sequences are briefly described as follows.

**FLASH** is the simplest method of rapid perfusion imaging, the most established and robust sequence. It collects one line of raw data per radiofrequency excitation, therefore being relatively slow and inefficient. However, it is considered a robust sequence because after each data readout the residual signal is discarded and gets a new signal for the next line. This sequence has an intrinsic poor SNR due to the low flip angle. The pulse diagram of a gradient echo sequence is illustrated in *Figure 3.6*.

**Hybrid EPI** requires faster gradients and collects multiple lines of raw data after each radiofrequency pulse, and is effectively an accelerated variant of the FLASH technique. Compared to FLASH, EPI is a faster sequence, therefore less prone to cardiac motion artefacts. However, this sequence is prone to off-resonance artefacts.
These can be reduced by running EPI faster, but at the cost of lower SNR, or reducing ETL but becomes slower and therefore losing its advantage compared to FLASH and becoming more prone to cardiac motion artefacts. The pulse diagram of a gradient echo sequence with EPI readout is illustrated in Figure 3.7.
SSFP is a promising sequence, but experience is limited.\textsuperscript{38,40,42} It has a higher SNR due to its higher flip angle. It is considered an efficient sequence because it re-uses residual magnetisation. Compared to EPI, SSFP has superior SNR and CNR but given the longer imaging time (125ms) is more prone to motion artefacts. Dark ring artefacts had been noted as more prominent with SSFP (visual analysis).\textsuperscript{46} The pulse diagram of an SSFP sequence is illustrated in \textit{Figure 3.8}.

\textbf{Figure 3.8.} Pulse diagram of a steady state free precession sequence (modified from Gebker\textsuperscript{44}).

Comparing the 3 sequences, hybrid EPI has the shortest time per image (~75ms, compared to ~180ms for FLASH and ~200ms for SSFP), pivotal for minimizing cardiac motion artefacts. However, in the fastest version with minimal off-resonance errors, EPI has lower SNR than the other two sequences.

Increase in cardiac heart rate that often occurs during hyperemic stress may limit the acquisition window, resulting in incomplete myocardial coverage. Parallel acquisition methods such as sensitivity encoding (SENSE)\textsuperscript{47} and k-t SENSE\textsuperscript{48} are used to shorten data acquisition time, with improved image quality, diagnostic accuracy and improved quantitative perfusion assessment.\textsuperscript{49,50,43}
In our centre and other laboratories hybrid-EPI is the preferred sequence for perfusion CMR\textsuperscript{51,52}. However, the other sequences are widely used in other institutions.

### 3.4.5 Arterial Input Function

Accurate assessment of arterial input function (AIF) is pivotal for quantifying myocardial perfusion because it serves as a reference for the analysis. In general, lower doses cause lower signal-to-noise (SNR) in the myocardium, whereas higher doses determine a non linear signal intensity in the left ventricular cavity (after contrast administration) resulting in an inaccurate input function, that influences the quantification of myocardial perfusion. In particular, the non linearity (contrast- enhancement saturation) of the contrast enhancement in the blood pool increases with the increase of contrast concentration. Eventually, the signal intensity would even start to decrease above a certain contrast level, due to T2* effects\textsuperscript{53}. In order to accurately measure the arterial input of contrast, signal saturation effects need to be avoided or corrected.

Dual contrast sequences or dual contrast bolus protocol are among the methods proposed to improve the assessment of the arterial input function. The latter involves giving a low dose of contrast bolus to characterize the arterial input function, followed by a second higher bolus to image the contrast enhancement in the myocardium.\textsuperscript{54} The dual contrast sequence allows during each cardiac cycle the acquisition of a low resolution short axis image with a short saturation recovery (10 ms for low T1 weighting) immediately after the R wave in order to measure the signal in the LV blood pool, which is then followed by higher resolution multiple short axis slices with long saturation-recovery time (in the range of 90-110 ms depending on the phase encoding field of view).\textsuperscript{55} This simple high-dose single bolus method has been validated against the dual bolus technique with no significant differences in the calculation of MPRs.

In our centre we have adopted the dual sequence approach. However, a conflicting report showed that dual-bolus perfusion imaging made no significant difference to global perfusion quantification with small improvements in segmental perfusion analysis results.\textsuperscript{56} The relevance of dual-bolus or dual-sequence methods depends on the contrast-agent dose and any other factors (such as injection rate, choice of saturation-recovery delay, etc) that impact upon the linearity of signal response to contrast-agent concentration. If lower doses are used, for example 0.04mmol/kg\textsuperscript{71} with a short saturation-recovery delay (e.g. 50ms), the dual-bolus or dual-sequence methods are probably unnecessary, although myocardial SNR is now reduced.
3.4.6 Adenosine

Normal resting flow in the coronary arteries is approximately 1 ml/min/g of myocardium. Coronary hyperemia caused by adenosine determines an increase in perfusion in normal coronary arteries reaching 3-4 ml/min/g, whereas in myocardial territories supplied by stenotic vessels perfusion is restricted to resting values of 1 ml/min/g (the vessel is already maximally dilated at rest to overcome the limited blood flow caused by the stenosis). Adenosine is infused at the rate of 140 μg Kg$^{-1}$ min$^{-1}$ using a syringe pump. CMR first-pass perfusion acquisition starts 3-4 minutes after the beginning of adenosine infusion. The safety profile of adenosine in the context of stress perfusion imaging was assessed in 9,256 consecutive patients undergoing radionuclide imaging. Adenosine infusion is safe, and its vasodilator and negative dromotropic effects are generally well tolerated. Serious side effects are relatively rare, and they rapidly reverse with termination of the infusion, due to adenosine’s ultrashort half-life (<10 seconds).

Dipyridamole is an alternative drug, which increases adenosine through indirect mechanisms. It is actively metabolized in the liver and, therefore, its vasodilator capacity is variably dependent on individual metabolism rate. Compared to adenosine, dipyridamole has a longer half-life (30 minutes), and prolonged side effects. Typically, the infusion dose is 0.56 mg/Kg for 4 minutes and the images acquisition starts after 6 minutes. Although the cost of dipyridamole is inferior to adenosine, adenosine has been shown to lower costs both for patients’ monitoring and adverse events management.

Both adenosine and dipyridamole are contraindicated in case of severe conduction abnormalities, chronic obstructive pulmonary disease (COPD) and asthma.

3.4.7 Imaging Protocol

Typically, 3 short-axis slices (basal, mid-cavity and apical) are acquired both during stress and at rest, in order to provide complete myocardial segmental coverage, according to the recommended 17-segment myocardial model for tomographic cardiac imaging model. And although there is variability in the coronary blood supply to myocardial segments, the 17 myocardial segments are assigned to one of the three major coronary arteries (Figure 3.9).

The 3 short axis images are acquired throughout the cardiac cycle and triggered to the R wave on the ECG tracing; approximately 40-60 images for each slice location. Breathing should be suspended for at least the early part of the image acquisition (during the first pass) to
minimize breathing motion artefacts and facilitate diagnostic interpretation. The short-axis planes can evaluate only 16 myocardial segments, failing to assess the ventricular apex. A combined long- and short-axis imaging protocol has been proposed; however, the long-axis views were not able to depict inducible perfusion defects in the apex, despite apical ischemia being demonstrated with recent SPECT in the same patients.\textsuperscript{61}

\begin{center}
\textbf{Figure 3.9.} Representative three LV short axis slices, myocardial segmentation and corresponding coronary artery supply. Modified from Cerqueria\textsuperscript{60}
\end{center}

The number of short-axis slices is strictly limited by the patient’s heart rate, i.e. in principle bradycardia could allow the acquisition of additional slices. Elkington and et. investigated the role of adding a long-axis view, but this did not increased the diagnostic accuracy of the test.\textsuperscript{37} The technique could potentially benefit from a 3D coverage. This is however not currently available clinically but indeed under investigation.

Fifty cardiac cycles are acquired to allow the complete track of the dynamic process of contrast bolus from the moment of the peripheral injection to the diffusion in the myocardium of the left ventricle. Probably only 30 cardiac cycles are needed, but the exact arrival time of the bolus is unpredictable. Resting perfusion images are acquired 20 minutes after the stress perfusion images, a time window to allow partial contrast wash-out from the previous injection.
3.4.8 Qualitative Assessment of Myocardial Perfusion

Visual assessment is commonly used in routine clinical practise.

Perfusion defects appear as focal areas of reduced myocardial enhancement (hypointense, darker) compared to normal segments (Figure 3.10). The extent of the perfusion defect can be either subendocardial or transmural. In contrast with SPECT where the severity of ischemia is related to the depth of perfusion abnormality, in CMR defect transmurality is taken as a surrogate. Given the increased spatial resolution of CMR, interpretation of ischemia superimposed upon myocardial damage allows for the identification of peri-infarct perfusion defect, as already described by the nuclear techniques.

Qualitative analysis can be challenging in the presence of suboptimal images quality, breath-holding related artefacts, ECG mistriigering and dark rim artefacts.

The rest perfusion scan is particularly useful to interpret the presence of artefacts. In CMR, a genuine inducible perfusion defect is normally present in the stress but not in the rest images. The persistence of a hypointense region in the rest images is indicative of artefacts (provided these images are acquired 15-20 minutes after the stress acquisition). In helping to distinguish a genuine myocardial perfusion defect from artefact, Klem proposed a visual interpretation algorithm that combines the information from stress/rest perfusion with LGE.62 Also, the duration of the perfusion defect (number of frames), its reoccurrence during the contrast recirculation (second-pass) can help guiding image interpretation.

When qualitative perfusion CMR was compared against angiography, the sensitivity and specificity of visual assessment was 93% and 60%, respectively.63 Qualitative CMR reporting was possible in 98% of cases. As in other imaging techniques, the qualitative approach is observer-dependent and potentially less accurate than quantitative analysis.

Whilst higher dose of contrast agents improve normal myocardial SNR for visual assessment, lower doses (0.025-0.05mmol/Kg) are usually preferred to measure absolute or relative changes in myocardial blood flow and volume to avoid non-linear response to the contrast agent.64
Figure 3.10. Stress (A) and rest (B) first pass perfusion imaging. Inducible perfusion defect is demonstrated in basal and mid-cavity inferior wall.

3.4.9 Quantification of Myocardial Perfusion

The aim of quantitative analysis is to remove dependence on observer and on bolus dispersion.

Myocardial perfusion reserve (MPR) was proposed since the early 1970s as an index of functional severity of coronary stenosis and it is calculated as the ratio of hyperemic and baseline myocardial blood flow. In humans, PET is the only validated imaging method to measure quantitative myocardial blood flow and MPR. Cullen et al. demonstrated the feasibility of performing myocardial perfusion reserve index measurement by first-pass CMR in normal volunteers and patients with CAD compared to quantitative angiography and PET data. Similar reliable assessment of MPR index by CMR perfusion in a clinical context was reported by other groups.
Approximately 40% of the intravenously injected (extracellular) contrast agent diffuses from the blood into the interstitium during the first pass. Most methods of quantitative analysis are based on tracking a bolus and its transit through a region of interest (ROI). This procedure requires tracing endo- and epicardial contours, as well as placing a ROI in the LV cavity, and signal intensities will be then converted into contrast agent concentration in order to allow for input correction (Figure 3.11). For the analysis, the left ventricle is divided into regions of interest (ROI), according to the 17-segments model.60

Some preliminary steps need to be taken before performing the quantitative analysis: data should be corrected for respiratory motion and coil sensitivity. Then different models may be applied to calculated perfusion: fully quantitative or semi-quantitative analysis.71

![Figure 3.11. Tracing ROIs in the LV myocardium and in the LV blood pool.](image)

For the semi-quantitative analysis the upslope of the signal-intensity curve during contrast enhancement is the most widely used parameter, being also the most sensitive parameter to differences in myocardial blood flow (Figure 3.12).72 Additionally, it correlates closely with microspheres (in dogs)73,74 and PET measurements (in humans).75 An underestimation of coronary flow reserve by CMR perfusion measurements compared to PET was reported by Ibrahim et al. in patients with angiographically documented CAD.76 The upslope index
yielded a sensitivity, specificity and diagnostic accuracy of 69%, 89% and 79%, respectively, for the localization of coronary artery stenosis (>75%, MPR <1.2) and a sensitivity, specificity and diagnostic accuracy of 86%, 84% and 5%, respectively, for detection of reduced coronary flow reserve (PET<2.0, MPR<1.3).

The signal intensity (SI) curve is a combination of perfusion and diffusion, both of which are influenced by blood flow.\textsuperscript{77} The early phase of SI time curve is mainly influenced by perfusion and to a lesser extent by diffusion, and the latter parts are increasingly influenced by diffusion. Both the wash-in and wash-out are strongly influenced by the compactness of the contrast bolus, and for a reliable calculation it should be small and compact. Ischaemic myocardial segments show a slower passage of the contrast agent.\textsuperscript{78}

\textbf{Figure 3.12. Signal intensity curves in the myocardium and in the LV blood pool during first-pass perfusion. Reproduced from Jerosch-Herold.}\textsuperscript{71}

(lower peak myocardial signal intensity, slower rate of signal increase and longer time to peak perfusion), resulting in a stronger influence of diffusion and a less pronounced or even nonexistent down slope. A linear fit of the upslope of the signal intensity-time curve was proposed by Al-Saadi as a new and easy method for the determination of MPR\textsuperscript{79} and to minimize the influence of diffusion. This parameter was demonstrated to be highly reproducible, with good inter- and intra-observer variability.
When the upslope was initially proposed to assess myocardial perfusion, the authors normalized it by the up-slope of the LV signal intensity. These adjustments for difference in AIF between hemodynamic states was used to define a perfusion reserve index (stress value/rest value) with a similar approach used to calculate coronary flow reserve.

**Fully quantitative analysis** (quantitative myocardial blood flow, MBF) may be estimated using deconvolution (based on a mathematical model of contrast agent kinetics).

In order to quantify perfusion, it is necessary to achieve an accurate estimate of the AIF, as described in paragraph 4.3.5. In most work, the contrast agent kinetics are based on the Fick’s principle that the rate at which a substance accumulates in a tissue ROI is given by the difference of the concentration of the tracer flowing into and leaving the region. Essentially this corresponds to the principle of mass balance: tracer that has entered and not exited has remained in the region of interest. Additional complexity could be added if the vascular compartment were to be considered in its spatial extent (with concentration of the tracer higher at the arterial inlet than further downstream), rather than a lumped compartment that would instead only consider contrast concentration as a function of time. In principle, a spatially lumped model has a significant positive effect on the accuracy of MBF estimations; however such models are not widely used.

The term “model” is used as above for the different tissue compartments. However, and somewhat confusingly, it is also used for some approaches to the deconvolution. The approaches that can be used for quantifying MBF by deconvolution of the AIF from the myocardial signal can be divided into two categories: 1) model based and 2) model independent analysis. Category 1 tends to use a “Fermi function model” to constrain the shape of the deconvolution result, which is otherwise very noisy. Category 2 avoids any fixed shape model but instead applies a series of slowly-varying curves to constrain the deconvolution.

The work in this thesis is based on the Fermi function constrained deconvolution, reviewed very clearly by Lee and Johnson (ADD ref). The main limitations of this approach are: 1- the tracer bolus re-circulates and the Fermi model does not account for the second pass of contrast agent; 2-the Fermi function does not model the interstitial contrast agent as it leaks into the extravascular compartment.
Despite the limitations described above, this method has been validated against microspheres showing an improved response to higher myocardial blood flow compared to the semi-quantitative analysis.73

“Fully quantitative” analysis of myocardial perfusion reserve is based on the ratio of stress/rest MBFs with one important modification, that calibrations for surface-coil response etc may be assumed to cancel between stress and rest if the surface-coil did not move. With this assumption, myocardial perfusion reserve may be derived from uncalibrated “indices” of myocardial blood flow. This approach was used to derive the “myocardial perfusion reserve index” referred to in other chapters. However, the perfusion protocol used for this work was not suitable for calculation of absolute rest or stress MBF. Firstly, the myocardial signal would require corrections for surface-coil response, which would otherwise make the septum have apparently higher MBF than lateral myocardium. This correction cannot be done with simple image normalisation and requires separate “proton-density” weighted prescans.51 Secondly, this high-dose protocol would have some non-linear response to contrast-agent concentration in myocardium. The high-dose was required for visual analysis and the effect of non-linearity in myocardium was accepted as probably reasonably small (around 20% underestimate of stress MBF).80
References


31 Pennell DJ. Cardiovascular magnetic resonance and the role of adenosine pharmacologic stress. Am J Cardiol 2004;94:26D-31D


52 Kim D, Axel L. Multislice, dual-imaging sequence for increasing the dynamic range of the contrast-enhanced blood signal and CNR of myocardial enhancement at 3T. J Magn Reson Imaging 2006;23(1):81-86.


4.1 CARDIOVASCULAR MAGNETIC RESONANCE

4.1.1 Scanner
With the exception of the study presented in Chapter 7, the equipment used for this thesis was a 1.5 Tesla Avanto CMR scanner (Siemens Medical Solutions, Erlangen, Germany) with a cardiac dedicated 12-channel phase array receiver surface coil (6 anterior and 6 posterior coils elements). All studies were gated with a multichannel ECG (vector ECG) and acquired during breath-hold in end-expiration.

The sites of recruitment and imaging were: 1) University “La Sapienza” in Rome, Italy for studies in Chapter 5 and Chapter 6; 2) S.Donato Hospital in Arezzo, Italy for study in Chapter 7 and 3) the Royal Brompton Hospital in London for the studies presented in Chapter 8 and Chapter 9.

4.1.2 Patient Preparation and Monitoring
Pacemaker, implantable cardiac defibrillator (ICD) and metallic cerebral clips were absolute contraindication to CMR. There was no specific preparation for patients undergoing a CMR scan, unless they were undergoing a stress perfusion scan.

In preparation for CMR perfusion, patients were asked to abstain from coffee, tea, chocolate and other substances containing caffeine at least 24 hours prior to the test. Aminophyline and nitrates were also discontinued the day before. A 12-lead ECG was performed prior to the test. Severe conduction abnormalities (atrio ventricular block > IIa), severe chronic obstructive pulmonary disease (COPD) and asthma, unstable angina represented contraindication for the test. Nevertheless, patients with a history of mild to moderate asthma were clinically evaluated, including review of medications in consideration for perfusion imaging with a modified titrated adenosine protocol, as in practice in the Nuclear Medicine Department, Royal Brompton Hospital.¹

Two venous accesses (normally the right and the left anterocubital veins) were secured using 18G (for Gd injection) and 20G (for adenosine infusion) cannulae.
Heart rate, rhythm and symptoms were continuously monitored throughout the duration of the scan. Blood pressure was measured before adenosine infusion (baseline), at 3 minutes of infusion (stress) and 20 minutes after completing the infusion (rest). The blood pressure cuff was positioned on the arm receiving the injection of contrast.

Criteria for termination of adenosine included a drop in systolic blood pressure >20mHg, persistent or symptomatic hypotension, severe respiratory difficulty, and persistent/symptomatic II-III degree atrio-ventricular (AV) blocks. Caution was adopted in presence of stenosis valvular disease, particularly aortic.

### 4.1.3 Imaging Protocol

The complete imaging protocol used in this work is described in **Figure 4.1**. It started with the acquisition of long and short-axis cines, followed by long and short-axis oedema imaging (T2 STIR). Upon completion of a 4-minute adenosine infusion, stress perfusion images were acquired during Gd injection. Adenosine infusion was then stopped and long and short-axis late gadolinium enhancement (LGE) images were acquired. Approximately 20 minutes after the first contrast administration, a second dose of Gd was injected and rest perfusion images were acquired. Cine, T2 STIR, and LGE images were acquired at the same long- and short-axis slice position. The total duration of the scan was approximately 50-60 minutes.

![SCANNING PROTOCOL](image)

**Figure 4.1. Complete imaging protocol used in this thesis**

Cine and LGE imaging were carried out in all scans for all studies. Additional oedema, first-pass stress/rest perfusion to assess for inducible perfusion defect or first-pass rest perfusion
imaging to assess for microvascular obstruction were performed according to the specific study designs and aim. Details on the pulse sequence and imaging protocol used in each of the above steps are provided in the next paragraphs.

### 4.1.4 Software for Image Analysis

Image analysis was performed using a semi-automated customised software (CMRtools, Cardiovascular Imaging Solutions, London, United Kingdom) with dedicated plug-ins (LV tools, Perfusion tools) for the assessment of LV function, infarct size, myocardial oedema, and myocardial perfusion (Figure 4.2).

![CMRtools and plug-ins](image)

*Figure 4.2. CMRtools and plug-ins.*

### 4.2 ASSESSMENT OF LEFT VENTRICULAR FUNCTION

CMR is considered the gold standard imaging technique for the assessment of ventricular dimensions and function, with a greater interstudy reproducibility compared to two-dimensional echocardiography. Given the increased spatial and temporal resolution soft tissues can be clearly visualised without the need for contrast agent and a full three dimensional dataset acquired. Also, as a tomographic technique, any desired image plane can be acquired by CMR and it is not limited by body habitus or acoustic window, or by geometrical assumptions in reconstructing three dimensional data from two dimensional measurements, as with standard 2D echocardiography.
4.2.1 Pulse Sequence
Cine images were acquired using a steady state free precession (SSFP) sequence. Typical parameters were TE= 1.6ms, TR=3.2ms, inplane resolution 1.4 x 1.8mm, slice thickness 8mm, temporal resolution 50ms, 25 phases, flip angle 60 degrees and matrix 256x256. All cines were ECG gated, and to ensure full coverage of the cardiac cycle, retrospective gating was used. Images were acquired during breath hold (at end-expiration) over multiple cardiac cycles (typically 12-15 heart beats). The final image was the average from the data acquired across these various cardiac cycles. In the presence of arrhythmia or limited breath hold, image parameters were optimised on a per subject case.

4.2.2 Image Acquisition
Following the acquisition of the initial localisers in the three orthogonal planes (transverse, coronal and sagittal), a free breathing multislice Half Fourier Single shot Turbo Spin Echo (HASTE) sequence was used to cover the entire thorax in the transverse plane. Breath-hold Steady State Free Precession (SSPP) vertical long axis (VLA) and basal short axis (SA) scouts were then acquired (Figure 4.3 step 1) and used to pilot the acquisition of the subsequent horizontal long axis (HLA) (Figure 4.3, steps 2 and 3). Multiple contiguous SA cines were acquired encompassing the left ventricle from base (AV ring) to the apex (Figure 4.4).
Figure 4.3. Piloting and acquisition of horizontal and vertical long axis views.
Figure 4.4. Piloting and acquisition of short axis slices.

4.2.3 Image Analysis

Image analysis was performed using a semi-automated software (CMRtools, Cardiovascular Imaging Solutions, London, United Kingdom) with a dedicated plug-in (LVtools) for the assessment of the left ventricle. With a step-by-step workflow the endocardial and epicardial borders were contoured in end-diastole and end-systole, and an intensity-based threshold applied to delineate individual voxels as blood or myocardium generating a 3D model of the myocardium and blood pool (Figure 4.5). Papillary muscles and trabeculae were included in
the calculation of LV mass. The motion of the mitral and aortic valve is taken into account for calculating 3D LV volumes and LV mass. The position and the orientation of the valve planes were identified in end-diastole and end-systole, and then automatically interpolated to exclude regions belonging to the left atrium (Figure 4.6).

The images were assessed according to the AHA/ACC 17-segment model⁴ (Figure 4.7). Wall motion score was calculate assigning to the all the segments the following score: 0 (normal), 1 (mildly hypokinetic), 2 (severely hypokinetic), 3 (akinetic), or 4 (dyskinetic). Wall thickening is an aspect of wall motion often taken in consideration in CMR for a more accurate assessment of regional function. This is an advantage of CMR over echocardiography since the former technique clearly defines the endocardial border as opposed to echocardiography where this is often blurred.

*Figure 4.5. Three-dimensional semi-automated LV assessment.*
4.3 ASSESSMENT OF MYOCARDIAL OEDEMA

4.3.1 Pulse Sequence

The T2-weighted (T2w) sequence used to assess myocardial oedema was a breath-hold black-blood segmented turbo spin echo (TSE) technique with triple inversion recovery preparation (short time (tau) inversion recovery). More specifically, this is a fast spin echo pulse sequence that uses radio frequency pulses for spin inversion of the blood pool and inversion recovery preparation for fat saturation (STIR), as described by Simonetti.\(^5\)

The STIR sequence is designed to suppress signal from fat but also enhance the signal from tissues with long T1- and T2-relaxation times, such as inflammatory/oedematous tissues.
Sequence parameters were: TR 2 R-to-R intervals, TE 75 ms, flip angle 180°, TI 170 ms, slice thickness 8 mm, no interslice gap, field of view 340 to 400 mm, matrix 256 × 256, and a voxel size of 2.3 × 1.3 × 8 mm.

### 4.3.2 Image Acquisition

The images were acquired on the short axis planes covering the entire left ventricle, in addition to long-axis slices, during 6 to 8 consecutive breath holds (Figure 4.8). Each slice was obtained during an end-expiratory breath-hold of 12 to 15 s, depending on the patient's heart rate. All T2 STIR images were acquired at the same long- and short-axis position as the cine and LGE images. Surface coil normalisation algorithm was used as provided by the vendor.

*Figure 4.8. T2-STIR short- and long-axis images.*
### 4.3.3 Image Analysis
Region of interest were drawn in the areas of increased signal intensity using a threshold approach: signal intensity of the affected region >2 SD of remote myocardium\(^6\). The level setting was set at the mean signal intensity of the unaffected area. Salvaged myocardium was then quantified as the difference between the area of increased signal on T2w-STIR (area at risk) and the area of LGE (infarct size) as previously described.\(^6\) All measurements were expressed as a percentage of total LV mass.

### 4.4 ASSESSMENT OF MYOCARDIAL PERFUSION

#### 4.4.1 Pulse Sequence
First-pass stress perfusion imaging was performed using a 3-slice (basal, mid-cavity and apical views) hybrid-EPI sequence with T-SENSE (TR 5.8ms, TI 110-140ms, FOV 360x270mm, voxel size 2.8 x 2.8 x 10mm, EPI factor 4) over 50 consecutive cardiac cycles. The images were acquired after 4 minutes of 140µg/kg/min adenosine infusion and following the injection of 0.1mmol/kg of Gd. Rest perfusion images were acquired >20 minutes after stress perfusion imaging.

Arterial input function was assessed using the dual sequence method (for additional details, please refer to Chapter 4, paragraph 3.4.5 “Arterial Input Function”).

#### 4.4.2 Image Acquisition
The 3 basal, mid-cavity and apical slices were piloted using the horizontal and vertical long-axis cine images. Images were put in their end-systolic frames in order to avoid imaging the LV outflow tract (*Figure 4.9*). In the absence of contrast injection, the endocardial border was not clearly visualised, but these images were indeed used to check slice positioning, and presence of artefacts-wrap.
4.4.3 Image Analysis
Visual assessment of regional myocardial perfusion was performed in all studies. With the use of the display tool of the software, perfusion images were played continuously, and subsequently frame by frame to assess the signal intensity pattern and location, as well as the dynamic filling pattern (Figure 4.10).

Figure 4.10 Dynamic contrast filling pattern with progressive contrast arrival.
Images were then displayed in two panels (stress images on the top and corresponding rest images on the lower panel) and inducible perfusion defects appeared as missing enhancement (white arrow) over a few frames (typically 5-7 frames) with consecutive signal increase in the stress images, but not in the rest scan (Figure 4.11). Perfusion images were also compared against the corresponding late gadolinium (LGE) images. Presence of artefact was considered when 1) filling myocardial defect was present at the time of contrast arrival in LV cavity before myocardial enhancement; 2) filling myocardial defect was present both in the stress and rest scans; 3) filling myocardial defect was very short-lived (2-3 frames).

The extension of perfusion defects were reported with their transmurality (transmural vs subendocardial) but was also scored visually in each segment as 0 (normal), 1 (defect <25% wall thickness), 2 (defect 25-50%), 3 (defect 50-75%), 4 (>75%), and its sum identified the visual perfusion score.

Myocardial perfusion reserve (MPR) was also calculated with Perfusion tools® (Cardiovascular Imaging Solutions London, UK), based on uncalibrated perfusion analysis as described in Chapter 3. Endocardial and epicardial contours were semi-automatically drawn in each frame of the 3 short axis slices before applying an automated motion correction algorithm to remove registration errors particularly during respiratory motion. If through-plane motion was still evident, individual frames of image series were disabled. A ROI was then drawn in the blood pool (attentively avoiding the papillary muscles or trabeculations) and its average signal intensity used to calculate AIF. ECG timing was then imported, and myocardial segmentation applied.

Finally, the software used a model-based deconvolution (i.e. constrained to fit a Fermi-function shape of tissue impulse response) to fit a smooth curve from which derived segmental stress and rest myocardial perfusion indexes, as well as the final MPR for each segment (Figure 4.12 and 4.13). The uncalibrated nature of these indices is explained further in Chapter 3.
Figure 4.11 Visual assessment of regional myocardial perfusion. Inducible perfusion defects appear as filling defect (hypointense areas) (white arrows). Perfusion images were then compared against the corresponding late myocardial enhancement slices.
Figure 4.12. Myocardial perfusion reserve in an ischaemic segment.

Figure 4.13. Myocardial perfusion reserve in a non ischaemic segment.
4.5 ASSESSMENT OF MYOCARDIAL INFARCTION

4.5.1 Pulse Sequence
Late gadolinium enhancement (LGE) images were acquired 10-15 minutes after the injection of 0.1mmol/Kg of Gd in the long and short-axis planes, using a segmented inversion recovery gradient echo sequence (TR 600ms, TE 3.8ms, $\alpha$ 25 degrees, slice thickness 8mm, gap 2mm, typical pixel size 1.7 x1.4mm). The inversion time was progressively optimised and adjusted to adequately null normal myocardium (typical values 320-440ms).

Cine and LGE images were acquired at the same long- and short-axis slice position.

4.5.2 Image Acquisition
The images were acquired on the short axis planes covering the entire left ventricle, in addition to long-axis slices, during 6 to 8 consecutive breath holds (Figure 4.14). Each slice was obtained during an end-expiratory breath-hold of 15 to 20 s, depending on the patient's heart rate. All LGE images were acquired at the same long- and short-axis position as the cine and STIR images.

Figure 4.14 LGE short- and long-axis images.
4.5.3 Image Analysis
Infarcted myocardial mass and microvascular obstruction were manually traced and calculated from the LGE short-axis images Region of interest were drawn in the areas of increased signal intensity using a threshold approach: signal intensity of the affected region >5 SD of remote myocardium.10

Figure 4.15. Quantification of infarct size and microvascular obstruction

Microvascular obstruction was defined as a dark zone within the infarcted segments, usually located in the subendocardium. Areas of microvascular obstruction were assessed separately but incorporated in the infarct size analysis (Figure 4.15). All measurements were expressed as a percentage of total LV mass.
References


CHAPTER 5

IMPACT OF PRIMARY PCI DELAY ON MYOCARDIAL SALVAGE, MICROVASCULAR OBSTRUCTION AND INFARCT SIZE

5.1 INTRODUCTION

Current therapeutic strategies in patients with ST-segment elevation myocardial infarction (STEMI) aim for a timely recanalization of the infarct-related artery (IRA) to reduce the progression of the ischemic-necrotic wavefront of myocardial injury and salvage the damaged but still viable myocardium within the area at risk\(^1,2\). In some patients microvascular obstruction (MVO) may occur within the ischemic region in addition to myocardial necrosis, and it is usually associated with greater left ventricular (LV) remodeling and a worse clinical outcome\(^3,4,5\). Delays in recanalizing the occluded artery in patients with STEMI influence the presence and extent of infarct size (IS) and of MVO\(^5,6,7\), with a strong impact on the rate of cardiac mortality and morbidity\(^8\). Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging represents a well-established and reproducible diagnostic tool to assess irreversible ischemic injury and to visualize the location and transmural extent of IS and MVO within the infarcted region\(^5,6,9\).

T2-weighted short tau inversion recovery (T2w-STIR) imaging is a sequence sensitive to increased myocardial water content, allowing the delineation of myocardial oedema after an acute ischemic insult, thus representative of the myocardium at risk. The T2w-STIR hyperintense areas usually include both reversible and irreversible injured myocardium\(^10,11,12\). However, by the use of a combined T2w-STIR and LGE CMR imaging protocol, salvaged myocardium can be quantified as the difference between the area of increased T2w-STIR signal (myocardium at risk) and the area of LGE (IS), as previously reported\(^10,11,12,13,14\). The authors of previous studies\(^1,2,6,7,15,16,17,18\) evaluating the influence of primary percutaneous coronary intervention (PPCI) delays on IS and myocardial salvage in patients with STEMI reported conflicting results. The present study was designed to determine the influence of time to reperfusion on myocardial damage assessed by CMR in patients with STEMI undergoing PPCI.
5.2 METHODS

5.2.1 Patients
Between October 2007 and May 2008, 75 consecutive patients with first STEMI undergoing PPCI within 12 h after the onset of symptoms were prospectively enrolled in the study. Creatine kinase and troponin I measurements were systematically performed at hospital admission, every 3 h for the subsequent 24 h, and then every 12 h for the following 2 days. The CMR study was carried out within 5 days from PPCI. A follow-up CMR study to assess LV remodelling was performed at 6 months. Exclusion criteria were unsuccessful PPCI, rescue percutaneous coronary intervention (PCI), facilitated PCI, contraindication to glycoprotein IIb/IIIa inhibitors, non-STEMI, previous MI, previous coronary artery bypass grafting, and contraindications to CMR. Patients with hemodynamic instability at the time of CMR also were excluded. All participants gave written informed consent to the protocol, and the study was approved by the local ethics committee.

5.2.2 Percutaneous Coronary Intervention
We performed PPCI and stenting of the IRA in all patients according to the clinical protocol used at our institution. Thrombolysis In Myocardial Infarction (TIMI) flow grade was semiquantitatively scored as previously described. The number of coronary vessels demonstrating significant coronary artery disease was reported. Collateral flow to the infarct zone was assessed on the initial angiogram before PPCI and graded on a scale of 0 to 3 by use of Rentrop classification. A successful angioplasty was defined a combination of postprocedural TIMI flow grade 3 and residual stenosis <30%. Time to reperfusion was defined as the interval from the onset of symptoms to the first balloon inflation.

5.2.3. CMR Protocol
We performed CMR imaging in all patients by using a 1.5-T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) equipped with SQ-engine gradients (amplitude: 45 mT/m; slew rate: 200 mT/m/ms) and a 12-channel phased-array cardiac coil. After obtaining scout images, cine steady-state free precession (SSFP) CMR images were acquired from patients during short breath holds in the short-axis, 2-chamber, and 4-chamber planes; on short-axis images, the left ventricle was completely encompassed from the base to the apex, from which we acquired a total of 10 to 12 images. Cine SSFP images were obtained by use of the following parameters: time per frame 51.3 ms, echo time (TE) 1.21 ms,
flip angle 80°, 8-mm slice thickness, no interslice gap, matrix of 256 × 256, field of view ranging from 340 to 400 mm, and a voxel size of 1.7 × 1.7 × 8.0 mm.

For T2w-STIR imaging, a breath-hold black-blood segmented turbo spin echo technique was adopted by the use of a triple inversion recovery preparation module (TR 2 R-to-R intervals, TE 75 ms, flip angle 180°, TI 170 ms, slice thickness 8 mm, no interslice gap, field of view 340 to 400 mm, matrix 256 × 256, and a voxel size of 2.3 × 1.3 × 8 mm). Technical details of this sequence are described elsewhere. The T2w-STIR images were acquired on short axis planes covering the entire left ventricle during 6 to 8 consecutive breath holds. Each slice was obtained during an end-expiratory breath-hold of 12 to 15 s, depending on the patient's heart rate.

Finally, short-axis LGE images were obtained by use of a segmented inversion recovery technique and acquired 10 to 15 min after injection (Gd-BOPTA, Multihance, Bracco, Milan, Italy; 0.1 mmol/kg body weight at 2 ml/s). Sequence parameters were the following: image data acquisition in 100 ms in diastole (adapted per patient), 23 raw data lines per alternate cycle, TE 4.33 ms, matrix 256 × 256, flip angle 30°, slice thickness 8.0 mm, no interslice gap, and voxel size 1.7 × 1.4 × 8 mm. The inversion time was progressively optimized to null the signal in the normal myocardium (typical values, 250 to 300 ms) to ensure matching slice position between T2w-STIR and LGE images, same acquisition planes were adopted. Cine, T2w-STIR, and LGE images were acquired at the same short-axis slice position.

### 5.2.4 Image Analysis

All CMR studies were analyzed off-line by the use of a dedicated workstation (Siemens Argus, Erlangen, Germany). Left ventricular volumes, systolic function, and mass were calculated from the short-axis SSFP cines. Infarcted myocardial mass and MVO were manually traced and calculated from the LGE short-axis images. As reported in Bondarenko et al., myocardial regions was considered infarcted if the IS signal intensity was >5 SDs above the remote myocardium. The MVO was defined as a dark zone within the infarcted segments, usually located in the subendocardium. The mass of myocardial oedema was traced and calculated from the T2w-STIR images by the use of a similar threshold-based approach (signal intensity >2 SDs of remote myocardium). Salvaged myocardium was quantified as the difference between the area of increased T2w-STIR signal (area at risk) and the area of LGE (IS) as previously described. All measurements were normalized to LV mass.
5.2.5. Statistical Analysis
Data were analyzed with SPSS software version 15.0 (SPSS Inc., Chicago, Illinois). The continuous variables were calculated as the average value considering the standard deviation, whereas those that were categorical were calculated as percentages. The differences between means of continuous variables at different times to reperfusion were analyzed by 1-way analysis of variance by the use of a linear trend analysis, and a post-hoc analysis with Bonferroni correction was made for differences between groups. The differences between categorical variables were analyzed with the chi-square test of Pearson. A Student t test for independent groups was used to assess differences in continuous variables between anterior versus non anterior infarction, whereas a Student paired-samples t test was used to highlight differences in LV parameters after primary PCI and at 6-month follow-up; these tests were made without correction for multiple comparisons. A linear regression analysis was used to evaluate the relationship between time to treatment and CMR extent of MVO, IS, and salvaged myocardium. Differences were considered statistically significant at a 2-sided p value ≤0.05.

5.3 RESULTS
5.3.1 Clinical and Angiographic Data
Seventy patients (89% men, mean age 58 ± 9 years) were studied with CMR 3 ± 2 days after PPCI. There were no differences between the 4 groups. Seventy-five patients were initially recruited, but 5 patients were excluded because of claustrophobia (n = 3) or clinical instability (n = 2). A follow-up CMR was performed in 58 patients; the remaining 12 patients declined. We performed PPCI in left anterior descending artery (LAD) in 43 patients, in the right coronary artery (RCA) in 26 patients, and in the left circumflex artery (LCx) in 1 patient. Mean time to reperfusion was 4.4 ± 4.7 h. No events suggesting reocclusion/stenosis were observed between PPCI and CMR examinations.

For the purpose of the study, patients were subcategorized into 4 quartiles on the basis of time from symptom onset to reperfusion: ≤90 min (group I, n = 19), >90 to 150 min (group II, n = 17), >150 to 360 min (group III, n = 17), and >360 min (group IV, n = 17). No differences on baseline clinical (Table 5.1) and angiographic characteristics were observed in the 4 groups (Table 5.2). In particular, no statistical differences between groups were observed in relation
to incidence of LAD disease, TIMI flow grade 3 before PPCI, and significant collateral circulation.

Table 5.1 Baseline clinical characteristics of the population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups (n = 70 Patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤90 Min (n = 19)</td>
<td>&gt;90–150 Min (n = 17)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>58 ± 7.3</td>
<td>57 ± 10</td>
</tr>
<tr>
<td>Sex, male</td>
<td>15 (78)</td>
<td>13 (76)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (26)</td>
<td>4 (23)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (5)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (63)</td>
<td>12 (70)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4 (21)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>5 (26)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Time to treatment, h</td>
<td>1.0 ± 0.1</td>
<td>2.4 ± 0.4</td>
</tr>
<tr>
<td>CK, UI/l</td>
<td>1,806 ± 934</td>
<td>2,012 ± 1,871</td>
</tr>
<tr>
<td>CK-MB, UI/l</td>
<td>284 ± 218</td>
<td>302 ± 243</td>
</tr>
<tr>
<td>Troponin I, ng/ml</td>
<td>8.7 ± 9.9</td>
<td>10.6 ± 11.4</td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>18 (95)</td>
<td>15 (88)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>17 (89)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Statins</td>
<td>19 (100)</td>
<td>17 (100)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CK = creatine kinase; CK-MB = creatine kinase-myocardial band;
Table 5.2 Angiographic characteristics of the population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups (n = 70 Patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct-related artery</td>
<td>≤90 min (n = 19)</td>
<td>&gt;90–150 min (n = 17)</td>
</tr>
<tr>
<td>LAD</td>
<td>14 (74)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>LCx</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>RCA</td>
<td>5 (26)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Number of vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10 (53)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>2</td>
<td>6 (31)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>3</td>
<td>1 (5)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>TIMI flow grade 3 before PCI</td>
<td>3 (15)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Collateral flow grade 2 to 3</td>
<td>2 (10)</td>
<td>3 (17)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

5.3.2. Time to Reperfusion and Infarct Size
An infarcted region on LGE images was visualized in all patients and corresponded to the territory distribution of the IRA. Mean IS among 4 groups was 12 ± 8% of LV mass. A significant increase of IS over time was found (8%, 11%, 12%, and 18%, respectively, p = 0.05) (Figure 5.1A). The largest increase in IS was observed in patients with the longest time to reperfusion (group IV vs. I, p = 0.002). Time to reperfusion expressed as a continuous variable significantly correlated with IS (r = 0.60, p = 0.0001) (Figure 5.2). On a separate analysis on LAD versus non-LAD infarcts, we observed that anterior infarcts were significantly larger than inferior ones. This phenomenon was consistently observed across the 4 reperfusion groups (Table 5.3).
Figure 5.1. Time to reperfusion and cardiovascular magnetic resonance parameters. Bar graphs show the influence of time to reperfusion on infarct size (A), myocardial oedema (B), myocardial salvage (C), and microvascular obstruction (MVO) (D). Data are expressed as % left ventricular mass.
Figure 5.2. Relationship between time to reperfusion and infarct size. Triangles represent anterior infarct location and circles non-anterior infarct location.
Table 5.3. Relationship among infarct location (LAD vs. Non-LAD) and time to treatment, infarct size, and LVEF.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤90 Min</td>
</tr>
<tr>
<td>LAD time to treatment, h</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Non-LAD time to treatment, h</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>LAD infarct size, %</td>
<td>12 ± 3.1</td>
</tr>
<tr>
<td>Non-LAD infarct size, %</td>
<td>6.8 ± 1.5</td>
</tr>
<tr>
<td>LAD LVEF, %</td>
<td>47 ± 12.4</td>
</tr>
<tr>
<td>Non-LAD LVEF, %</td>
<td>50 ± 10.7</td>
</tr>
</tbody>
</table>

LAD = left anterior descending artery; LVEF = left ventricular ejection fraction.
5.3.3. Time to Reperfusion and Myocardial Salvage

Increased signal intensity on T2w-STIR imaging (myocardial oedema) was observed in 62 of 70 patients (89%); in the remaining 8 (11%) patients, T2w signal intensity was not homogeneous throughout segments because of the presence of a central hypointense core with peripheral hyperintense rim related to underlying microvascular damage. The mean size of oedema among 4 groups was 16 ± 8% of LV mass. In all patients the location of T2w-STIR increased signal intensity corresponded to the territory of distribution of the IRA. The extent of myocardial oedema did not changed significantly as time to reperfusion progressed (16%, 15%, 15%, and 19%, respectively, p = 0.37) (Figure 5.1 B). Conversely, the extent of salvaged myocardium (oedematous but not necrotic myocardium) was significantly reduced overtime (8.5%, 3.2%, 2.4%, and 2.1%, respectively, p = 0.003) (Figure 5.1 C). In particular, a marked reduction in salvaged myocardium was observed when reperfusion occurred area after 90 min of coronary occlusion (group I vs. II, p = 0.0001; group I vs. III, p = 0.0001; group I vs. IV, p = 0.0001), whereas no significant changes were observed between groups II, III, and IV. In late reperfused patients (group IV), an almost complete absence of salvaged myocardium was observed (Figure 5.1 C). A significant inverse correlation was found between time and salvaged myocardium by linear regression analysis (r = −0.53, p = 0.005).

5.3.4. Time to Reperfusion and Microvascular Obstruction

Mean size of MVO was 2.1 ± 3.4% of LV mass. The incidence and extent of MVO progressively increased as time to reperfusion increased (0.5%, 1.5%, 3.7%, and 6.6%, respectively, p = 0.039) (Figure 5.1 D). In particular, the larger MVO area was observed in the latest reperfused group (group IV vs. I, p = 0.034); a weak but statistically significant correlation was observed between time to reperfusion and MVO (r = 0.39, p = 0.005). Furthermore, in patients with MVO, IS was significantly greater than in patients without MVO (16 ± 9.8% vs. 10 ± 6.9%, respectively, p = 0.012).

5.3.5. Time to Reperfusion and LV function

Significant increase in LV volumes and reduction in ejection fraction over time was observed (Table 5.4). However, these changes were not homogeneous because both left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) increased and left ventricular ejection fraction (LVEF) reduced only in the group reperfused the latest
(group IV). There were no differences in LVEF across the 4 reperfusion groups between anterior and non anterior infarcts (Table 5.3).

Table 5.4. Influence of time to reperfusion on left ventricular function assessed by CMR.

<table>
<thead>
<tr>
<th>Variables</th>
<th>≤90 Min (n = 19)</th>
<th>&gt;90–150 Min (n = 17)</th>
<th>&gt;150–360 Min (n = 17)</th>
<th>&gt;360 Min (n = 17)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV, ml</td>
<td>128 ± 32</td>
<td>131 ± 37</td>
<td>130 ± 41</td>
<td>153 ± 22</td>
<td>0.03</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>62 ± 22</td>
<td>69 ± 30</td>
<td>68 ± 24</td>
<td>94 ± 21</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>47 ± 10</td>
<td>46 ± 9</td>
<td>47 ± 6</td>
<td>38 ± 7</td>
<td>0.06</td>
</tr>
</tbody>
</table>

CMR = cardiovascular magnetic resonance; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

5.4 DISCUSSION

In this study we describe the benefits associated with early coronary reperfusion as assessed by CMR in patients with STEMI treated with PPCI. Noninvasive myocardial tissue characterization provided by CMR enabled us to differentiate reversible and irreversible myocardial injury (myocardium at risk and myocardial infarction, respectively) and consequently to determine the presence and extent of salvaged myocardium.

The main findings of this study are that: 1) patients reperfused early (≤90 min) demonstrated smaller IS and microvascular damage and larger salvaged myocardium, whereas patients reperfused later (time to reperfusion >360 min) presented larger IS and MVO and very limited, if any, salvaged myocardium; and 2) the presence and extent of salvaged myocardium markedly decreased when reperfusion occurred after >90 min of coronary occlusion. To the best of our knowledge, this is the first in vivo, clinical, and non-invasive evaluation of the impact of time to reperfusion on infarct size, microvascular obstruction and myocardial salvage in patients with STEMI undergoing PPCI.
5.4.1. Time to Reperfusion and Myocardial Damage

Reimer and Jennings\(^1\) have demonstrated that approximately one-half of the ischemic myocardium progresses towards necrosis within 40 min of coronary occlusion, one-third of the ischemic myocardium is still salvageable at 3 h, and that the process of myocardial necrosis is complete about 6 h after the onset of coronary occlusion. After this time, the potential for salvage myocardium is considered minimal or absent\(^1,2\). The benefits of reperfusion persist up to 12 h, but these are of decreasing magnitude over time\(^5,7,9\). According to the “open artery hypothesis,” most of the clinical benefits of late recanalization (>6 h) are independent from myocardial salvage and are mostly related to attenuation of LV remodeling processes and reduction of clinical instability\(^2,7,24\).

Multiple randomized clinical trials\(^6,7,8\) showed a significantly lower rate of mortality among patients achieving TIMI flow grade 3 within 90 min after the onset of STEMI (golden hour). For these reasons, the European Society of Cardiology and American College of Cardiology/American Heart Association clinical guidelines on STEMI recommend PCI within 90 min from first medical contact. Our CMR data confirm this experimental and clinical evidence by demonstrating a progressive increase over time in IS and MVO extent. However, by using CMR we were able to observe, for the first time, that salvaged myocardium consistently reduces after 90 min of coronary occlusion, both in the LAD and non LAD infarctions. (Figure 5.3). As time to reperfusion progresses, infarct size (thin arrows) and microvascular obstruction (MVO) (*) both increase. Of note, in group I (patients early reperfused) the area of myocardial oedema (open arrows) largely exceeds the area of infarct size, demonstrating presence of myocardial salvage; conversely in group IV (reperfused the latest), the area of myocardial oedema almost corresponds to the infarcted area, suggesting limited myocardial salvage.
Previous studies \(^1,2,5,6,7,15,16,17,18\) in which the authors evaluated the influence of time to reperfusion on IS and salvaged myocardium yielded conflicting results. As previously underlined, Reimer and Jennings\(^1\) demonstrated in dogs a substantial reduction of salvaged myocardium in the first hours after coronary ligation. Whereas a reduced efficacy of lytic treatment overtime has been well documented, a recent meta-analysis by Boersma\(^18\) suggests that time delays are largely unimportant in primary PCI. In particular, with clinical data obtained by the use of myocardial scintigraphy, Schomig et al.\(^16\) found no significant relation

**Figure 5.3.** Influence of time-to-reperfusion on myocardial salvage, infarct size and microvascular obstruction in two patients with inferior (A) and anterior (B) STEMI. Top panels: T2-weighted short tau inversion recovery (T2w-STIR) images; the arrows identify the extension of myocardium at risk; the asterisks identifies microvascular obstruction. Lower panels: corresponding late gadolinium enhancement (LGE) images; the arrows identify the extension of necrotic myocardium (infarct size); the asterisks identifies microvascular obstruction.
between time to reperfusion and IS and a constantly high myocardial salvage index in patients treated with PCI even after 12 h from symptom onset. Conversely, by analyzing the T2W-STIR and LGE images, our CMR data support the hypothesis that myocardium potentially salvaged by reperfusion significantly reduces after 90 min of coronary occlusion even in patients treated with PPCI.

The main determinants of MVO are still unclear. In agreement with Tarantini et al., we observed a progressive MVO increase over time. In particular MVO was detected only in 6 of 19 patients (31%) treated within 90 min and in 14 of 17 patients (82%) treated after 6 h. Thus, both incidence and extent of MVO are time-dependent phenomenon, as observed for IS. These results are consistent with previous experimental data hypothesizing that the extent of microvascular injury is also driven by the extent of IS.

Finally, the impact of time to reperfusion on LV volumes and LVEF was significantly more pronounced in patients reperfused late (group IV) compared with the other groups (I, II, and III). This finding was confirmed also in the CMR at 6 months, demonstrating a significant increase in LVEDV and LVESV in the later reperfused groups (group III, >150 to 360 min and group IV, >360 min); LVEF significantly decreased only in group IV.

5.4.2. Myocardium at Risk and Salvaged Myocardium

Increased signal intensity in the T2w-STIR images is related to increased water content. In patients with STEMI this phenomenon is likely to represent post-ischemic intracellular edema either related to altered transmembrane sodium gradients or to the inflammatory response to the acute ischemic insult. The authors of recent CMR studies demonstrated that the increased signal intensity on T2w-STIR images corresponds indeed to the area of myocardium at risk determined histologically. Aletras et al. demonstrated in animal model of 90-min coronary occlusion followed by reperfusion that the area at risk measured by microspheres was comparable with the area of increased signal in the T2w images 2 days later. The increased signal intensity on T2w-STIR images consist of both reversibly and irreversibly injured myocardium. In addition, areas of LGE identified IS with detailed precision compared with histology, confirming that IS acutely is not overestimated because of the contribution of oedematous areas, which are indeed characterized and quantified only by the T2w images. Therefore, on the basis of the histological evidence that myocardium at risk is identified by the T2w areas and IS by LGE areas, the amount of salvaged myocardium can be derived by subtracting the area of LGE from the T2w area.

Cury et al. recently applied T2w imaging by using a double inversion-recovery with chemical fat saturation and LGE protocol to improve the accuracy in the diagnosis of acute
coronary syndrome in the emergency department. The authors of previous studies showed that areas of increased T2 signal intensity are consistently larger than the LGE areas of the irreversible injury. Similarly, in our study, the oedematous zone is consistently larger than the infarcted zone but only in patients treated early and progressively reduces with delays on reperfusion evolving in irreversible myocardial damage. The amount of myocardium successfully salvaged dramatically reduces after 90 min of coronary occlusion; thus, clinical benefits of IRA reopening are after this period are largely not attributable to myocardial salvage.

Milavetz et al. reported the influence of time to reperfusion on myocardial salvage assessed by technetium-99m sestamibi demonstrating that in patients with first anterior MI undergoing successful reperfusion therapy (PPCI or thrombolysis) the greatest degree of myocardial salvage was achieved with an early reperfusion therapy (<2 h). Our data confirm these findings by the use of CMR as an alternative noninvasive imaging modality. The retrospective determination of myocardium at risk, IS—and consequently myocardial salvage—by CMR up to 5 days after reperfusion appears logistically very attractive as compared with the tracer injection before reperfusion therapy required by technetium-99m sestamibi. Finally, our study provides additional insight on the association of 4 different time-to-reperfusion intervals and the extent of reversible and irreversible damage.

5.4.3. Clinical Implications

The results of our study suggest that any strategy to shorten the delay in the reperfusion of patients with STEMI (i.e., pre-hospital lysis or a direct catheter laboratory notification bypassing the emergency department) is crucial. Although Boersma hypothesizes that that time delays are less important for primary PCI, the present study demonstrated the amount of myocardial salvage reduces significantly already after 90 min of coronary occlusion. Our data might explain the unsatisfactory clinical results of myocardial protection therapy. Agents directed toward improving the myocardial reperfusion itself are time-limited to the period when myocardial salvage occurs. Thus, possibly only patients presenting very early after symptom onset may take advantages from cardioprotective drugs.

Finally, this work confirms and emphasizes the important diagnostic role of CMR with LGE and T2w-STIR techniques in providing in vivo characterization of myocardial tissue damage at different temporal stages of coronary reperfusion. The use of CMR can identify and quantify areas of salvaged myocardium in patients with STEMI treated with PPCI, representing a potentially valuable tool to be used in large clinical trials assessing the efficacy
of different reperfusion strategies. Large clinical trials are needed to assess the role of CMR in the risk stratification after acute myocardial infarction and possibly improve patient management.

5.4.4. Study Limitations

Despite the limited study population, a relatively high percentage of our patients were treated very early (24% of patients ≤90 min from the symptom onset, 51% within 150 min), which was made possible by an integrated hospital network system activated in our city and region. For the same reason the mean IS detected in our study population was slightly smaller than previously reported. The influence of time to reperfusion on the extent of myocardial salvage IS and MVO needs to be confirmed in larger longitudinal studies. Currently, there is no consensus on which technique can be used to perform the best MVO quantification. With first-pass myocardial perfusion imaging, the area of MVO is larger than using LGE imaging. In our study MVO was assessed in LGE images. Although the size of MVO may be underestimated by use of the LGE sequences, the persistence of MVO in these images is likely to reflect a more severe form of MVO. Finally, in this study CMR was performed as part of a research protocol and did not contribute to the care of patients.

5.4.5. Conclusion

According to previous prognostic data, in patients with STEMI “time is muscle”. Using state-of-the-art CMR technology, this study has assessed in a novel (imaging) way that in fact “time is muscle”. It has identified that in patients reperfused early (<90 minutes) infarct size is limited and the extent of myocardial salvage is significantly larger than in patient reperfused later (>360 minutes). Conversely, patients reperfused later present much larger infarct size and reduced myocardial salvage. Of note, the presence of microvascular obstruction was identified only in patients reperfused later.

Infarct size, myocardial salvage and microvascular obstruction by CMR can represent surrogate endpoints to be used in prospective clinical trials comparing different reperfusion strategies or cardioprotective agents.
References

1 Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979;40:633–44.


4 Chaitman BR, Lim MJ. No reflow and the quest to achieve optimal perfusion during the acute phase of myocardial infarction. J Am Coll Cardiol 2004;44:313–5.


19 Galiuto L, Garramone B, Scarà A, et al. The extent of microvascular damage at myocardial contrast echocardiography is superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodeling. Results of the multicenter study “Acute Myocardial Infarction Contrast Imaging” (AMICI). J Am Coll Cardiol 2008;51:552–9.


CHAPTER 6
THROMBUS ASPIRATION DURING PRIMARY PCI IMPROVES MYOCARDIAL
PERFUSION AND REDUCES INFARCT SIZE.
THE EXPIRA PROSPECTIVE RANDOMIZED TRIAL
(THROMBECTOMY WITH EXPORT CATHETER IN INFARCT-RELATED ARTERY DURING PRIMARY
PERCUTANEOUS CORONARY INTERVENTION)

6.1 INTRODUCTION
Primary percutaneous coronary intervention (PPCI) is the standard treatment in patients
with STEMI achieving a Thrombolysis In Myocardial Infarction (TIMI)-3 in >90% of
patients. However, despite a “brisk” epicardial coronary flow in the infarct-related artery,
microvascular damage frequently limits the efficacy of PPCI. Recent studies suggest that
thrombectomy improves myocardial perfusion and reduces left ventricular remodeling by
reducing microvascular damage. Cardiovascular magnetic resonance (CMR) represents
the gold-standard technique to identify and quantify microvascular obstruction (MVO) and
infarct size (IS) and to date this imaging technique has not been applied to assess the
efficacy of thrombectomy. The aim of this trial was to evaluate the impact of a manual
intracoronary aspiration thrombectomy device (Export®, Medtronic) as adjunctive therapy
in emergency PPCI (EM-PCI) on traditional procedural outcomes as myocardial blush
grade (MBG) and ST-segment resolution (ST-R) but also on imaging outcomes as MVO
and IS by CMR in patients with an anterior ST elevation myocardial infarction (STEMI).

6.2 METHODS
6.2.1 Study Design and Population
One-hundred-and seventy-five consecutive patients admitted with STEMI and candidates
to undergo PPCI were enrolled. Patients were randomly assigned in a 1:1 manner to EM-
PCI or standard-PCI (S-PCI). In the CMR substudy, a second randomization (1:1) was
performed within anterior STEMI patients only (Figure 6.1). All patients were pre-treated
immediately before the revascularization with aspirin 300 mg, intravenous heparin,
abciximab at a standard dose (weight proportional) and clopidogrel 300 mg. Following a
wire being passed across the lesion thrombectomy was performed by more than two
passages of the aspiration catheter across the lesion. Subsequently patients received aspirin, Clopidogrel (12 months), nitrates, beta-blockers, ACE inhibitors and statins.

The protocol was accepted by the institutional ethical board, and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent. The inclusion criteria were: STEMI within 9 hours from symptoms onset, infarct related artery ≥2.5 mm in diameter, TIMI ≤1, and age >18 years.

Exclusion criteria were: previous PCI on infarct-related artery, previous myocardial infarction, previous coronary artery bypass grafting, cardiogenic shock, three vessel disease, left main stem disease, severe valvular heart disease, thrombolysis, contraindication to GP IIb/IIIa inhibitors.

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**Figure 6.1. EXPIRA study design, comprehensive of the CMR substudy.**

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### 6.2.2 Angiographic and ECG Analysis

TIMI flow grade and MBG were estimated visually by two experienced observers, as previously described.\(^7,8\) Thrombus burden at lesion site was graded from 0 to 5 according to the Thrombus Score.\(^9\) Inter- and intraobserver coefficients of variation assessed in 20 randomly selected patients were 8% and 5% for MBG, 5% and 3% for TIMI. All patients underwent a 12-lead ECG at baseline and 90 minutes after revascularization. ST-segment resolution (ST-r) was measured as previously described.\(^10\)
6.2.3 CMR Protocol
CMRI was performed at day 3 to 5 after PPCI and at 3 months using a 1.5-T scanner (Avanto Siemens, Germany). Left ventricular function was assessed by standard steady-state free precession technique. Consecutive short-axis views were obtained by encompassing the left ventricle from base to apex; vertical and horizontal long-axis views were acquired. Typical image parameters were: TE=1.6ms, TR=3.2ms, \( \alpha = 60 \) degrees, matrix=256x256, slice thickness 8mm, gap 2mm.

Rest myocardial perfusion was evaluated with a first-pass technique using a T1-weighted multishot gradient-echo echo planar inversion-recovery sequence (TR=6.6ms, TE=1.3ms, TI=240ms, 25° flip angle, slice thickness 10mm). Three short-axis slices (basal, mid-cavity and apical levels) were obtained injecting 0.1 mmol/kg of gadolinium-BOPTA (Multihance, Bracco, Italy) at 2mL/sec followed by 20mL saline flush in the right anterocubital vein. CMR images were acquired in long- and short-axis views with a segmented inversion-recovery fast gradient echo sequence 15 minutes after contrast injection. Sequence parameters were: TR=\(~9\) ms, 23 raw data lines per alternate cycle, TE=3.8ms, \( \alpha = 25 \) degrees, slice thickness 8mm, gap 2mm. The inversion time was progressively optimized to null normal myocardium.

6.2.4 CMR Image Analysis
All measurements were performed by two fully blinded operators using an off-line dedicated workstation (Siemens Argus). Left ventricular ejection fraction, end-diastolic and end-systolic volumes and LV mass were calculated from the short-axis views.

MVO and IS were quantified by manual drawing the regions of hypointensity on the first-pass perfusion images and the regions of hyperintensity on the CMR short-axis slices, respectively. MVO was included in the infarcted area. MVO and IS are expressed in grams (assuming 1.05 g/ml the specific gravity of the myocardium) and as a percentage of the LV mass. Inter- and intraobserver coefficients of variation, assessed in 20 randomly selected patients, were 3% and 1% for MVO, 3% and 2% for IS, respectively.

6.2.5 Clinical Follow-up and End-Points
Clinical follow-up was performed at 9 months in all patients to assess the occurrence of the following major adverse coronary events (MACE): cardiac death, non fatal reinfarction, target vessel revascularization. The incidence of stent thrombosis was also evaluated. Primary study end-points were the occurrence of final MBG \( \geq 2 \) and the rate of ST-r.
End-points of the CMR substudy were the presence and extent of MVO in the acute phase and IS extent at 3 months.

6.2.6 Statistical Analysis
We estimated that 45 patients would be required in each study group to have a power of 80% to detect an absolute difference in the occurrence of MBG ≥2 of 30% with a two-sided alpha value of 0.05. Categorical variables were analyzed by the chi-square or Fisher exact test, as appropriate. All continuous variables were expressed as mean ± SD and analyzed by Student t test. Event-free survival curve for MACE was constructed using Kaplan-Meier method, and statistical differences between curves were assessed by log-rank test. Statistical analysis was performed with StatView, version 5.0 (SAS Institute, Cary, North Carolina).

6.3 RESULTS
6.3.1 Baseline Characteristics
Two-hundred-fifty-six consecutive STEMI patients were recruited and 81 patients were excluded (Figure 6.1). Clinical and angiographic characteristics of EM-PCI and S-PCI are shown in Table 6.1 and Table 6.2.

6.3.2 Angiographic and Periprocedural Findings
EM-PCI showed a significant reduction of the thrombus burden (TS 0-1: EM-PCI, 63% vs. S-PCI, 42% vs., p=0.006). The rate of post-thrombectomy TIMI ≥2 was higher in EM-PCI (92% vs. 77%, p=.006) with a similar final rate (EM-PCI 100% vs. S-PCI 98% p=0.9) (Table 6.3). Primary end-points occurred more frequently in EM-PCI (MBG≥2: 88% vs. 59%, p<0.0001; ST-r: 63% vs. 39%, p=0.001) (Table 6.3, Figure 6.2).

6.3.3 Clinical Outcomes
At 9 months no differences were observed in terms of cumulative MACE (log-rank test p=0.14) (Figure 6.2). However, S-PCI had a higher incidence of cardiac death (log-rank test p = 0.02) than EM-PCI (Figure 6.3). No stent thrombosis occurred in both groups.
### Table 6.1 Baseline clinical and demographic characteristics of all study patients.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=175)</th>
<th>S-PCI (n=87)</th>
<th>EM-PCI (n=88)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65.3±11.2</td>
<td>64.6±12.5</td>
<td>66.7±14.1</td>
<td>0.298</td>
</tr>
<tr>
<td>Males, (%)</td>
<td>105 (60.0)</td>
<td>48 (55.1)</td>
<td>57 (64.7)</td>
<td>0.218</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, (%)</td>
<td>102 (58.3)</td>
<td>43 (49.4)</td>
<td>59 (67.0)</td>
<td>0.021</td>
</tr>
<tr>
<td>Diabetes, (%)</td>
<td>37 (21.1)</td>
<td>16 (18.4)</td>
<td>21 (23.8)</td>
<td>0.459</td>
</tr>
<tr>
<td>Smoking, (%)</td>
<td>66 (37.7)</td>
<td>23 (26.4)</td>
<td>43 (48.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Obesity, (%)</td>
<td>7 (4.0)</td>
<td>2 (2.3)</td>
<td>5 (5.7)</td>
<td>0.443</td>
</tr>
<tr>
<td>Familiar history of CAD, (%)</td>
<td>58 (33.1)</td>
<td>32 (36.8)</td>
<td>26 (29.5)</td>
<td>0.338</td>
</tr>
<tr>
<td>Cholesterol, mg/dl ± SD</td>
<td>163±27</td>
<td>167±15</td>
<td>161±11</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglycerides, mg/dl ± SD</td>
<td>122±37</td>
<td>125±26</td>
<td>124±31</td>
<td>0.817</td>
</tr>
<tr>
<td>Renal Failure, %</td>
<td>14 (8.0)</td>
<td>7 (8.0)</td>
<td>7 (7.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Killip class III, %</td>
<td>42 (24.0)</td>
<td>25 (28.7)</td>
<td>17 (19.3)</td>
<td>0.160</td>
</tr>
<tr>
<td><strong>Symptoms to balloon, hrs ± SD</strong></td>
<td>6.1±1.3</td>
<td>6.1±1.8</td>
<td>6.2±0.9</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>LVEF, % ± SD</strong></td>
<td>41±13</td>
<td>40.7±9.3</td>
<td>42±10.5</td>
<td>0.192</td>
</tr>
<tr>
<td><strong>ST-segment elevation (mV)</strong></td>
<td>22.9±13.5</td>
<td>22.3±9.3</td>
<td>23.6±10.5</td>
<td>0.384</td>
</tr>
</tbody>
</table>

### Table 6.2 Baseline procedural characteristics of all study population.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=175)</th>
<th>S-PCI (n=87)</th>
<th>EM-PCI (n=88)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location of IRA, (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>76 (43.4)</td>
<td>38 (43.7)</td>
<td>38 (43.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>LCX</td>
<td>42 (24.0)</td>
<td>20 (23.0)</td>
<td>22 (25.0)</td>
<td>0.859</td>
</tr>
<tr>
<td>RCA</td>
<td>57 (32.6)</td>
<td>29 (33.3)</td>
<td>28 (31.8)</td>
<td>0.872</td>
</tr>
<tr>
<td><strong>BARI score, %</strong></td>
<td>28.9±10.3</td>
<td>28.1±9.2</td>
<td>29.7±6.1</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Multivessel disease, (%)</strong></td>
<td>37 (26.8)</td>
<td>16 (18.4)</td>
<td>21 (23.8)</td>
<td>0.459</td>
</tr>
<tr>
<td><strong>Bifurcation, (%)</strong></td>
<td>23 (13.1)</td>
<td>11 (12.7)</td>
<td>12 (13.6)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Lesion length, mm ± SD</strong></td>
<td>14.5±5.3</td>
<td>14.4±6.6</td>
<td>14.7±3.9</td>
<td>0.714</td>
</tr>
<tr>
<td><strong>Vessel reference diameter, mm ± SD</strong></td>
<td>2.9±0.6</td>
<td>2.9±0.5</td>
<td>2.9±0.6</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>MLD before thrombectomy, mm ± SD</strong></td>
<td>0.85±0.4</td>
<td>0.86±0.2</td>
<td>0.83±0.3</td>
<td>0.438</td>
</tr>
<tr>
<td><strong>Pre-thrombectomy Thrombus Score, (%)</strong></td>
<td>18 (10.3)</td>
<td>9 (10.3)</td>
<td>9 (10.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>62 (35.4)</td>
<td>32 (36.8)</td>
<td>30 (34.1)</td>
<td>0.753</td>
</tr>
<tr>
<td>5</td>
<td>95 (54.3)</td>
<td>47 (54.0)</td>
<td>48 (54.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Table 6.3. Post-procedural angiographic characteristics of all study population.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=175)</th>
<th>S-PCI (n=87)</th>
<th>EM-PCI (n=88)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Direct” stenting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>69 (39.4)</td>
<td>2 (2.3)</td>
<td>67 (76.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stent Type, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bare-Metal Stent</td>
<td>73 (41.7)</td>
<td>34 (39.1)</td>
<td>39 (44.3)</td>
<td>0.540</td>
</tr>
<tr>
<td>Drug-Eluting Stent</td>
<td>102 (58.3)</td>
<td>53 (60.9)</td>
<td>49 (55.7)</td>
<td>0.540</td>
</tr>
<tr>
<td><strong>Post-stenting MLD, mm ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.9±0.8</td>
<td>2.9±0.7</td>
<td>2.9±0.1</td>
<td>1.00</td>
</tr>
<tr>
<td>CK-MB peak, ng/ml</td>
<td>105±125</td>
<td>108±111</td>
<td>109±119</td>
<td>0.605</td>
</tr>
<tr>
<td>90 min ST-segment resolution, (%)</td>
<td>90 (51.4)</td>
<td>34 (39.1)</td>
<td>56 (63.6)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>ST-segment elevation (mV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.2±15.3</td>
<td>12.8±12.3</td>
<td>7.6±9.7</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Post-stenting TIMI flow grade, (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>174 (99.4)</td>
<td>86 (98.9)</td>
<td>88 (100)</td>
<td>0.975</td>
</tr>
<tr>
<td>0-1</td>
<td>1 (0.6)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>0.997</td>
</tr>
<tr>
<td><strong>Post-stenting MBG, (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>130 (74.3)</td>
<td>52 (59.8)</td>
<td>78 (88.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0-1</td>
<td>45 (25.7)</td>
<td>35 (40.2)</td>
<td>10 (11.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 6.4. Clinical and angiographic characteristics of patients in CMR substudy.

<table>
<thead>
<tr>
<th></th>
<th>S-PCI (n=37)</th>
<th>EM-PCI (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>55.2±13.7</td>
<td>60.7±9.6</td>
<td>0.288</td>
</tr>
<tr>
<td>Males, (%)</td>
<td>81.8</td>
<td>90</td>
<td>0.593</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, (%)</td>
<td>28.2</td>
<td>59</td>
<td>0.071</td>
</tr>
<tr>
<td>Diabetes, (%)</td>
<td>9.2</td>
<td>10.1</td>
<td>0.943</td>
</tr>
<tr>
<td>Smoking, (%)</td>
<td>72.7</td>
<td>60.2</td>
<td>0.537</td>
</tr>
<tr>
<td><strong>Familiar history of CAD, (%)</strong></td>
<td>78.9</td>
<td>65.4</td>
<td>0.269</td>
</tr>
<tr>
<td>Time to balloon, (min)</td>
<td>306±108</td>
<td>372±105</td>
<td>0.570</td>
</tr>
<tr>
<td>TnT levels, (ng/ml)</td>
<td>112±45</td>
<td>134±50</td>
<td>0.458</td>
</tr>
<tr>
<td><strong>Location of IRA, (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>56</td>
<td>42</td>
<td>0.125</td>
</tr>
<tr>
<td>LCX</td>
<td>0.5</td>
<td>6</td>
<td>0.217</td>
</tr>
<tr>
<td>RCA</td>
<td>18.1</td>
<td>30</td>
<td>0.091</td>
</tr>
<tr>
<td>Other</td>
<td>25.4</td>
<td>22</td>
<td>0.875</td>
</tr>
<tr>
<td><strong>TIMI 3 post, (%)</strong></td>
<td>98</td>
<td>97.5</td>
<td>0.901</td>
</tr>
</tbody>
</table>
**Figure 6.2** Kaplan-Meier 9-month cumulative event-free survival (cardiac death, non fatal MI, and revascularization).

**Figure 6.3** Kaplan-Meier 9-month event free survival for end point of death.
6.3.4 CMR Evaluation
Seventy-five patients underwent CMR. One patient was excluded from the analysis due to incomplete image acquisition (due to claustrophobia) and 2 patients declined the follow-up scan at 3 months.
No differences on the baseline ejection fraction, volumes and IS were observed between the two groups. Post-procedural rate of MBG≥2 and ST-r >70% was higher in EM-PCI (89% vs 59% and 84% vs 40%, p=0.0001, respectively). In the acute phase greater incidence and extent of MVO was observed in the S-PCI vs EM-PCI (72.9% vs 31.5%, p=0.0005 and 3.7±2.6g vs 1.7±1.9g, p=0.0003, respectively); no differences were observed in IS (Table 6.4) (Figure 6.4).

### Table 6.5. CMR Results.

<table>
<thead>
<tr>
<th></th>
<th>S-PCI (n=37)</th>
<th>EM-PCI (n=38)</th>
<th>P value</th>
<th>S-PCI (n=37)</th>
<th>EM-PCI (n=36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute Phase</td>
<td>3-Month Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>137.5±18.6</td>
<td>131.5±14.4</td>
<td>0.1</td>
<td>144.5±20.3</td>
<td>136.2±19.9</td>
<td>0.08</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>77.4±15.4</td>
<td>71.3±17.3</td>
<td>0.1</td>
<td>76.1±16.5</td>
<td>69.3±17.7</td>
<td>0.09</td>
</tr>
<tr>
<td>EF (%)</td>
<td>44.3±9.5</td>
<td>46.3±8.6 #</td>
<td>0.3</td>
<td>46.7±10.6</td>
<td>49.0±9.3 #</td>
<td>0.3</td>
</tr>
<tr>
<td>IS (%)</td>
<td>13±6.7</td>
<td>14±12 §</td>
<td>0.6</td>
<td>11±8.7</td>
<td>9±4.5 §</td>
<td>0.2</td>
</tr>
<tr>
<td>IS (g)</td>
<td>14±7.5</td>
<td>17±15*</td>
<td>0.2</td>
<td>13±12</td>
<td>11±8.7*</td>
<td>0.4</td>
</tr>
<tr>
<td>MVO(n)</td>
<td>27 (72.9%)</td>
<td>9 (31.5%)</td>
<td>0.0005</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MVO (g)</td>
<td>3.7±2.6</td>
<td>1.7±1.9</td>
<td>0.0003</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

#p=0.08; § p=0.001; *p=0.004.
At 3 months a reduction in final IS was detected in EM-PCI (IS mass from 17±15g to 11±8.7g; p=0.004; IS% from 14±12% to 9±4.5%, p=0.001) whereas no changes were observed in S-PCI. MVO was not observed in either group at follow-up. However, when comparing infarct size between the 2 groups, a non significant difference was found both at baseline, and at follow-up.

6.4 DISCUSSION

In accordance with previous data manual thrombectomy improves MBG and increases ST-segment resolution in selected STEMI patients with angiographically visible thrombus. The present study showed a lower incidence and extent of MVO after recanalization and a reduced IS at 3 months in patients undergoing thrombectomy as compared to standard-treated group. To our knowledge this is the first study evaluating the effects of thrombectomy on MVO and IS using CMR.

CMR is a non-invasive and high resolution imaging modality that identifies myocyte necrosis (IS) and microvascular damage (MVO) providing in-vivo tissue characterization in patients with myocardial infarction. Poor contrast penetration due to microvascular
damage reflects the complex pathophysiological mechanisms of no-reflow, from endothelial cell swelling and contracture to microvascular plugging and microemboli of atherosclerotic debris.

Restoration of epicardial coronary blood flow by PPCI is highly successful in patients with acute myocardial infarction; however, this is not always followed by restoration of microvascular perfusion. Mechanical thrombus removal followed by direct stenting may explain the better results obtained in EM-PCI group. Conversely, mechanical damage occurring during pre-dilatation may explain the higher incidence and extent of MVO and IS detected in standard-treated patients.

Infarct shrinkage at five months was reported by Ingkanisorn\textsuperscript{12} and Baks\textsuperscript{5} (34% and 31% decrease in infarct size, respectively). In our study infarct size decreased at 3 months by 35% in the EM-PCI group and by 7% in the S-PCI group. In this latter group, impaired restoration of normal blood flow may have lead to inadequate scar healing. The smaller definitive IS may explain the lower incidence of MACE and the higher survival observed in EM-PCI group. Recently the TAPAS trial showed a surprisingly low rate of death in thromboaspiration group at 30 days and at 1 year follow-up.\textsuperscript{13} Improved myocardial reperfusion and higher infarct shrinkage achieved in EM-PCI group is likely related to a protective effect of thrombus aspiration on microvascular flow and might explain the significant lower incidence of cardiac death in the Export pre-treated patients. These findings are valuable despite the fact that the study was not powered to assess MACE.

In this cohort of patients we did not observed significant LV remodeling at 3 months. In agreement with Galiuto\textsuperscript{14}, there was a trend toward higher increase in end-diastolic volumes in S-PCI group. However, in our study population IS was relatively small; prompt revascularization and use of state-of-the-art pharmacological therapy could partially account for this. In conclusion, the most interesting findings of the study are a lower incidence of microvascular obstruction, and greater infarct shrinkage in the thrombectomy group compared to standard PCI suggesting a role of the microcirculation in infarct healing and particularly in infarct shrinkage. This latter aspect is further investigated in Chapter 7.

6.4.1 Study Limitations

This study represents a single-centre experience in a limited number of patients. Assessing MVO only on the 3 short-axis rest perfusion slices (basal, mid and apical) is likely to underestimate size of MVO. Some Authors have recently observed the presence of MVO in the delayed enhancement images.\textsuperscript{15} However, the classical definition of MVO
by CMR is based on the images acquired early after contrast injection (either first-pass imaging, as used in this study, or images acquired 1-3 minutes after contrast injection\textsuperscript{6}, MVO represents areas of poor contrast penetration but these areas usually ‘fill-in’ with time. Therefore assessing MVO in the late images could also potentially underestimate the areas of MVO. In fact, in the time frame of 15 minutes (as opposed to 1-3 minutes), these areas of poor contrast penetration could ‘fill-in’ with contrast. In conclusion, both methods (first pass perfusion with 3 representative short-axis slices or complete short-axis stack acquired at 15 minutes after contrast injection) present some advantages and limitations. Also, the limited number of patients recruited in the study and the relative small infarct size observed at baseline could account for the detection of a non-significant difference in infarct size between the 2 groups. Only patients with LAD infarcts were recruited in the CMR substudy and the results of the study should be therefore confined to this patients’ population, and not necessarily applicable to patients with infarcts in other coronary territories.

6.4.2 Conclusions

Manual aspiration thrombectomy preserves microvascular integrity and reduces final infarct size (greater infarct shrinkage) after STEMI, thus it may represent a useful adjunct to pharmacotherapy. Based on these findings, CMR could provide a very useful tool for large clinical trials on adjunctive therapies in PPCI.
References


9. The TIMI IIIA Investigators. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest. Results of the thrombolysis in myocardial ischemia (TIMI IIIA) Trial. Circulation 1993;87:38-52


CHAPTER 7
MICROVASCULAR DYSFUNCTION AFTER PCI BY CMR PERFUSION AND LATE GADOLINIUM ENHANCEMENT IMAGING.
IMPACT ON INFARCT HEALING AND LEFT VENTRICULAR REMODELLING

7.1 INTRODUCTION
Timely restoration of normal antegrade flow and tissue-level perfusion are both key factors in the reduction of mortality in ST-segment elevation myocardial infarction (STEMI). Despite restoration of epicardial blood flow with primary percutaneous coronary intervention (PCI), microvascular obstruction with reduced myocardial perfusion occurs in a large proportion of patients, contributing to increased infarct size, left ventricular (LV) remodelling and reduced survival.1,2,3 Cardiovascular magnetic resonance (CMR) can delineate with high resolution the presence and extent of infarct size and microvascular injury, both in patients with acute and chronic ischemic heart disease.4 The ability of CMR to identify infarcted and viable myocardium, microvascular damage and to perform sequential measurements of ventricular volumes, suggests that a great potential of this imaging technique to provide important insights into the pathophysiology of infarct healing and LV remodeling. Two methods have been described for the detection of microvascular obstruction using gadolinium-enhanced CMR: first-pass perfusion5,6 and late gadolinium enhancement (LGE)7. Currently, there is no consensus on the best technique to use and a number of clinical studies have used one or other3,8,9,10,11,12,13 or, in few cases, both techniques,14,15,16,17,18 yielding conflicting results on the significance and extent of microvascular obstruction by CMR.

Furthermore, the time course of microvascular damage, infarct size, infarct healing and LV remodelling after acute myocardial infarction (AMI) has not yet been completely clarified. Understanding the natural course of infarct healing and the effect of early reperfusion on ischemic myocardium might contribute to the understanding and development of new therapies for ischemic heart disease.

The purpose of the present study was to evaluate the predictive value of CMR characteristics of microvascular injury on recovery of global and regional LV function, and LV remodeling after primary PCI followed by optimal pharmacological treatment. In addition we sought to investigate the time-dependent complex relationship between microvascular dysfunction, infarct healing, and LV remodelling.
7.2 METHODS

7.2.1 Study Design and Population

This is a single-centre, prospective study on the impact of microvascular dysfunction on infarct healing and left ventricular remodelling. From February 2008 to March 2009 we prospectively enrolled forty-one consecutive patients presenting with a first STEMI undergoing primary PCI presenting at S.Donato Hospital in Arezzo, Italy. Inclusion criteria were: (1) confirmed first AMI and (2) successful primary coronary angioplasty, defined as Thrombolysis in Myocardial Infarction trial [TIMI] flow grade 3 and residual stenosis (<30%) within 6 hours of the onset of symptoms or between 6 and 24 hours if there was evidence of continuing ischaemia. Exclusion criteria were (1) IRA diameter stenosis <70% with TIMI grade 3 flow, or inability to identify IRA, (2) unsuccessful primary PCI, (3) rescue or facilitated PCI, (4) previous myocardial infarction, (5) significant other cardiac disease, (6) life-limiting non-cardiac disease, (7) contraindications to CMR (claustrophobia, pacemaker, implantable cardioverter defibrillator, cerebral clips). Other exclusion criteria were the absence of an optimal echocardiographic apical view and the presence of hemodynamic instability at the time of CMR. No upper age limit was used. Echocardiographic acoustic window was assessed in the emergency department or in the cath-lab by a cardiologist before the procedure. Patients with a poor image quality were not enrolled in the study. All participants gave written informed consent to the protocol and the study was approved by the local Ethics Committee. Angiographic markers of epicardial flow and tissue-level perfusion were assessed on completion of diagnostic coronary angiography and shortly after PCI. Blood samples for cardiac troponin (TnI), creatine kinase (CK), and CK-MB levels were obtained on admission and every 6 hours thereafter up to 48 hours and at 6, 12, 18, and 24 hours after PCI. Serial 2-dimensional echocardiographic and CMR studies were performed in each patient at baseline after PCI, at 1 month and at 6 months after the index infarction.

7.2.2 CMR Protocol

CMR was performed 5 ± 2 days after primary PCI, at 1 month and at 6 months using a 1.5 Tesla scanner (Signa CV/I, GE Medical Systems, Milwaukee, Wisconsin) with a cardiac dedicated 4-channel phased array receiver surface coil. A breath-hold steady-state free-precession (SSFP) pulse sequence with standard parameters was used to evaluate regional and global left ventricular function. A stack of short-axis
images were obtained encompassing the left ventricle from base to apex (typically 9-12 images), in addition to 2 long-axis views (vertical and horizontal long-axis views). Slice thickness was 8 mm with a slice gap of 2 mm. The matrix and field of view were 256 × 160 and 360 to 400 mm, respectively.

Rest myocardial perfusion was evaluated with a first pass technique using a single shot spoiled gradient echo pulse sequence (slice thickness 10 mm) during 40-50 consecutive heartbeats. Three short-axis slices (basal, mid cavity, and apical levels) were acquired injecting 0.1 mmol/kg of gadolinium-BOPTA (Multihance, Bracco, Milan, Italy) at 3 ml/s followed by 20 ml saline flush in the right anterocubital vein.

Late gadolinium enhancement (LGE) images were obtained using an inversion recovery prepared breath-hold gradient-echo technique 15 minutes after contrast injection. Typical image parameters were flip angle 25°; slice thickness 8 mm; slice gap 2 mm; number of excitations 1; matrix 256 × 192, field of view ranging from 340 to 400 mm. The inversion time was progressively optimized to null normal myocardium. Cine and LGE images were acquired at the same long- and short-axis slice position.

7.2.3 CMR Image Analysis

All measurements were performed by an expert operator blinded to clinical, angiographic, and echocardiographic data. Quantitative analysis was performed using a semi-automated software program (CMRtools, Cardiovascular Solutions, London, UK). Quantitative LV volumes, LVEF and LV mass were calculated from the short axis views excluding the papillary muscles. Regional wall motion and infarct-zone wall motion score index (IZ-WMSI) was assessed as described for echocardiography.

Infarct size and microvascular damage were calculated as previously described.12,13 Transmural segments were defined as myocardial segments with nearly transmural (>75% wall thickness) myocardial infarction; infarcted segments as myocardial segments with any degree of myocardial infarction (from 1% to 100% wall transmurality).

Microvascular damage was calculated in the rest first-pass perfusion images (microvascular obstruction, MVO) and on the LGE short-axis images (persistent microvascular obstruction, PMO). PMO was included in the infarcted area. MVO, PMO and IS are expressed in grams (assuming 1.05 g/ml as the specific gravity of the myocardium) and as a percentage of the LV mass. Presence and absence of MVO or PMO will be expressed as MVO+/PMO+ and MVO-/PMO-, respectively.
7.2.4 Echocardiography Image Analysis

Only one patient was excluded because of poor echocardiographic window at baseline. Two-dimensional echocardiographic images were analyzed by 2 readers who had no knowledge of the clinical, angiographic, and CMR data. Images were saved for off-line analysis. Regional wall motion was assessed according to the 16-segment model.\textsuperscript{19} For each segment, wall motion was scored as 1 (normal), 2 (hypokinetic), 3 (akineti\textsuperscript{c}), or 4 (dyskinetic). In each patient, an infarct-zone wall motion score index (IZ-WMSI) was derived by averaging the scores from each segment within the area at risk, as previously described.\textsuperscript{20} LV volumes and LV ejection fraction (LVEF) were measured with the modified Simpsons rule algorithm.\textsuperscript{21} Intraobserver and interobserver variability values in the evaluation of end-diastolic volumes were <5%, as previously reported.\textsuperscript{20} The definition used for LV remodelling was an increase of end-diastolic volume ≥20% at 6 months compared to baseline.\textsuperscript{1}

7.2.5 Statistical Analysis

Continuous data are expressed as a mean ± SD. Baseline data were compared by means of the chi-squared test for categorical variables and unpaired \textit{t} test for continuous variables. Changes in LV volumes, LVEF and IZ-WMSI (both by echocardiography and CMR) were analyzed by the analysis of variance (ANOVA) for repeated measurements, followed by a post-hoc analysis with a Bonferroni correction for differences between groups. A Student \textit{t}-test for independent groups was used to assess differences in continuous variables, while a Student paired-samples \textit{t}-test was used to highlight differences in left ventricular parameters at baseline, 1 month and at 6-months. A multivariate logistic regression analysis was conducted in all patients considering as dependent variable the occurrence of remodelling at follow-up (assessed by CMR) and, on a separate analysis, the occurrence of PMO. All the variables presenting a significance value <0.25 at univariate analysis were included in the model. A linear regression analysis was used to evaluate the relationship between CMR and echocardiographic parameters and between the AUC CK-MB and infarct size by CMR. Differences were considered statistically significant at 2-sided p-value of ≤ 0.05. Statistical analyses were performed with SPSS software v. 15.0.
Chapter 7  MVO, Healing and Remodelling

7.3 RESULTS

7.3.1 Baseline Characteristics

Of the 41 patients initially recruited, 37 patients completed the study protocol (31 men, mean age: 60±12 years; range: 35 to 82 years). Four patients were excluded due to incomplete imaging follow-up (CMR, n=2; echocardiography, n=2).

Clinical and angiographic characteristics of patients are showed in Table 7.1. Mean ST-segment elevation at baseline electrocardiogram was 11.8±7.5 mV; time from symptoms-to-first medical contact was 163±144 min, with a door-to-balloon time of 74±37 min.

Medical therapy at discharge included beta-blockers and ACE-inhibitors (in 89% and 86% of patients, respectively).

7.3.2 Angiographic Characteristics

All patients included in the study had successful PCI of the infarct related artery. All patients had single vessel disease. In 19 patients (51%) the culprit vessel was the left anterior descending artery (LAD), in 16 patients (43%) the right coronary artery (RCA), and the left circumflex artery (LCx) in 6% (n=2) of patients (Table 7.1). TIMI flow 0 pre-PCI was observed in 78% of the cases and TIMI flow 3 post-PCI was achieved in 97% of patients. Glycoproteins IIb/IIIa inhibitors were administered in 95% of the patients. The number of coronary lesions was 1.3±0.5 with a mean length of 14.4±4.7 mm. Complex coronary lesions (tandem lesions, calcification and bifurcations) were observed in 10% of patients.

7.3.3 Microvascular Damage and Infarct Size by CMR

MVO was more frequently observed than PMO (92% vs. 43% of patients, p=0.004) and involved a larger but non-significant myocardial extent (4.2±3.9 g vs. 3.0±5.2 g, respectively p=ns). Seventeen patients (46%) had MVO without PMO and 16 patients (43%) had MVO and PMO. MVO was always present in all patients with PMO. Only in four patients (11%) there was no MVO or PMO.

All patients had LGE in the territory of the culprit artery representing myocardial infarction. At baseline mean infarct size in all patients population was 28.4±20.7 g (15±10%). Infarct size was significantly larger in the PMO+ than in the PMO- group (42.5±22.6 g vs. 17.7±10.5 g, p<0.0001), with more total infarcted segments (n=6.6 ± 1.7 vs n=4.6 ± 2.1, p=0.005) and transmural infarcted segments than PMO- (n=5.3 ± 2.3 vs n=2.7 ± 2.4 p=0.002) (Table 7.2).
Table 7.1. Baseline demographics, clinical and angiographic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>60 ± 12</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>31 (84)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>7 (19)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>18 (49)</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>14 (38)</td>
</tr>
<tr>
<td><strong>Smokers</strong></td>
<td>20 (54)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>12 (32)</td>
</tr>
<tr>
<td><strong>Previous CAD</strong></td>
<td>3 (8)</td>
</tr>
<tr>
<td><strong>Previous PCI</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Previous CABG</strong></td>
<td>2 (5)</td>
</tr>
<tr>
<td><strong>Killip at presentation</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>34 (92)</td>
</tr>
<tr>
<td>II</td>
<td>2 (5)</td>
</tr>
<tr>
<td>III</td>
<td>1 (3)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Symptom-to-balloon time, min</strong></td>
<td>236 ± 155</td>
</tr>
<tr>
<td><strong>Symptom-first medical contact, min</strong></td>
<td>163 ± 144</td>
</tr>
<tr>
<td><strong>Door-to-balloon, min</strong></td>
<td>74 ± 37</td>
</tr>
<tr>
<td><strong>Peak MB, ng/ml</strong></td>
<td>301 ± 265</td>
</tr>
<tr>
<td><strong>AUC MB</strong></td>
<td>5462 ± 4562</td>
</tr>
<tr>
<td><strong>ST-segment elevation at baseline, mV</strong></td>
<td>11.8 ± 7.5</td>
</tr>
<tr>
<td><strong>ST-segment elevation at 90min, mV</strong></td>
<td>5 ± 4.7</td>
</tr>
<tr>
<td><strong>TIMI pre PCI</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29 (78)</td>
</tr>
<tr>
<td>1</td>
<td>4 (11)</td>
</tr>
<tr>
<td>2</td>
<td>4 (11)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Glycoprotein IIb/IIIa</strong></td>
<td>35 (95)</td>
</tr>
<tr>
<td><strong>Culprit vessel, n</strong></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>19 (51)</td>
</tr>
<tr>
<td>LCx</td>
<td>2 (6)</td>
</tr>
<tr>
<td>RCA</td>
<td>16 (43)</td>
</tr>
<tr>
<td><strong>Angiographic no-reflow</strong></td>
<td>8 (22)</td>
</tr>
<tr>
<td><strong>TIMI post PCI</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>3</td>
<td>36 (97)</td>
</tr>
<tr>
<td><strong>Beta-blockers at discharge</strong></td>
<td>33 (89)</td>
</tr>
<tr>
<td><strong>ACE inhibitors at discharge</strong></td>
<td>32 (86)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or numbers and percentage (%).
CAD= coronary artery disease; PCI= percutaneous coronary intervention; CABG= coronary artery bypass surgery; AUC MB= area under the curve CK-MB; TIMI= Thrombolysis in Myocardial Infarction; LAD=left anterior descending coronary artery; LCx= left circumflex coronary artery; RCA= right coronary artery
Table 7.2. CMR characteristics of patients with and without persistent microvascular obstruction.

<table>
<thead>
<tr>
<th></th>
<th>PMO- n=21</th>
<th>PMO+ n=16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with transmural infarct (&gt;51%), n</td>
<td>13 (62)</td>
<td>15 (94)</td>
<td>0.06</td>
</tr>
<tr>
<td>Infarcted segments, n</td>
<td>4.6 ± 2.1</td>
<td>6.6 ± 1.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Transmural segments (&gt;51%), n</td>
<td>2.7 ± 2.4</td>
<td>5.3 ± 2.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Segments with PMO, n</td>
<td>0</td>
<td>3.1 ± 1.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>MVO size, g</td>
<td>1.7 ± 1.4</td>
<td>5.6 ± 3.8</td>
<td>0.0003</td>
</tr>
<tr>
<td>PMO size, g</td>
<td>0</td>
<td>6.9 ± 6.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Baseline CMR**

<table>
<thead>
<tr>
<th></th>
<th>PMO- n=21</th>
<th>PMO+ n=16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, mL</td>
<td>136 ± 34</td>
<td>146 ± 23</td>
<td>ns</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>58 ± 22</td>
<td>68 ± 16</td>
<td>ns</td>
</tr>
<tr>
<td>EF, %</td>
<td>58 ± 9</td>
<td>53 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td>IZ-WMSI</td>
<td>1.8 ± 0.6</td>
<td>2.3 ± 0.7</td>
<td>0.008</td>
</tr>
<tr>
<td>IS, g</td>
<td>16.9 ± 10.4</td>
<td>42.5 ± 22.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>IS, % LV</td>
<td>10.0 ± 6.2</td>
<td>22.3 ± 11.0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**CMR at 1 month**

<table>
<thead>
<tr>
<th></th>
<th>PMO- n=21</th>
<th>PMO+ n=16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, mL</td>
<td>132 ± 36</td>
<td>155 ± 24</td>
<td>0.01</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>51 ± 23</td>
<td>75 ± 23</td>
<td>0.001</td>
</tr>
<tr>
<td>EF, %</td>
<td>62 ± 10</td>
<td>52 ± 11</td>
<td>0.005</td>
</tr>
<tr>
<td>IZ-WMSI</td>
<td>1.5 ± 0.6</td>
<td>2.2 ± 0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>IS, g</td>
<td>12.7 ±8.0</td>
<td>31.7 ± 18.0</td>
<td>0.001</td>
</tr>
<tr>
<td>IS, %</td>
<td>8.6 ± 5.7</td>
<td>18.4 ± 10.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**CMR at 6 months**

<table>
<thead>
<tr>
<th></th>
<th>PMO- n=21</th>
<th>PMO+ n=16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, mL</td>
<td>128 ± 41</td>
<td>159 ± 34</td>
<td>0.01</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>50 ± 23</td>
<td>76 ± 33</td>
<td>0.006</td>
</tr>
<tr>
<td>EF, %</td>
<td>63 ± 9</td>
<td>53 ± 10</td>
<td>0.008</td>
</tr>
<tr>
<td>IZ-WMSI</td>
<td>1.4 ± 0.4</td>
<td>1.9 ± 0.8</td>
<td>0.008</td>
</tr>
<tr>
<td>IS, g</td>
<td>12.5 ± 9.8</td>
<td>28.1 ± 14.8</td>
<td>0.001</td>
</tr>
<tr>
<td>IS, %</td>
<td>8.2 ± 6.0</td>
<td>16.0 ± 7.7</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (%) of patients.
PMO= persistent microvascular obstruction; CMR= cardiovascular magnetic resonance; IS=infarct size; EDV=end-diastolic volume; ESV=end-systolic volume; EF=ejection fraction; WMS=wall motion score; WMSI=wall motion score index; IZ-WMSI=infarct zone wall motion score index.
7.3.4 Microvascular Damage and Infarct Size by CMR versus Biomarker, Electrocardiographic and Angiographic Measures

Infarct size by CMR correlated with peak serum creatine kinase level ($r=0.7$, $p<0.0001$). There was a moderate correlation between the presence of PMO and baseline infarct size (Spearman $\rho=0.64$, $p<0.001$); a weaker correlation was observed with MVO (Spearman $\rho=0.48$, $p=0.002$). There was a statistically significant relation between MVO and PMO and TIMI frame count ($p=0.03$ and $p=0.03$, respectively), but not with TIMI flow grade. Infarct size by CMR correlated with baseline ST-elevation ($r=0.49$, $p=0.002$), ST-elevation at 90min ($r=0.45$, $p=0.005$) and ST-elevation at 180min ($r=0.59$, $p<0.001$). The presence of PMO was related to incomplete ST segment resolution ($p=0.03$), whereas no significant correlation was found with MVO.

**Table 7.3. Clinical, angiographic characteristics of patients with and without persistent microvascular obstruction.**

<table>
<thead>
<tr>
<th></th>
<th>PMO- ($n=21$)</th>
<th>PMO+ ($n=16$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms-to-balloon, min</td>
<td>209.4 ± 127.3</td>
<td>270.0 ± 185.0</td>
<td>ns</td>
</tr>
<tr>
<td>Door-to-balloon, min</td>
<td>69.0 ± 33.0</td>
<td>78.0 ± 42.0</td>
<td>ns</td>
</tr>
<tr>
<td>Symptoms-FMC, min</td>
<td>140 ± 118</td>
<td>192 ± 171</td>
<td>ns</td>
</tr>
<tr>
<td>Killip Class, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20 (95)</td>
<td>14 (88)</td>
<td>ns</td>
</tr>
<tr>
<td>2</td>
<td>1 (5)</td>
<td>2 (12)</td>
<td>ns</td>
</tr>
<tr>
<td>TIMI pre PCI, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (67)</td>
<td>15 (94)</td>
<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>3 (14)</td>
<td>1 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>2</td>
<td>4 (19)</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>TIMI post PCI, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21 (100)</td>
<td>15 (94)</td>
<td>ns</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>TFC, frames</td>
<td>14.6 ± 5.2</td>
<td>16.8 ± 7.4</td>
<td>ns</td>
</tr>
<tr>
<td>cTFC, frames</td>
<td>11.0 ± 2.7</td>
<td>12.6 ± 4.7</td>
<td>ns</td>
</tr>
<tr>
<td>AUC CK-MB</td>
<td>3904 ± 1223</td>
<td>7409 ± 2321</td>
<td>0.02</td>
</tr>
<tr>
<td>Patients with &gt;75% ST elevation at 180min, n</td>
<td>13 (62)</td>
<td>8 (50)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (%) of patients.
FMC= first medical contact; TIMI= Thrombolysis in Myocardial Infarction; PCI= Primary Coronary Intervention; TFC= TIMI Frame Count; AUC MB= Area under the Curve MB.
When grouping patients based on the presence and absence of PMO (PMO+ and PMO-, respectively), patients PMO+ presented more frequently with TIMI 0 flow pre-PCI, larger AUC of CK-MB. Symptom-to-balloon and door-to-balloon time were not different between patients PMO+ and PMO- (Table 7.3).

### 7.3.5 LV Function and LV Remodelling by Echocardiography

At baseline, patients PMO+ showed an increased end-systolic volume (ESV) (59±13 ml vs. 49±15 ml, p=0.03) and more impaired systolic function compared to PMO- (LVEF 50±5 % vs. 55±7%, p=0.03). No differences in EDV and IZ-WMSI between the two groups were detected at baseline (Table 7.4). LV remodelling was observed in 20% of the overall patient population. At 1- and at 6-month follow-up, LV volumes were consistently larger in the PMO+ group.

#### Table 7.4. Baseline, 1 month and 6 months echocardiography in patients with and without persistent microvascular obstruction.

<table>
<thead>
<tr>
<th></th>
<th>PMO- n=21</th>
<th>PMO+ n=16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echo at Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV, mL</td>
<td>109±28</td>
<td>119±20</td>
<td>ns</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>49±15</td>
<td>59±13</td>
<td>0.03</td>
</tr>
<tr>
<td>EF, %</td>
<td>55±7</td>
<td>49±5</td>
<td>0.03</td>
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<tr>
<td>IZ-WMSI</td>
<td>2.0±0.3</td>
<td>2.1±0.4</td>
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</tr>
<tr>
<td><strong>Echo at 1 month</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EDV, mL</td>
<td>108±31</td>
<td>134±25</td>
<td>0.01</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>47±21</td>
<td>67±21</td>
<td>0.01</td>
</tr>
<tr>
<td>EF, %</td>
<td>57±9</td>
<td>51±8</td>
<td>0.03</td>
</tr>
<tr>
<td>IZ-WMSI</td>
<td>1.5±0.6</td>
<td>1.9±0.6</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Echo at 6 months</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>EDV, mL</td>
<td>108±35</td>
<td>137±28</td>
<td>0.008</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>47±22</td>
<td>71±24</td>
<td>0.005</td>
</tr>
<tr>
<td>EF, %</td>
<td>57±8</td>
<td>50±9</td>
<td>0.01</td>
</tr>
<tr>
<td>IZ-WMSI</td>
<td>1.4±0.5</td>
<td>1.7±0.7</td>
<td>ns</td>
</tr>
</tbody>
</table>

EDV= end-diastolic volume; ESV= end-systolic volume; EF= ejection fraction; IZ-WMSI= infarct zone wall motion score index.
From baseline to 1-month and 6-month follow-up, a greater improvement in LVEF was observed in the PMO- group compared with patients PMO+ (from 55±7% to 57±9% to 57±7% vs 50±5% to 51±8 to 50±9%, p=0.009 by ANOVA) (Figure 7.1). Accordingly, a significant increase in EDV (119±20mL to 134±25mL to 137±28mL vs 109±28mL to 108±31mL to 108±35mL, p=0.02 by ANOVA) and a significant increase in ESV (59±13mL to 67±21mL to 71±24mL vs 49±15mL to 47±21mL to 47±22mL, p= 0.006 by ANOVA) were observed in the PMO+ group compared to PMO-. No significant changes in IZ-WMSI were detected.

**Figure 7.1 Serial LV volumetric evaluation by echocardiography.**

### 7.3.6 LV Function and LV Remodelling by CMR

At baseline, there was no significant difference in LV function between the PMO+ and PMO-group, except for a lower IZ-WMSI in the PMO+ group (p=0.008) (Table 7.2).

From baseline to 1-month and 6-month follow-up, a greater improvement in LVEF was observed in the PMO- group compared with patients PMO+ (from 58±9% to 62±10% to
63±9% vs 53±8% to 52±11 to 53±10%, p=0.01 by ANOVA). Accordingly, a significant increase in EDV (146±23mL to 155±24mL to 159±34mL vs 136±34mL to 132±36mL to 128±41mL, p=0.03 by ANOVA) and a significant increase in ESV (68±16mL to 75±23mL to 76±33mL vs 58±22mL to 51±23mL to 50±23mL, p= 0.007 by ANOVA) (Figure 7.2) were observed in the PMO+ group compared to PMO-. IZ-WMSI progressively improved over time in the 2 groups. However, in PMO- the improvement started to occur at 1 month (from 1.8±0.6 baseline to 1.5±0.6 1 month, p=0.03), and continuing to improve significantly at 6 months (1.5±0.6 1 month to 1.4±0.4 6 months, p=0.02).

In PMO+ improvement of IZ-WMSI was observed only later at 6 months (from 2.3±0.7 baseline to1.9±0.8 6 months, p=0.04). No significant improvements were seen between baseline-1 month and 1 month-6 months follow-up.

**Figure 7.2** Serial LV volumetric evaluation by CMR.

A significant strong correlation between CMR and echocardiography in the assessment of EDV (r=0.8, p<0.0001), ESV (r=0.9, p<0.0001), LVEF (r=0.9, p<0.0001) and wall motion
score index (WMSI) \( (r=0.8, \ p<0.0001) \) was demonstrated (\textit{Figure 7.3}). A good agreement between the two techniques was also observed in the Bland-Altman analysis (\textit{Figure 7.4}).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures.png}
\caption{Echocardiography vs CMR on the evaluation of LV volumes, systolic function and regional wall motion abnormalities. There is a good correlation between the two techniques in assessing global and regional left ventricular function.}
\end{figure}

\section*{7.3.7 Predictors of LV Functional Recovery and Remodeling}

The predictors of LV remodeling at the univariate analysis were baseline CMR ESV and EDV, baseline infarct size (%), presence of PMO, presence of diabetes and ST deviation at baseline. PMO+ was the strongest predictor of LV remodeling \( (p=0.032) \) followed by ST deviation at baseline \( (p=0.037) \) (\textit{Table 7.5}).

Among all the parameters considered the presence of microvascular obstruction (MVO) at first-pass perfusion, TIMI pre and TIMI post were not predictive of LV remodeling. In fact, MVO was observed in the majority of patients (92%), and TIMI 3 post-PCI achieved in 97% of the cases.
Table 7.5. Multivariate baseline predictors of LV remodeling.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio* (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMR EDV1, mL</td>
<td>0.950 (0.865-1.043)</td>
<td>0.2838</td>
</tr>
<tr>
<td>CMR ESV1, mL</td>
<td>1.004 (0.882-1.144)</td>
<td>0.9469</td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>0.918 (0.772-1.092)</td>
<td>0.3339</td>
</tr>
<tr>
<td>PMO+</td>
<td>1010.03 (1.808-564218.4)</td>
<td><strong>0.0321</strong></td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.736 (0.370-161.719)</td>
<td>0.1871</td>
</tr>
<tr>
<td>ST deviation baseline</td>
<td>1.248 (1.013-1.537)</td>
<td><strong>0.0374</strong></td>
</tr>
</tbody>
</table>

In **bold** statistical significant values.
CMR= cardiovascular magnetic resonance; EDV1= baseline end-diastolic volume; ESV1= baseline end-systolic volume; PMO+ = presence of persistent microvascular obstruction.
7.3.8 Predictors of Persistent Microvascular Damage

The parameters predicting the presence of PMO at the univariate analysis were time symptoms-first medical contact, baseline ESV and EF, number of infarcted segments, number of transmural segments and infarct size (Table 7.6). Among all these variables the only independent predictor of PMO at the multivariate analysis was infarct size (g) (p=0.002).

7.3.9 Time Course of Microvascular Damage by CMR

Although angiographic no-reflow was observed only in 8 patients (22%), microvascular damage by CMR (MVO or PMO) was identified in a larger percent of patients: MVO by first-pass perfusion imaging was present in almost all patients (34/37 patients, 92%) and it was localized in the subendocardium with a variable degree of transmural extension. This perfusion defect was superimposed to the infarcted area (as assessed in the subsequent LGE imaging), and its calculated size was 4.2±3.9g. PMO on LGE images was observed in 16 patients (43%), located predominantly within the infarcted area and appearing as a dark inner core; in patients PMO+ its calculated size was 3.0±5.2g.

MVO was larger in patients PMO+ than PMO- (5.6±3.8g vs 1.7±1.4g, p<0.0003).

The presence of PMO was always associated with MVO at first-pass perfusion (100% of patients). However, not all patients with MVO showed PMO in the late images (seen in only 53% of patients). PMO appears to be a better index of microvascular damage than MVO to predict LV remodelling, as demonstrated by the uni- and multi-variate analysis and with ANOVA.

There was no evidence of MVO and PMO on the CMR scans at 1 month and 6 months and these areas of hypoperfusion were replaced by myocardial scar.

7.3.10 Time Course of Infarct Healing by CMR

In all patients population baseline infarct size was 28.4±20.7g and decreased significantly by 34% at 6 months (18.8±13.3g) (p<0.0001).

Infarct size reduction (from baseline to 1-month and 6-month follow-up) was significantly greater in patients PMO+ (22.3±11.0% to 18.4±10.6% to 16.0±7.7%) than in PMO- (10.5±6.1% to 8.6±5.7% to 8.2±6.0%) (p< 0.006 by ANOVA). Shrinkage of infarct size occurred mainly between baseline and 1-month follow-up (p<0.0001 in both groups), followed by non-significant additional changes between 1- and 6-months (p=ns in both groups).
Table 7.6. Univariate and multivariate baseline predictors of PMO.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio* (95% CI)</th>
<th>p Value</th>
<th>Odds Ratio† (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms-FMC</td>
<td>1.003 (0.999-1.007)</td>
<td>0.173</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Door-to-balloon</td>
<td>0.999 (0.993-1.005)</td>
<td>0.677</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI pre</td>
<td>0.774 (0.353-1.699)</td>
<td>0.523</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI post</td>
<td>0.846 (0.069-10.327)</td>
<td>0.896</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR EDV1, mL</td>
<td>1.012 (0.989-1.035)</td>
<td>0.312</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR ESV1, mL</td>
<td>1.029 (0.992-1.067)</td>
<td>0.121</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR EF1, %</td>
<td>0.932 (0.856-1.014)</td>
<td>0.103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarcted segments, n</td>
<td>1.512 (0.973-2.351)</td>
<td>0.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmural segments, n</td>
<td>1.419 (0.991-2.031)</td>
<td>0.056</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct size, g</td>
<td>1.105 (1.022-1.195)</td>
<td>0.013</td>
<td>1.130 (1.047-1.220)</td>
<td>0.002</td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>1.140 (1.028-1.265)</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST elevation at baseline</td>
<td>1.044 (0.953-1.144)</td>
<td>0.350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50% 90min ST resolution</td>
<td>1.650 (0.421-6.464)</td>
<td>0.472</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75% 90min ST resolution</td>
<td>0.500 (0.128-1.949)</td>
<td>0.318</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Univariate analysis; † multivariate analysis. In *italics* parameters that entered the multivariate analysis and in **bold** statistical significant values. FMC= First Medical Contact; TIMI= Thrombolysis in Myocardial Infarction; EDV1= baseline end-diastolic volume; ESV1= baseline end-systolic volume; EF1= baseline ejection fraction.
7.4 DISCUSSION

To the best of our knowledge, this is the first in vivo, clinical and non-invasive serial evaluation (at baseline, 1 month, 6 months) of microvascular dysfunction and infarct size, their time course and impact on LV remodelling after successful primary PCI and optimal pharmacological treatment to prevent LV remodelling.

The main findings of this study are that (1) CMR can detect two degrees of microvascular dysfunction: PMO is the most severe form, associated with larger infarct size and strongly related to LV remodelling; MVO of less clinical relevance because highly prevalent; (2) microvascular dysfunction is a dynamic process with a peculiar time course, (3) infarct shrinkage is a phenomenon occurring early (within the first month after the acute event) in the evolving phase of myocardial infarction, mirroring the resolution of microvascular dysfunction (4) echocardiography and CMR are equally valuable in serial LV volumetric evaluation but CMR, giving its unique non-invasive tissue characterization, can delineate the nature and extent of myocardial/microvascular damage which play a pivotal role in LV remodelling.

7.4.1 Patterns and Time Course of Microvascular Dysfunction

In our patient cohort we identified 2 patterns of microvascular dysfunction: MVO at first-pass perfusion imaging and PMO at LGE imaging. This is the first study that analyzed both these aspects in 3 serial CMR scans. Other authors recently promoted the serial evaluation of microvascular obstruction at three different intervals (baseline, 3- and 6-months), but the results for the evaluation at 3 months were actually not formally presented and discussed.22

The main findings of our study on microvascular dysfunction are: 1) the size of MVO was consistently larger than PMO; 2) all patients that had PMO, necessarily presented MVO; 3) the presence of MVO does not necessarily imply the presence of PMO. All these observations have not been completely reported previously and demonstrate that microvascular obstruction is a dynamic process. In fact, as time progresses (minutes) the contrast agent ultimately ‘fills in’ the areas of microvascular dysfunction that present reduced contrast penetration. This explains why the areas of PMO are smaller than MVO, but also why not all patients with MVO present with PMO.

PMO was associated with larger infarct size, more transmural and infarcted segments by CMR, but also by clinical electrocardiographic, angiographic and biomarker measurements compared to MVO. This suggests that although MVO in first-pass perfusion was more sensitive in detecting microvascular damage, PMO had a greater clinical relevance.
Both MVO and PMO were detected only in the acute scan (Figure 7.4). Although this phenomenon was previously reported, its time course has not been completely clarified. The serial CMR evaluation performed in this patient cohort, demonstrated that at 1 month MVO and PMO were no longer present and replaced by myocardial scarring. This finding was also confirmed in the 6-month scan.

Interestingly, although angiographic no-reflow was present only in 22% of the patients, microvascular dysfunction at a myocardial tissue level defined by imaging was identified in 92% of the patients (when using MVO) or in 43% of the patients when considering PMO. This suggests that TIMI 3 flow post PCI alone it not an adequate parameter for assessing microvascular perfusion.

Studies using myocardial contrast echocardiography, similarly demonstrated that among patients with TIMI 3 flow, the extent of microvascular damage is the most powerful independent predictor of LV remodelling.\textsuperscript{23} However, compared to CMR, this imaging technique is limited in the accurate delineation of complementary aspect of myocardial damage such as infarct size and infarct shrinkage.

In the majority of previous studies MVO or PMO have been assessed qualitatively by using a semi-quantitative approach (score)\textsuperscript{15,16,18,16}. In this study MVO and PMO were assessed both qualitatively (presence/absence) and quantitatively (planimetry, g). Whether a precise quantitative approach, although provides insights on the extent of microvascular damage within the infarcted area, has an additional value over the qualitative evaluation remains unclear. However, similarly to infarct size, the accurate quantification of the extent of microvascular damage has been previously used by our group as a useful endpoint in clinical trials assessing reperfusion strategies.\textsuperscript{12,13}

### 7.4.2 Infarct Size, Microvascular Dysfunction and LV Remodelling

PMO was strongly associated with worse regional and global recovery, as demonstrated both by CMR and echocardiography. Whilst LV volumes were consistently larger, and systolic function more impaired, in patients with PMO+, IZ-WMSI progressively improved in both patients. Interestingly, a significant improvement was achieved earlier (1 month) in patients PMO-, whereas in PMO+ was observed later (6 months), suggesting more myocardial stunning in the latter group.

Bolognese et al reported that LV remodelling occurred in a relevant proportion (30%) of patients with AMI successfully treated with primary PCI.\textsuperscript{1} In our patients cohort the percent
of LV remodelling was 20% despite the large majority of patients were treated with beta-blockers and ACE-I.

In our study, infarct size was the strongest predictor of persistent microvascular damage (PMO), which in turn predicted LV remodelling. Also, larger and more transmural infarcts are more likely to present microvascular damage. These findings confirm the important relationship between infarct size, microvascular dysfunction and LV remodelling previously observed with CMR.\textsuperscript{11,11,18}

Echocardiography and CMR were equally valuable techniques to assess LV volumes and LV remodelling. Whilst echocardiographic is a widely available and can be performed at the
bedside, CMR has the intrinsic advantage of proving high resolution delineation of infarct size and microvascular dysfunction which are important determinants of LV remodelling.

### 7.4.3 Infarct Healing

Infarct healing is a dynamic process during which the necrotic tissue is replaced by collagenous contracted scar. Some of the underlying mechanisms are represented by the retraction of the collagen fibres, along with the “overestimation” of acute infarct size due to the myocardial oedema/inflammation and microvascular damage within the infarct zone, as earlier suggested by Reimer and Jennings.\(^{24}\) Although infarct healing is a complex process, infarct shrinkage (infarct remodelling) could be considering a surrogate.

In our study group, infarct size decreased by 34%. This is in agreement with previous reports: Hombach reported an infarct size reduction of 31\(\%\), Baks 31\(\%\) reduction at 5 months\(^9\); Inkangison and Choi found a reduction of 31\(\%\) and 27\(\%\), respectively.\(^{25,26}\) However, two novel aspects of our study are that 1) we investigated the time course of infarct healing at two different points in time (1 month, 6 months), 2) we studied the impact of microvascular dysfunction on infarct healing. The time frame of infarct healing was similar between the two groups, occurring at 1 month. However, the percentage of infarct size reduction was greater in patients with PMO+. No additional significant changes in infarct healing were observed between 1 and 6 months. Interestingly, 1 month after the acute event also coincides with the resolution of microvascular obstruction and its evolution into myocardial scarring was also completed.

Our results complement previous findings that in patients PMO+ a significant reduction of infarct size was only observed between 1 week and 2 months.\(^{18}\) This study is the first to demonstrate that infarct size reduction was greater in patients PMO+ than in patients without microvascular obstruction. This finding is consistent with the overestimation of infarct size in the acute phase, followed by the repair of microvascular damage and evolution in myocardial scarring.

### 7.4.4 Clinical Implications

CMR can identify and quantify areas of microvascular and myocardial damage in patients with STEMI treated with primary PCI. LV remodelling occurs in a significant percentage of patients despite successful recanalization of the IRA, restoration of perfusion at myocardial tissue level and optimal pharmacological treatment.
Microvascular damage as assessed by CMR is an important determinant of LV remodelling and infarct shrinkage, which occur at specific time frames. CMR could therefore provide potentially valuable endpoints for clinical trials that aim to assess the efficacy of different reperfusion strategies.

### 7.4.5 Study Limitation

The study was a single centre with limited patient population and the results should be confirmed in larger clinical studies. Due to the small sample size, we did not have adequate power to examine clinical endpoints and to directly compare the prognostic value of PMO and MVO. However, serial CMR examinations allowed us to assess the temporal course of microvascular dysfunction and the relative role of PMO and MVO in predicting functional recovery and LV remodeling.
References


CHAPTER 8
CARDIOVASCULAR MAGNETIC RESONANCE GUIDANCE FOR RECANALIZATION OF CORONARY CHRONIC TOTAL OCCLUSION

8.1 INTRODUCTION
One or more coronary chronic total occlusions (CTO) are identified in approximately one third of diagnostic coronary angiograms in patients with known or suspected coronary artery disease (CAD). The benefits of percutaneous coronary intervention (PCI) of a CTO are controversial for three main reasons: first, PCI of a CTO is technically challenging for the interventional cardiologist, with a lower success rate than achieved in other coronary lesions; secondly, the OAT trial demonstrated a lack of benefit of PCI versus medical therapy in patients with an occluded infarct-related artery. However, these results cannot be widely applied to patients with CTO (occlusion duration ≥ 3 months) because the OAT patient cohort presented with an occluded infarct-related coronary artery 3 to 28 days after acute myocardial infarction, and PCI was not guided by the presence of residual myocardial viability and ischemia; thirdly, the procedure can last several hours with significant radiation exposure, contrast dose and cost. Selection criteria aimed at identifying patients who can benefit from PCI of CTO have not yet been proposed. Cardiovascular magnetic resonance (CMR) is a high resolution non-invasive imaging technique that can assess regional and global left ventricular (LV) function, and detect the presence and the extent of infarction and ischemic burden. We therefore hypothesised that CMR could improve the selection of patients suitable for PCI of CTO.

8.2 METHODS
8.2.1 Study Design and Population
This was a single-centre, prospective study of patients with a CTO considered suitable for recanalization following coronary angiography. CTO was defined as the presence of TIMI 0 flow within the occluded artery with an estimated occlusion duration of ≥ 3 months, as suggested in the EuroCTO Club consensus document. CMR was performed 1 month before intervention and 3 months after recanalization. The CMR criteria for proceeding to
revascularization were: 1) a majority of the segments in the CTO territory had <75% transmural extent of infarction by late gadolinium enhancement (LGE) and 2) inducible myocardial ischemia was present in the CTO territory. Myocardial segments were assigned to coronary arteries as described in the American Heart Association 17 segment model, with 7 segments for the left anterior descending artery (LAD), 5 for the right coronary artery (RCA) and 5 for the left circumflex artery (LCx). If the LCx was dominant, 2 inferior segments were reassigned from the RCA to the LCx. Of the 52 patients initially recruited, 32 completed the study. The patient flow in the study is summarized in Figure 8.1. Exclusion criteria were: 1) significant other cardiac disease, 2) eGFR <30mL/min, 3) contraindications to CMR (eg; claustrophobia, pacemaker, implantable cardioverter defibrillator, cerebral clips), 4) contraindication to adenosine (eg; severe asthma, >first degree heart block). All participants gave written informed consent and the study was approved by the local Ethics Committee.

Figure 8.1. Patients flow in the study.
8.2.2. CMR Image Acquisition

CMR was performed in a 1.5T scanner (Avanto, Siemens) with a dedicated cardiac 8-channel phased array receiver surface coil. Cine images were obtained with a steady-state free-precession (SSFP) sequence in 2 long-axis and multiple contiguous short-axis views encompassing the left ventricle (LV) from base to apex. Typical image parameters were: TE 1.6ms, TR 3.2ms, time per cine frame 51ms, α 60 degrees, matrix 256x256, slice thickness 8mm, gap 2mm. First-pass stress perfusion imaging was performed using a 3-slice (basal, mid-cavity and apical views) hybrid-EPI sequence with T-SENSE (TR 5.8ms, TI 110-140ms, FOV 360x270mm, voxel size 2.8 x 2.8 x 10mm) over 50 consecutive cardiac cycles. The images were acquired after 4 minutes of 140µg/kg/min adenosine infusion and following the injection of 0.1mmol/kg of Gd-DTPA. Late gadolinium enhancement (LGE) images were acquired 10-15 minutes after gadolinium injection in long and short-axis planes, using a segmented inversion recovery gradient echo sequence (TR 600ms, TE 3.8ms, α 25 degrees, slice thickness 8mm, gap 2mm, typical pixel size 1.7 x1.4mm). The inversion time was progressively optimised and adjusted to adequately null normal myocardium (typical values 320-440ms). Cine and LGE images were acquired at the same long- and short-axis slice position. Finally, first-pass rest perfusion images were acquired >20 minutes after stress perfusion imaging.

8.2.3. CMR Image Analysis

Image analysis was performed by an experienced operator blinded to the clinical and angiographic data, using semi-automated software (CMRtools, Cardiovascular Imaging Solutions, London, United Kingdom). Quantitative LV volumes, LV ejection fraction (EF) and LV mass were calculated from the short axis views excluding the papillary muscles. The images were assessed according to the AHA/ACC 17 segment model. For each segment, wall motion was scored as 0 (normal), 1 (mildly hypokinetic), 2 (severely hypokinetic), 3 (akinetic), or 4 (dyskinetic). Infarcted myocardial mass was calculated from the LGE images. Myocardial regions were considered infarcted if the signal intensity was >5 SD above the remote myocardium. Myocardial perfusion reserve (MPR) was calculated in all CTO and remote myocardial territories as previously described. The extension of the perfusion defect was also scored visually in each segment as 0 (normal), 1 (defect <25% wall thickness), 2 (defect 25-50%), 3 (defect 50-75%), 4 (>75%), and its sum identified the visual perfusion score.
8.2.4 CTO Revascularization
In the majority of cases (>70%) patients were treated using a bilateral anterograde approach (right and left femoral artery puncture). This approach was attempted using microcatheters or OTW balloon for support and wire exchange, wires used included the Miracle, Confianza and Fielder XT (Asahi Intecc, Japan). Retrograde coronary approach was mainly attempted in 25% of the patients after 1 or more unsuccessful anterograde attempts.

8.2.5. Seattle Angina Questionnaire
The Seattle Angina Questionnaire (SAQ) is a widely used questionnaire to assess health outcome measures in patients with CAD. In our study, we used the UK version of the SAQ which consists of 14 items that measure three different aspects of quality of life: a seven-item scale of physical limitations (how daily activities are limited by angina), a four-item angina frequency and perception scale (frequency of symptoms and use of medications, and effect of angina on quality of life), a three-item treatment satisfaction scale. All items use five-point descriptive scales and scores are calculated by summing all the single scores within each group and transforming them to a 0-100 scale, where 0 is the worst and 100 is the best. The questionnaire was given to the patients at the time of their CMR scans (baseline and follow-up).

8.2.6. Statistical Analysis
Continuous normal data are expressed as mean ± SD. Wilcoxon paired-sample test or Student paired-sample t test respectively were used to compare paired non-parametric and parametric data before and after revascularization. Chi-squared test was used to compare categorical variables. Differences were considered statistically significant with a 2-sided p-value of ≤ 0.05. Statistical analyses were performed with SPSS software v12.

8.3 Results
8.3.1 Clinical and Angiographic Data
Thirty-two patients completed the study (94% men, mean age 65±9 years). Sixteen patients were excluded due to: absent myocardial viability in a majority of segments (n=6), absence of inducible myocardial ischaemia (n=7), and failed PCI to CTO at the second attempt (n=3) (Figure 8.1). Baseline characteristic are shown in Table 8.1. There was a high incidence of cardiovascular risk factors, and the majority of patients had previous myocardial infarction
(MI, n=21, 66%), previous PCI (n=13, 41%) and multi-vessel disease (n =21, 66%). Some patients had previous PCI to a CTO artery (n=3, 9%). There was a 28% incidence of previous failed PCI to CTO. Collaterals were present in 70% of the patients. There was a low incidence of symptoms: the majority of patients had limited or no angina (CCS class I and II) (n=26, 81%) and NYHA functional class I and II (n=21, 66%). The angiographic characteristics of the CTO are summarized in Table 8.2. The majority of the vessels recanalized were right coronary artery (62%) with the remainder being left anterior descending artery (38%).

8.3.2. LV Function

From baseline to follow-up, there was significant decreased of end-systolic volume (ESV) from 65 ±38mL to 56 ±38mL (p<0.001) with no significant change in end-diastolic volume (EDV) (166 ±42mL to 161 ±42mL, p=0.18) (Figure 8.2). LVEF increased from 62 ±13% to 67 ±12% (p<0.0001). Baseline regional wall motion was abnormal in 19 patients (58%) and improved after revascularization in 47% of the patients. Visual wall motion score improved from 5.9 to 4.5 (p=0.003).

8.3.3. Presence and Extent of Myocardial Ischaemia

The presence of reversible perfusion defect was identified in all 32 patients, and was limited to the subendocardium in 12 (37%) patients, transmural or near transmural in 4 (13%) patients, and peri-infarct ischemia in the subepicardial viable rim was detected in 16 (50%) patients (Figure 8.3). A complete or near-complete resolution of ischemia after PCI was seen in 90% of patients (p<0.0001) (Figure 8.4). Visual perfusion score improved from 10.9 to 1.6 (p< 0.0001).

8.3.4. Myocardial Perfusion Reserve

At baseline, MPR in the CTO territory was reduced compared to remote territory (1.8 ±0.7 vs 2.2 ±0.7; p=0.01; Figure 8.5), and improved significantly after recanalization (to 2.3 ±0.9; p=0.02) and was similar to the remote territory (2.5 ±1.2; p=ns). There were no differences of MPR in the remote territory before and after PCI.
Table 8.1. Baseline demographics, clinical and angiographic characteristics

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age, [years]</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Males</td>
<td>30 (94%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>24 (75%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (66%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>23 (72%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (22%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>22 (69%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>21 (66%)</td>
</tr>
<tr>
<td>Previous PCI to CTO</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Previous PCI, other vessel</td>
<td>13 (41%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>21 (66%)</td>
</tr>
<tr>
<td>CCS class at presentation</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11 (34%)</td>
</tr>
<tr>
<td>II</td>
<td>15 (47%)</td>
</tr>
<tr>
<td>III</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>NYHA class at presentation</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12 (38%)</td>
</tr>
<tr>
<td>II</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>III</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Medication at presentation*</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>31 (97%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>24 (75%)</td>
</tr>
<tr>
<td>Statin</td>
<td>32 (100%)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>21 (66%)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>20 (62%)</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (%) of patients. CAD= coronary artery disease; MI= myocardial infarction, CABG= coronary artery bypass surgery, PCI= percutaneous coronary intervention; CTO= chronic total occlusion, CCS= Canadian Cardiovascular Society, NYHA= New York Heart Association.

*Medications post-recanalisation did not change significantly.
Table 8.2. Angiographic and revascularization characteristics

<table>
<thead>
<tr>
<th>CTO vessel</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>20 (62%)</td>
</tr>
<tr>
<td>LAD</td>
<td>12 (38%)</td>
</tr>
<tr>
<td>LCx</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of collaterals</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous failed PCI to CTO</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>Retrograde approach</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>Tapered stump</td>
<td>27 (66%)</td>
</tr>
<tr>
<td>Total stent length [mm]</td>
<td>64 ± 34</td>
</tr>
<tr>
<td>Maximum balloon size [mm]</td>
<td>3.2 ± 1.1</td>
</tr>
<tr>
<td>Maximal balloon pressure [atm]</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Number of wires</td>
<td>3 ± 1.3</td>
</tr>
<tr>
<td>Final TIMI 3 flow</td>
<td>34 (83%)</td>
</tr>
<tr>
<td>Fluoroscopy time [min]</td>
<td>55 ± 25</td>
</tr>
<tr>
<td>Contrast volume [mL]</td>
<td>382 ± 115</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (%) of patients. CTO= chronic total occlusion; RCA= right coronary artery; LAD= left anterior descending coronary artery; LCx= left circumflex coronary artery; PCI= percutaneous coronary intervention.
Figure 8.2. Left ventricular volumes and ejection fraction assessed by cine CMR before and 3 months after CTO recanalization.

Figure 8.3. Stress perfusion and LGE in a patient with CTO of the RCA. Adenosine stress perfusion images (top panel) show the presence of subendocardial inducible defect in the basal and mid-cavity inferior wall (white arrows), not present at rest (middle panel). Late gadolinium enhancement (LGE) images demonstrate a viable inferior wall with absent myocardial enhancement (=no infarction) (bottom panel).
Figure 8.4. Stress perfusion and LGE in patient with CTO of the LAD. The LAD is proximally occluded (top panel, white arrowhead) and adenosine stress perfusion demonstrated inducible perfusion defect in the mid-cavity and apical septum (top panel, white arrow). After recanalization, adenosine stress perfusion showed complete resolution of the inducible perfusion defect previously observed (bottom panel).

Figure 8.5. Myocardial perfusion reserve (MPR) before and after revascularization in the CTO and remote coronary artery territories.
8.3.5. Presence and Extent of Myocardial Infarction
In the 32 patients, 12 (38%) had no myocardial infarction (MI), 15 (47%) had subendocardial infarct (<50% transmurality), and in 5 (16%) patients, MI was 50-75% transmural but with peri-infarct ischemia. Mean MI size was 11.5 ± 9.3 g. At follow-up, new but limited post-procedural MI was identified in 8/32 patients (25%). In particular, we observed septal perforation in 3 patients (38%) (size of new myocardial damage: 0.65 g), distal embolization in 2 patients (25%) (0.42 g), and side-branch impairment in 3 patients (38%; 10.6 g).

8.3.6. Quality of Life Questionnaire
The total SAQ score significantly improved from 59 to 86 after recanalization (p<0.0001). The SAQ individual subgroup components also improved: physical limitation (Phys Lim) from 63 to 83 (p<0.0001), treatment satisfaction (Treat Sat) from 74 to 95 (p<0.001), and frequency and perception (Freq Perc) from 42 to 78 (p<0.0001) (Figure 8.6).

Figure 8.6. Seattle Angina Questionnaire before and after revascularization. The first column represents the total score. The other three columns represent individual subgroup components of physical limitation (Phys Lim), treatment satisfaction (Treat Sat) and frequency and perception (Freq Perc).

8.4 DISCUSSION
The main findings of this study are that: 1) CMR can select patients suitable for PCI of CTO by demonstrating myocardial viability and the presence of inducible myocardial ischemia; 2) recanalization of CTO guided by CMR reduces ischemic burden and improves left ventricular function; 3) successful revascularization is associated with health outcome measures. To our
knowledge, this is the first study prospectively assessing the role of CMR in guiding the selection of patients with CTO for revascularization.

8.4.1. CTO Recanalization and Improvement of LV Function

Changes in left ventricular volumes, function and wall motion after successful recanalization of CTO have been demonstrated in small series with mixed results. Sirnes described improvement in EF and regional radial shortening from baseline to 6 months assessed by left ventricular angiography.\textsuperscript{12} EF improvement using left ventricular angiography was also reported by the Total Occlusion Study of Canada (TOSCA) investigators; this was, however, confined to patients with recent occlusions (<6 weeks), compared to those with longer duration of occlusion (>6 weeks).\textsuperscript{13} More recently, a significant decrease in ESV and EDV, without significant change in EF, was reported using cine CMR after revascularization in CTO patients.\textsuperscript{14,15} Fiocchi used low-dose dobutamine CMR to predict functional recovery, and found improved EF and systolic wall thickening at 6 months after recanalization.\textsuperscript{16} Pavlovic demonstrated a significant reduction in EDV using gated SPECT, but no improvement in ESV or EF.\textsuperscript{17} The discrepancy in LV functional recovery after recanalization reported in these studies could relate to small sample size (usually 20 patients) and the different imaging techniques applied. We studied a larger cohort of patients with >3 months chronic total occlusion using CMR as a gold standard imaging technique and showed a significant improvement of EF with improved regional wall motion and reduction of ESV, but no changes in EDV.

8.4.2. CTO and Myocardial Viability

CMR can identify the presence and extent of viable but dysfunctional myocardium, and predict its recovery following successful revascularization.\textsuperscript{18} In our study, we demonstrated that the majority of patients with CTO in our cohort have limited or no MI, and therefore have the potential to improve ventricular function after successful recanalization. In selected patients with CTO of the LAD, Bellenger demonstrated with dobutamine CMR that the extent of viable myocardium in the infarct zone is related to improvements in left ventricular remodelling in patients undergoing late recanalization of an occluded infarct related artery.\textsuperscript{19} In particular, they observed a significant relation between the number of viable myocardial segments in the infarct zone and the improvement in ESV and EF. Additional small studies have also reported that myocardial segmental wall thickening improved significantly in segments with no or subendocardial infarction, whereas no improvement was observed in
segments with almost full thickness myocardial scar. In our study, patients were only considered candidates for CTO recanalization if myocardial viability was present in a majority of CTO territory segments and inducible myocardial ischemia was present. The majority of patients (84%) in our cohort had no or limited myocardial infarction; larger myocardial infarction but with peri-infarct ischemia was demonstrated only in 16% of patients. Another factor possibly affecting viability and patient choice for CTO is the presence of collaterals, which were present in 70% of patients. Although controversial, the development of collaterals does not depend on the presence of viable myocardium. Whilst myocardial ischemia triggers the development of collaterals, they may not be completely protective against myocardial ischemia, and this was borne out in our cohort in which myocardial ischemia was detected despite the presence of functioning collaterals. Also, infarct size was predominantly limited in keeping with the evidence that in patients with acute MI, infarct size can be smaller up to 35% in the presence of collaterals.

8.4.3. CTO Recanalization and Resolution of Ischaemia
Pavlovic demonstrated improved perfusion in the CTO territory 1 year after successful recanalization by 99mTc SPECT. CMR is an alternative radiation-free imaging modality with increased spatial resolution for monitoring the ischemic burden. In a small cohort of 17 patients, Cheng demonstrated that PCI of CTO improved regional hyperemic myocardial blood flow that persisted at 6 months. Our study confirms these findings in a larger scale. Complete or almost complete resolution of perfusion defect (qualitative assessment) was coupled with an increased MPR (quantitative assessment). We also demonstrated that after successful recanalization, normal perfusion was restored in the treated segments to a similar extent as in the remote myocardium.

8.4.4. CTO Recanalization and Quality of Life
The measurement of health status is important for assessing the outcomes of patients with CAD. The effect of PCI on quality of life in patients with stable coronary artery disease has been investigated by the COURAGE trial, demonstrating a marked improvement in health status in patients treated with PCI versus those treated with optimal medical therapy. This, however, disappeared at 36 months. Quality of life was also assessed by OAT trial investigators that found that PCI was associated with a marginal advantage in cardiac physical function at 4 months, but not thereafter, and no difference in the psychological well-being aspect of quality of life. Our study is the first to selectively assess quality of life with the
Seattle questionnaire after PCI in a population with CTO. In our study, all patients underwent PCI guided by the presence of myocardial viability and ischemic burden by CMR, while in OAT and COURAGE imaging was carried out only in a subgroup of patients. These two aspects have not been combined in previous studies. Interestingly, the ischemic burden was reduced and quality of life improved also in those patients with limited symptoms (mainly in CCS I-II).

8.4.5. Clinical Implications
There are many economic disincentives to CTO recanalization. These procedures are technically challenging and require a long learning curve, longer procedural times, greater contrast volume use and radiation exposure, as well as more material utilization. Our study suggests that CMR might play a role in improving patient selection for revascularization, helping in directing resources to those patients most likely to benefit from the procedure with reduced ischemic burden, improved LV function and quality of life.

8.4.6. Study Limitations
No consensus exists with regards to the definition of CTO and in some patients the age of the CTO cannot be determined with confidence. This is a single centre study and the rate of success in CTO recanalization with anterograde and retrograde approach reflects the experience of a single operator. The findings of this study are hypothesis generating and should be confirmed in larger randomised trials using CMR to guide intervention.

8.4.7. Conclusion
CMR identifies myocardial viability and inducible myocardial ischemia in a majority of patients with CTO. Revascularization of these patients reduces ischemic burden, improves LV EF and improves health outcomes.
References


20 Werner GS. Collaterals, how important are they? Heart 2007;93:778–779.


CHAPTER 9

NOVEL PROTOCOL FOR PERFUSION IMAGING

9.1 INTRODUCTION

Non-invasive evaluation of myocardial perfusion with cardiovascular magnetic resonance (CMR) is clinically useful in patients with known or suspected coronary artery disease (CAD)\(^1,2,3,4\) and is also valuable for clinical research.\(^5\) Despite many comparison studies\(^6,7,8,9,10,11,12\), the perfusion protocol (pulse sequence, contrast agent dose and injection parameters) giving highest diagnostic confidence is not yet standardised.\(^13\)

Unfortunately, dark rim artefacts which mimic genuine perfusion defects remain a diagnostic problem. The three identified different likely sources of dark rim artefacts\(^4,14\) are: Gibbs artefact\(^15\), cardiac motion\(^16\) and magnetic susceptibility effects from the transient high concentration of the contrast agent.

Fast single-shot gradient echo (FLASH) is the most established and robust sequence but its coarse temporal resolution (~180ms per image without parallel RF acceleration) limits the acquisition of numerous imaging planes, especially during stress. The intrinsic advantage of hybrid echo-planar imaging (EPI) over FLASH is that it collects multiple data lines after each radiofrequency pulse and the smaller number of RF pulses may in some circumstances confer an increased contrast-noise ratio (CNR).\(^10\) In addition, the shorter imaging time (~75ms per image) makes EPI less prone to artefacts caused by cardiac motion than slower sequences.

However, a fast multiple echo readout of EPI is required for its reliability with respect to off-resonance errors, and this reduces its image signal-to-noise ratio (SNR) compared to balanced steady state free precession (SSFP) or even FLASH imaging. All first-pass CMR perfusion techniques suffer from suboptimal SNR, which particularly affects EPI, usually mandating the use of a higher dose of contrast agent. More recently, SSFP sequences have been used, but experience is limited.\(^7,9,11\) Compared with FLASH, SSFP has superior performance, providing higher SNR and CNR,\(^17\) but the longer imaging time than EPI (~125ms per image) but not FLASH, increases motion related dark rim artefacts. In principle, the intrinsic high SNR of SSFP allows the use of lower dose contrast agent however, which could reduce dark rim artefacts.
The aim of our study was therefore to compare first pass myocardial perfusion imaging using a hybrid-EPI sequence at full contrast dose versus SSFP at half contrast dose.

9.2 METHODS

9.2.1 Study Design and Population

We studied 17 patients (14 men, mean age 54 ± 9 years, table 1) with known or suspected CAD scheduled for x-ray coronary angiography, with all patients undergoing both first-pass perfusion protocols. Perfusion imaging with EPI was the standard clinical investigation; patients were then invited to participate in the SSFP trial within a week of the initial scan. Patients with contraindication to CMR or adenosine were excluded. Subjects abstained from caffeine containing products for 24 hours prior to each study.

All patients participating in the study had a glomerular filtration rate (GFR)> 30 mL/min/1.73m². The study was approved by the local ethics committee and each participant gave written informed consent.

Patient characteristics are described in Table 9.1.

Table 9.1 Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>Males</td>
<td>14 (82)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Smokers</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2 (17)</td>
</tr>
</tbody>
</table>

Values are mean ± SD (%). PCI= percutaneous coronary intervention; CABG= coronary bypass graft
9.2.2 CMR Image Acquisition

Patients underwent CMR in a 1.5T scanner (Avanto, Siemens) with a cardiac dedicated 12-channel phased array receiver surface coil (6 anterior and 6 posterior coil elements). Stress perfusion images were acquired for 50 cycles, covering the left ventricular first-pass, after 4 minutes of 140µg/kg of intravenous adenosine infusion. Patients held their breath as long as comfortable at end-expiration. Resting perfusion images were acquired >20 minutes after stress using identical acquisition parameters. Heart rate was monitored continuously and blood pressure measured preceding and 3 minutes following initiation of adenosine infusion. Eleven patients received Gadopentate dimeglumine (0.5mol/L, Bayer Shering) at the dose of 0.1mmol/kg for the EPI sequence and 0.05mmol/kg for SSFP sequence. Contrast was injected in the contralateral antecubital fossa to the adenosine infusion at 7mL/s with 15mL saline flush at 7mL/s. The last six patients enrolled in the study received 0.1mmol/Kg of Gadobutrol (1mol/L, Bayer Schering) for EPI and 0.05mmol/kg for SSFP, injected at 3.5mL/s followed by a 15mL saline flush at 7mL/s. The change of contrast agent during the study coincided with changes in our departmental policy because of concerns related to the association of nephrogenic systemic sclerosis and use of gadolinium chelates. All patients received the same contrast dose for the EPI and SSFP studies.

Centre-out hybrid EPI (TR 5.8ms, 30°, echo train length, ETL 4, 1860Hz/pixel) acquired 2.8 x 2.8 x 8mm voxels over typically 360x270mm FOV (adapted per patient) at TI=110-160ms for each of 3 fat-suppressed slices per cycle, using TSENSE (R2), typical image time 75ms (excluding prepulses). Linear-ordered SSFP (TR 2.6ms, 70°, 930Hz/pixel) acquired the same voxel size at the same TI for central k-space for each of 3 fat-suppressed slices per cycle, using TSENSE (R2), typical image time 125ms (Table 9.2). The slice acquisition order was the same in EPI and SSFP, resulting in approximately similar image timings through the cardiac cycle in both. To ensure consistent imaging, perfusion short-axis slice positions were reproduced by viewing the first study while piloting the second and using identical slice separation.
Table 9.2 Pulse sequence parameters.

<table>
<thead>
<tr>
<th></th>
<th>Pulse Sequence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPI</td>
<td>SSFP</td>
</tr>
<tr>
<td><strong>Contrast dose</strong></td>
<td>0.1 mmol/kg</td>
<td>0.05 mmol/kg</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>5.8</td>
<td>2.6</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Flip angle</td>
<td>30°</td>
<td>70°</td>
</tr>
<tr>
<td>Read FOV (cm)</td>
<td>36x27</td>
<td>36x27</td>
</tr>
<tr>
<td>TI (ms)</td>
<td>110-160</td>
<td>110-160</td>
</tr>
<tr>
<td>Image data acquisition time (ms)</td>
<td>75</td>
<td>125</td>
</tr>
<tr>
<td>Bandwidth (Hz/pixel)</td>
<td>1860</td>
<td>930</td>
</tr>
<tr>
<td>Parallel acquisition method</td>
<td>TSENSE</td>
<td>TSENSE</td>
</tr>
<tr>
<td>Effective acceleration factor (R)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

9.2.3 CMR Image Analysis

All image analysis was performed offline using dedicated software (CMRtools, Cardiovascular Imaging Solutions, UK). Scans were anonymized and randomised; 2 blinded experienced observers scored them based on the AHA/ACC 16-segment model. The diagnostic confidence of perfusion scans was assessed subjectively (score from 0=unusable to 4=excellent). Stress perfusion scans were scored as normal (no perfusion defect), abnormal (true perfusion defect) or dark-rim artefact. Dark-rim artefacts were identified based on transience, particularly the temporal correlation of a dark rim with blood brightness, or if the artefact was also clearly present at rest in segments that showed no late gadolinium enhancement. Other artefacts such as parallel imaging effects were not scored. A total of 544 segments were analyzed (272 segments per sequence).

9.2.4 Statistical Analysis

Scan results were compared to coronary angiography as the gold standard for CAD, and chi-squared was used to compare the proportion of dark-rim artefacts in the two sequences. Comparison of agreement between observers and scan methods was assessed by kappa coefficients.
9.3 RESULTS

The three major coronary arteries and their first-order branches >2mm were assessed. Significant CAD (>50% stenosis) was detected in 6/17 patients (35%). Eleven patients had unobstructed coronary arteries: smooth coronary arteries (n=8) or with minor atheroma (n=3). There was no significant difference in the hemodynamic recordings between the two studies (Table 9.3).

Table 9.3. Hemodynamic response during the 2 perfusion scans

<table>
<thead>
<tr>
<th></th>
<th>EPI</th>
<th>SSFP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>69 ± 11</td>
<td>65 ± 9</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>133 ± 15</td>
<td>131 ± 17</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>81 ± 12</td>
<td>78 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>96 ± 15</td>
<td>92 ± 25</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>132 ± 20</td>
<td>135 ± 19</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>78 ± 11</td>
<td>79 ± 14</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean ± SD. BP= blood pressure.

9.3.1 Agreement Between Scans

According to Observer 1, EPI and SSFP agreed on normal perfusion in 151 segments, the presence of dark-rim artefacts in 8 segments and stress perfusion defects in 19 segments. According to Observer 2, EPI and SSFP agreed on normal perfusion in 117 segments, dark-rim artefact in 2 segments and stress perfusion defects in 25 segments. The agreement between SSFP and EPI scans on the presence of normal perfusion, dark-rim artefact, genuine perfusion defects was 68% (k=0.25, 95% CI: 0.18-0.30, p<0.0001) for observer 1 (Table 9.4) and 56% (k=0.14, 95% CI: 0.09-0.20, p<0.0001) for observer 2 (Table 9.5).

Table 9.4. Agreement between sequences for observer 1.

<table>
<thead>
<tr>
<th></th>
<th>SSFP</th>
<th>0</th>
<th>99</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>123</td>
<td>13</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>56</td>
<td>26</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td><em>Total</em></td>
<td>179</td>
<td>39</td>
<td>218</td>
<td></td>
</tr>
</tbody>
</table>
Table 9.5. Agreement between sequences for observer 2.

<table>
<thead>
<tr>
<th></th>
<th>EPI</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSFP</td>
<td>Observer 1</td>
<td>Observer 2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>93</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>178</strong></td>
<td><strong>40</strong></td>
<td><strong>218</strong></td>
</tr>
</tbody>
</table>

9.3.2 Agreement Between Observers

For EPI scans, Observer 1 and 2 agreed on normal perfusion in 195 segments and stress perfusion defects in 31 segments. There were no segments with agreed dark-rim artefact.

For SSFP scans, observer 1 and 2 agreed on normal perfusion in 94 segments, dark-rim artefact in 31 segments and stress perfusion defects in 16 segments. The agreement between observer 1 and 2 on the presence of normal perfusion, dark-rim artefact or genuine perfusion defects was 86% (k=0.52, 95% CI: 0.45-0.59, p<0.0001) for EPI scans Table 9.6) and 60% (k=0.2, 95% CI: 0.14-0.27, p<0.0001) for the SSFP scans Table 9.7).

Table 9.6. Agreement for the EPI sequence.

<table>
<thead>
<tr>
<th></th>
<th>Observer 2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observer 1</td>
<td>0</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>163</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>178</strong></td>
<td><strong>40</strong></td>
<td><strong>218</strong></td>
</tr>
</tbody>
</table>

Table 9.7. Agreement for the SSFP sequence.

<table>
<thead>
<tr>
<th></th>
<th>Observer 2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observer 1</td>
<td>0</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>123</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>56</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>179</strong></td>
<td><strong>39</strong></td>
<td><strong>218</strong></td>
</tr>
</tbody>
</table>
9.3.3 Artefacts

125 segments were labelled as artefact on the SSFP scan (62 segments for observer 1 and 63 segments for observer 2). Twenty-two segments from the EPI scans were labelled as dark-rim artefact (17 segments for observer 1 and 5 segments for observer 2). True artefacts (compared against no obstructions on CA) occurred more frequently with SSFP (59 segments, 22%) than with EPI (14 segments, 5%) ($X^2$, p<0.001) (*Figure 9.1 and Figure 9.2*).

*Figure 9.1* CMR stress perfusion images in a 60 year old female with atypical chest pain. Top panel shows EPI with full contrast dose and the lower panel SSFP with half dose. The large hypointense area in the apical septum of the SSFP scan was interpreted as genuine perfusion defect. However, the angiogram showed unobstructed coronary arteries. The corresponding apical EPI image did not show areas of hypointensity, confirming the occurrence of dark rim artefact in the SSFP scan.
Figure 9.2 Comparison of EPI and SSFP scans in a patient with agreement for the finding of true perfusion defect in the RCA territory, confirmed by coronary angiography.

9.3.4 Diagnostic Confidence
Observer 1 noted a significant lower diagnostic confidence for SSFP vs EPI scans (3.1 vs 3.5, respectively, p<0.05) (Figure 9.3). Both observers reported a similar diagnostic confidence for EPI scans. Image quality of the SSFP and EPI were similar for both observers.

Figure 9.3 Observer scoring of diagnostic confidence displaying mean value and 95% confidence interval. EPI had a significantly higher score which represents greater diagnostic confidence.
9.4 DISCUSSION
9.4.1 General Observations

This study showed significant differences in the interpretation and scoring between the EPI and SSFP perfusion sequences. Dark rim artefacts occurred more frequently in the SSFP than EPI scans, even despite the use of the half-contrast dose. Only fair agreement between EPI and SSFP was found in normal segments, as many such segments in the latter sequence showed dark rim artefacts. Greater agreement between observers was achieved with EPI scans, compared to SSFP. Finally, although the observers were usually able to read-through the dark rim artefacts, the confidence ascribed to the EPI scans was significantly higher than for SSFP. Overall therefore, these findings favour clinical use of the EPI sequence.

The three sequences available (FLASH, EPI, SSFP) for first-pass contrast agent perfusion imaging each has advantages and limitations. SSFP readout has the greatest SNR compared to FLASH and especially EPI. Although EPI is a fast sequence reducing cardiac motion artefact by its short imaging time, it has the lowest myocardial CNR of all three and a highly deleterious off-resonance “splitting” distortion, requiring careful attention to the scanner centre-frequency adjustment in the left ventricle. SSFP has greater SNR but previously has been reported as more prone to dark subendocardial rim artefacts, the greater blood/myocardium contrast and the sensitivity of SSFP to field distortion by the high-dose bolus are suspected reasons. Thus one study of direct comparison of EPI, FLASH and SSFP first pass perfusion readouts, scored EPI as the best (lower number of artefact and highest observer confidence) despite the SSFP having greater CNR and SNR.

Dark rim artefacts are considered to have three likely causes: Gibbs artefact, cardiac motion and magnetic susceptibility of the contrast agent. The transient dark rim artefacts visible in the subendocardial layer can mimic a hypoperfused area and are therefore a clinical concern, as they can reduce observer diagnostic confidence. However, dark rim artefacts last only for a few heart beats, and vary temporally as the contrast bolus passes through the left ventricular blood pool, while a real perfusion defect tends to be visible for longer duration.

The main diagnostic problem is a mild perfusion defect which fills in quickly, as differentiation may then be difficult to identify in the presence of artefact. Di Bella demonstrated in ex-vivo (motionless hearts) that Gibbs ringing plays a major role in producing dark rim artefacts. It is most prominently located to the blood–myocardium interface perpendicular to the direction with the lowest spatial resolution (which is typically the phase-encoding direction). The artefacts width decreases with increasing spatial
resolution, as has been achieved by k-space and time (k-t) sensitivity encoding (SENSE) at both 1.5T and 3T.\textsuperscript{24} Higher concentrations of contrast agent increase the Gibbs ringing in the endocardial border, and the same effect is expected from a higher injection rate of the contrast agent.\textsuperscript{25} Our group and others have opted for fast (7mL/s) Gd-DTPA contrast injection rate that guarantees a compact concentrated contrast bolus, and consequent accurate measurement of the arterial input function, which is pivotal for quantitative perfusion measurements.\textsuperscript{26,27} Although previous comparisons of sequence have kept the dose and injection parameters fixed for the sequences being compared, there is a case for allowing these to vary between sequences. The SSFP sequence is more likely to suffer from Gibbs ringing because of higher signal intensity difference between the blood pool and myocardium. Also, Gibbs artefact is very dependent on the position of subendocardial wall with respect to pixels, and sub-pixel shifts have been advocated to explain its variability during perfusion imaging.\textsuperscript{28} This particular type of variability is eliminated by ensuring the reconstruction performs image interpolation by zero-filling prior to FT.

Susceptibility can also cause dark (and bright) artefacts at high gadolinium concentrations. These artefacts are due to dephasing and signal pile-up, and are predictable for simple geometries oriented perpendicular to the main magnetic field. Although TE is very short (\(~1\text{ms}\)) for perfusion sequences, which reduces susceptibility effects, it must be remembered that SSFP relies on achieving steady-state free-precession over a longer period than TE. Susceptibility artefact may occur at the border of the myocardium and contrast-enhanced blood of the ventricles. However, susceptibility artefacts appear only at the peak bolus transit through the LV (and far more prominently around the RV/septum earlier on) and last only for few images in the perfusion series. Increased magnetic field distortion in the subendocardium during this time may cause dephasing of individual voxels, which is also dependent on the heart orientation in relation to B0. However, in a typical perfusion sequence the distortion of the main magnetic field B0 is too weak to cause dark rim artefacts due simply to intravoxel dephasing; however, when added to routine off-resonance error it may conceivably cause dark rims in particular regions of the myocardium wall in balanced-SSFP sequences.\textsuperscript{29} Thus SSFP dark rim artefacts are likely to be reduced by using a smaller peak concentration of contrast agent, trading off the high SNR.

All known reasons for dark-rim artefact tend to strengthen the artefact when the blood signal is bright compared to the myocardium. Even with half-dose contrast agent, the ratio between
the peak-enhancement of blood/myocardium was approximately 4 in SSFP compared to full-dose 2.5 in EPI. The longer image acquisition time of SSFP (125ms per image) compared to EPI (75ms per image) was another potential factor with regard to cardiac motion which cannot be avoided in a multislice protocol. However, using the matched TI values, the SNR of half-dose SSFP appeared similar to the full-dose EPI. In principle, half-dose SSFP is also more likely to avoid the compression of myocardial response curves associated with greater myocardial longitudinal magnetisation recovery.\(^{30}\)

In conclusion, SSFP showed lower diagnostic accuracy compared to EPI because dark-rim artefacts occurred more frequently even when the half-contrast dose was used. Although two experienced observers were usually able to correctly identify dark-rim artefacts, the use of SSFP in clinical practice by less experienced observers may not be ideal because of reduced diagnostic confidence.

### 9.4.2 Study Limitations

The order of the scans could not be randomly assigned, because all patients underwent the clinical EPI scan, followed by recruitment for the SSFP research scan. Therefore, the influence of the order of the sequences could not be assessed. When comparing a saturation-recovery SSFP vs saturation recovery FLASH sequence, Fenchel demonstrated that the detection of perfusion defects was influenced by the order of sequences.\(^{9}\) The second perfusion examination missed more hypoperfused segments. Although the influence of the order of sequence was not assessed in the current study, our second perfusion examination (always the SSFP scan) tended to overestimate the number of hypoperfused segments, rather than missing it. Only a small percentage of patients had significant CAD. This might confirm the Bayesian principle dictating that many positive tests results will be false positive (rather than true positive) if the test is used extensively in low-risk patient population. The cohort of patients included in this study was limited and the findings should be confirmed in larger studies and in a larger cohort of patients with obstructive coronary artery disease.

### 9.4.3 Conclusion

At the contrast doses used in this study, SSFP perfusion imaging had more frequent dark rim artefacts and had lower diagnostic agreement than EPI. Although experienced observers were often able to correctly identify dark rim artefacts, clinical practise in less experienced centres may be affected by the reduced diagnostic confidence.
References


CHAPTER 10
CONCLUSIONS

CMR is an attractive non invasive imaging modality in patients with acute and chronic myocardial ischaemia. CMR can provide in vivo noninvasive tissue characterisation by identifying reversible and irreversible myocardial damage. In this thesis, I have used CMR to investigate a number of acute and chronic clinical conditions involving coronary artery disease.

I investigated the impact of primary angioplasty delay on the presence and extent of myocardial salvage, microvascular obstruction and infarct size using T2- and T1-weighted imaging. I found that “time is muscle” and in particular that shorter time to reperfusion was associated with smaller infarct size, smaller MVO and increased salvage myocardium.

Microvascular obstruction was then used as endpoint in a prospective randomised trial assessing the impact of a thrombectomy device as adjunctive therapy in primary PCI. I found that the incidence and extent of microvascular damage was significantly lower in the thrombectomy group compared to standard primary PCI. Subsequently, I investigated the role of two degrees of microvascular damage assessed by CMR in left ventricular remodelling and infarct healing.

When applied to a selected patient cohort with CTO, CMR demonstrated to be helpful in identifying patient that could benefit from recanalization and to predict functional improvement after revascularisation, as well as improvement on quality of life. The results of this study could potentially impact the clinical management of these patients.

Given the lack of standardisation in perfusion CMR, I sought to test a novel perfusion protocol. I expected to see improved image quality while reducing the occurrence of artefacts. However, this did not occur and the commonly used EPI sequence proved to provide greater diagnostic confidence.

The results of this work suggest that CMR could emerge as clinical valuable technique in numerous clinical settings, in addition to providing surrogate endpoints for clinical trials.
CHAPTER 11

SUMMARY OF ORIGINAL CONTRIBUTIONS

- “Time is muscle”: longer time-to-reperfusion is associated with larger infarct size, greater microvascular damage and less myocardial salvage. These results apply to patients with STEMI undergoing PPCI.

- The use of thrombectomy in the setting of PPCI reduces microvascular damage in patients with STEMI. In this study, microvascular obstruction was assessed by CMR.

- CMR can detect two degrees of microvascular dysfunction: PMO is the most severe form, associated with larger infarct size and strongly related to LV remodelling; MVO of less clinical relevance because highly prevalent.

- Microvascular dysfunction is a dynamic process with a peculiar time course.

- Infarct shrinkage is a phenomenon occurring early (within the first month after the acute event) in the evolving phase of myocardial infarction, mirroring the resolution of microvascular dysfunction.

- Echocardiography and CMR are equally valuable in serial LV volumetric evaluation but CMR

- CMR with viability and ischaemia testing can identify patients with CTO that could benefit from recanalisation, as well as predicting their improvement after revascularization.

- Stress perfusion imaging with SSPF sequence and half-dose of contrast is more prone to artifacts than the standard EPI sequence and full contrast dose.
There are several areas of further research that have been identified. These include improving methods for quantification (simplified and more robust algorithm, post-processing), strategies to overcome artefacts, sequence development and sequence comparison.

12.1 PERFUSION IMAGING

12.1.1 Quantification
CMR perfusion offers important advantages over other imaging modalities but its further progress depends on the successful dissemination of the perfusion quantification technique among the CMR community. Currently, perfusion quantification is not standardised, it is laborious and time consuming and therefore not applicable in clinical practice. Simplified and more robust algorithms for quantification are warranted if they were to be introduced in clinical practice.

12.1.2 Intravascular contrast agents
Limited data are available regarding the application of intravascular gadolinium-based contrast media. Intravascular contrast media yield lower signal intensity in the myocardium than extracellular contrast agents because of reduced exchange into the extracellular space during the first pass. Dose effects on peak signal enhancement have been described in inversion recovery EPI using intra- and extravascular gadolinium-based contrast agents. Jerosch-Herold et al. have demonstrated that perfusion index with an intravascular contrast agent (MS-325) is accurately estimated if corrected by the time-to maximum upslope. Similarly, other groups have identified advantages of intravascular agents for first-pass perfusion imaging. However, the value of quantitative perfusion with intravascular contrast agent in humans with CAD is currently not known and further research is needed.

12.1.3 Selective Tracers
As in SPECT, an agent that could directly assess areas of ischaemia which persist after stress is highly desirable for CMR, so that first-pass imaging is not needed. Manganese is a
paramagnetic ion with pharmacokinetic properties similar to those of 99mTC-sestamibi and there are experimental studies with manganese-enhanced CMR. However, the cardiotoxic and cardio depressant effects of manganese make its clinical application not feasible at this time.

12.1.4 High Field (3 Tesla) Scanner
CMR perfusion at 3T offers potential advantages over 1.5T. Higher field strengths have the advantage of higher SNR, but not without a number of possible disadvantages: at 3T both B0 and B1 field inhomogeneities are increased, the T1 relaxation time s are longer, and the T1 shortening effect of the contrast agent is reduced. Also, at 3.0T the susceptibility effect is greater and hence banding artefacts will be more prevalent. But the higher SNR can be used to improve the spatial or temporal resolution by applying a parallel imaging technique. Preliminary investigations on CMR perfusion at 3T versus 1.5 T are promising showing the predictable benefit of the higher SNR and improved correlation between microspheres and absolute myocardial blood flow by CMR. In humans, Plein demonstrated a comparable image quality to 1.5T when five fold k-t SENSE acceleration was used at 3T. Diagnostic performance of CMR perfusion imaging at 3.0T versus 1.5T for detecting myocardial ischaemia in patients with CAD needs to be investigated.

12.2 OEDEMA IMAGING
The clinical application of oedema imaging with T2-weighted imaging is promising and attractive both in ischaemic and non ischaemic heart disease. However, the technique suffers from a variety of technical limitations, including sensitivity to myocardial motion, variation of surface coil intensity, high subendocardial signal from static blood and the subjective nature of image interpretation. To overcome some of these limitations Coil intensity correction algorithms have been proposed and the initial experience of the T2-prepared single shot SSFP sequence in a clinical study appears promising. More recently, a novel T2 mapping SSFP sequence has been advocated as a more accurate technique because overcomes most the aforementioned limitations, including binging the advantage of quantification. However, direct comparison of T2-prepared SSFP and T2 mapping techniques in the clinical setting of patients with acute myocardial infarction need to be investigated.
References


6 Wolf GL, Baum L. Cardiovascular toxicity and tissue proton T1 response to manganese injection in the dog and rabbit. AJR Am J Roentgenol 1983;141:193-197.


CHAPTER 13
APPENDIX A

13.1 PERSONAL CONTRIBUTION TO THE RESEARCH

I was appointed in October 2006 as the research fellow in perfusion CMR imaging under the supervision of Professor Dudley J Pennell with funding from CORDA, a charity dedicated to the early diagnosis and treatment of heart disease and stroke.

My predecessors Dr Andrew Elkington and Dr Jonathan Lyne had previously worked in the technical development, sequence optimization and early clinical validation of CMR perfusion techniques both in normal volunteers and in patients with ischaemic heart disease.

My research project had five main elements mainly based on the clinical validation of CMR in patients with acute and chronic myocardial ischaemia and the common theme to all studies is the role of CMR for the interventional cardiologist. The first study was to validate CMR myocardial tissue characterisation (and its parameters of reversible and irreversible myocardial damage) in patients with STEMI in relation to time to reperfusion. The second study used microvascular damage as an endpoint to assess the impact of a thrombectomy device as an adjunctive treatment in primary PCI. The third study investigated two different degrees of microvascular damage by CMR and their impact on LV remodelling and infarct healing. For all these three projects, I personally conceived the study designs and plan, contribute in part to image acquisition, performed image analysis and interpretation. Data was collected at the University “La Sapienza” in Rome Italy. I was assisted by Dr Emanuele Canali, cardiology SpR for patient recruitment in the coronary care unit and by Dr Marco Francone and Dr Iacobo Carbone, consultants from the radiology department, for CMR image acquisition and image analysis.

The forth study was to validate the clinical use of CMR perfusion in a cohort of patients with chronic coronary occlusion whose management is controversial. I personally conceived the study, from its design and plan to image acquisition and data interpretation.

I am grateful to Professor Carlo di Mario and his team in the cardiology department, Royal Brompton Hospital, for patient selection, and to Mr Ricardo Wage, deputy CMR
superintendent radiographer, and to Mrs Karen Symmonds, CMR superintendent radiographer, for assistance in image acquisition. I was assisted in analysing the perfusion images by Dr Joanna Petryka, CMR Fellow, Royal Brompton Hospital.

The fifth study was to validate a new clinical CMR perfusion protocol aiming at improving the diagnostic performance of the technique. I personally conceived the study, designed the imaging protocol, granted ethical approval, recruited patients, acquired images and interpreted the data. I am very grateful to Dr Peter Gatehouse, senior physicist, CMR Unit, Royal Brompton Hospital for assistance in protocol design and to Mr Ricardo Wage for assistance in image acquisition. Analysis of perfusion images was provided by Dr Peter Gatehouse, senior physicist, and by Dr Rory O’Hanlon, CMR Research Fellow, Royal Brompton Hospital.

For all projects, statistical analysis was performed by me with the assistance of Mr Michael Roughton, former Medical Statistician at the Royal Brompton Hospital. All papers and chapters were written by me under the supervision of Professor Dudley J Pennell.

13.2 SUPERVISION

This thesis was supervised by Dudley J Pennell, Professor of Cardiology at Imperial College London, UK, and Director of the Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, London, United Kingdom.

Professor Francesco Fedele, Professor of Cardiology at the University of Rome “La Sapienza”, acted as a guarantor for the work conducted in Italy.

13.3 FUNDING

CORDA- a cardiovascular research charity, provided personal support for this research though a fellowship from the van Geest Foundation.
13.4 PUBLICATIONS ARISING FROM THIS WORK

13.4.1 PEER REVIEWED ARTICLES


13.4.2 INVITED REVIEW


13.4.3 LETTERS


13.4.4 CASE REPORTS


13.4.5 OTHER RELATED PAPERS


Locca D, Bucciarelli-Ducci C, Ferrante G, La Manna A, Keenan NG, Grasso A, Barlis P, Del Furia F, Prasad SK, Kaski JC, Pennell DJ, Di Mario C. New universal definition of


### 13.4.6 ABSTRACTS


of coronary chronic total occlusion guided by left ventricular function, perfusion and viability imaging by cardiovascular magnetic resonance. *AHA meeting 2009.*


13.4.7 OTHER RELATED ABSTRACTS


13.5 INVITED LECTURES


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American Heart Association, Orlando, United States of America, 2009. “Chronic Total Occlusion: Role of CMR in Patient Selection and Guiding Procedure”.

European Society of Cardiology, Barcelona, Spain, 2009. “How can we detect myocardial oedema?”.

2nd Advanced Cardiac Imaging Course for the Interventional Cardiologist, London, United Kingdom. “CMR for the interventionist: why bother?”

Italian Society of Cardiology meeting, Rome, Italy, 2008. Cardiac MRI in acute coronary syndrome”.


8th Cardiovascular MRI Workshop, Athens, Greece, 2008. “CMR perfusion”.

Acute Cardiac Care, Versailles, France, 2008. “MRI: ischemia and plaque imaging”.

Italian Society of Cardiology, Rome, Italy, 2007. “Role of cardiovascular magnetic resonance in the evaluation of infarct size and microvascular obstruction”.

European Association of Nuclear Medicine, Copenhagen, Denmark, 2007. Cardiovascular magnetic resonance in coronary artery disease”.

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4th International Summit on Acute Coronary Care, Verona, Italy, 2007. “Cardiovascular magnetic resonance in the post-infarction”,

Romanian Society of Cardiology, Poiana Brasov, Romania, 2006. “The role of magnetic resonance imaging in ischemic heart disease”.

10th World Congress of Echocardiography and Cardiovascular Imaging, Rome, Italy 2006. “Acute myocardial infarction: assessment of microvascular damage by MRI”.

12.6 PRIZES AND AWARDS
Finalist, Melvin Judkins Young Clinical Investigator Award, Council of Cardiovascular Radiology and Intervention, “Impact of primary coronary angioplasty delay on myocardial salvage, infarct size and microvascular damage in patients with ST-elevation myocardial infarction: insight from cardiovascular magnetic resonance”, American Heart Association, Orlando, United States, 2009.


12.7 ACKNOWLEDGMENTS
I am really grateful to Dr Peter Gatehouse and to Dr Jonathan Lyne for inspiring and fruitful discussions. Profound gratitude to Mr Steve Collins for impeccable IT support, and expert help with many other technical related issues over the years.
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# LIST OF ABBREVIATIONS

## A

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>AAR</td>
<td>Area At Risk</td>
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<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>AIF</td>
<td>Arterial input function</td>
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<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>ASNC</td>
<td>American Society of Nuclear Cardiology</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<td>AV</td>
<td>Atrio-ventricular</td>
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## B

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BARI</td>
<td>Bypass Angioplasty Revascularization Investigation</td>
</tr>
<tr>
<td>BOPTA</td>
<td>Gadobenate dimeglumine</td>
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## C

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CABG</td>
<td>Coronary artery bypass surgery</td>
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<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>CBF</td>
<td>Coronary blood flow</td>
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<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CMR</td>
<td>Cardiovascular magnetic resonance</td>
</tr>
<tr>
<td>CNR</td>
<td>Contrast-to-noise ratio</td>
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<tr>
<td>COURAGE</td>
<td>Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>------------</td>
<td>-------------------------------------------------</td>
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<tr>
<td>CTO</td>
<td>Chronic total occlusion</td>
</tr>
<tr>
<td>D</td>
<td><strong>2D</strong> 2-Dimensional</td>
</tr>
<tr>
<td></td>
<td><strong>3D</strong> 3-Dimensional</td>
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<tr>
<td></td>
<td><strong>DTPA</strong> Diethylenetriaminepentaacetic acid</td>
</tr>
<tr>
<td>E</td>
<td><strong>ECG</strong> Electrocardiogram</td>
</tr>
<tr>
<td></td>
<td><strong>EDV</strong> End-diastolic volume</td>
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<tr>
<td></td>
<td><strong>EF</strong> Ejection fraction</td>
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<td></td>
<td><strong>EM-PCI</strong> Export Medtronic percutaneous coronary intervention</td>
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<tr>
<td></td>
<td><strong>EPI</strong> Hybrid echo planar imaging</td>
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<tr>
<td></td>
<td><strong>ESV</strong> End-systolic volume</td>
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<tr>
<td></td>
<td><strong>ETL</strong> Echo train length</td>
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<tr>
<td>F</td>
<td><strong>18FDG</strong> 18-Fluorodeoxyglucose</td>
</tr>
<tr>
<td></td>
<td><strong>FISP</strong> Fast imaging with steady-state precession</td>
</tr>
<tr>
<td></td>
<td><strong>FLASH</strong> Fast low angle shot</td>
</tr>
<tr>
<td></td>
<td><strong>FOV or FoV</strong> Field of view</td>
</tr>
<tr>
<td></td>
<td><strong>FT</strong> Fourier transform</td>
</tr>
<tr>
<td>G</td>
<td><strong>G</strong> Gauge</td>
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<tr>
<td></td>
<td><strong>Gd</strong> Gadolinium</td>
</tr>
<tr>
<td></td>
<td><strong>Gd-BOPTA</strong> Gadobenate dimeglumine</td>
</tr>
<tr>
<td></td>
<td><strong>GE</strong> General Electric</td>
</tr>
<tr>
<td></td>
<td><strong>GFR</strong> Glomerular filtration rate</td>
</tr>
<tr>
<td></td>
<td><strong>GRE</strong> Gradient echo</td>
</tr>
</tbody>
</table>
### H

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HASTE</td>
<td>Half Fourier Single shot Turbo Spin Echo</td>
</tr>
<tr>
<td>HLA</td>
<td>Horizontal long axis</td>
</tr>
</tbody>
</table>

### I

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>Implantable cardiac defibrillator</td>
</tr>
<tr>
<td>IRA</td>
<td>Infarct related artery</td>
</tr>
<tr>
<td>IS</td>
<td>Infarct size</td>
</tr>
<tr>
<td>IZ-WMSI</td>
<td>Infarct-zone wall motion score index</td>
</tr>
</tbody>
</table>

### J

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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### K

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>KeV</td>
<td>Kilo electron volt</td>
</tr>
</tbody>
</table>

### L

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>Left anterior descending (coronary artery)</td>
</tr>
<tr>
<td>LCx</td>
<td>Left circumflex (coronary artery)</td>
</tr>
<tr>
<td>LGE</td>
<td>Late gadolinium enhancement</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricular or left ventricle</td>
</tr>
<tr>
<td>LVEDV</td>
<td>Left ventricular end-diastolic volume</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVESV</td>
<td>Left ventricular end-systolic volume</td>
</tr>
</tbody>
</table>

### M

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>Major adverse cardiovascular (coronary) events</td>
</tr>
<tr>
<td>MBG</td>
<td>Myocardial blush grade</td>
</tr>
<tr>
<td>MBq</td>
<td>Megabecquerel</td>
</tr>
<tr>
<td>MCE</td>
<td>Myocardial contrast echo</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MIBI</td>
<td>Methoxy-IsoButyl Isonitrile</td>
</tr>
<tr>
<td>MPR</td>
<td>Myocardial perfusion reserve</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mSv</td>
<td>Millisievert</td>
</tr>
<tr>
<td>MVO</td>
<td>Microvascular obstruction</td>
</tr>
<tr>
<td>MVO₂</td>
<td>Myocardial oxygen consumption</td>
</tr>
<tr>
<td>N</td>
<td>Number</td>
</tr>
<tr>
<td>NHLI</td>
<td>Nation Heart and Lung Institute</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>NSF</td>
<td>Nephrogenic systemic fibrosis</td>
</tr>
<tr>
<td>OWR</td>
<td>Over the Wire</td>
</tr>
<tr>
<td>P</td>
<td>Pressure</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PMO</td>
<td>Persistent microvascular obstruction</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PPCI</td>
<td>Primary percutaneous coronary intervention</td>
</tr>
<tr>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>Resistance</td>
</tr>
<tr>
<td>RCA</td>
<td>Right coronary artery</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricular or ventricle</td>
</tr>
<tr>
<td>S</td>
<td></td>
</tr>
<tr>
<td>SA</td>
<td>Short axis</td>
</tr>
<tr>
<td>SAQ</td>
<td>Seattle Angina Questionnaire</td>
</tr>
<tr>
<td>SCMR</td>
<td>Society of Cardiovascular Magnetic Resonance</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SENSE</td>
<td>Sensitivity encoding</td>
</tr>
<tr>
<td>SI</td>
<td>Signal Intensity</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-noise ratio</td>
</tr>
<tr>
<td>S-PCI</td>
<td>Standard percutaneous coronary intervention</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>SSFP</td>
<td>Steady state free precession</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>STIR</td>
<td>Short T₁ inversion recovery</td>
</tr>
<tr>
<td>T</td>
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<tr>
<td>T</td>
<td>Tesla</td>
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<tr>
<td>T₁W</td>
<td>T₁-weighted</td>
</tr>
<tr>
<td>T₂W</td>
<td>T₂-weighted</td>
</tr>
<tr>
<td>TAPAS</td>
<td>Thrombus Aspiration During Percutaneous Coronary Intervention in Acute MI</td>
</tr>
<tr>
<td>TE</td>
<td>Echo time</td>
</tr>
<tr>
<td>TI</td>
<td>Inversion time</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis In Myocardial Infarction</td>
</tr>
<tr>
<td>TMP</td>
<td>TIMI Myocardial Perfusion</td>
</tr>
<tr>
<td>TOSCA</td>
<td>Total Occlusion Study of Canada</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time</td>
</tr>
<tr>
<td>TSE</td>
<td>Turbo spin echo</td>
</tr>
<tr>
<td>TTC</td>
<td>Triphenyl-Tetrazolium Chloride</td>
</tr>
</tbody>
</table>
U

UK United Kingdom

US United States

V

VLA Vertical long axis

W

X

Y

Z