



University  
of Glasgow

McGeoch, Ross James (2012) *The assessment of microvascular injury in patients undergoing emergency PCI for ST - elevation myocardial infarction.*

MD thesis

<http://theses.gla.ac.uk/3560/>

Copyright and moral rights for this thesis are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the Author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the Author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

**The Assessment of Microvascular Injury in  
Patients undergoing Emergency PCI for ST –  
Elevation myocardial infarction**

**Dr Ross James McGeoch MB/ChB, MRCP (UK)**

**A thesis submitted for the degree of Doctor of Medicine in the Faculty of  
Medicine of the University of Glasgow**

**Departments of Cardiology, Western Infirmary and Golden Jubilee  
National Hospital**

**April 2012**

## **Acknowledgements**

I would like to thank my supervisor Professor KG Oldroyd and co-supervisor Professor Colin Berry for their help and support from the inception of this project until the writing of the thesis. I am very grateful to Professor Henry Dargie for his support and for his financing of the project in the early stages. I am grateful to Dr Alex Payne, Dr Jamie Layland and Professor Colin Berry and Ms Tracey Steedman for help with MRI and angiographic data analysis and to Professor I Ford at the Robertson Centre for Biostatistics for support with statistical analysis throughout the project.

.I am extremely grateful to the interventional cardiology consultants (Prof KG Oldroyd, Dr MM Lindsay, Dr SD Robb, Prof WS Hillis, and Prof Colin Berry) at the Western Infirmary in Glasgow who recruited patients into this study and performed pressure wire studies, often in the middle of the night, and to the catheter laboratory staff for their patience.

I would like to thank the Chief Scientist's Office of Scotland who provided funding for the project.

Finally, I would like to acknowledge the patients who took part in this study, many of whom gave up their spare time to return to the Western Infirmary for a follow up cardiac MRI scan.

<b>Contents</b>	<b>Page</b>
<b>Title</b>	<b>1</b>
<b>Acknowledgements</b>	<b>2</b>
<b>Contents</b>	<b>4</b>
<b>List of Figures</b>	<b>18</b>
<b>List of Tables</b>	<b>20</b>
<b>List of Presentations, Publications and Prizes</b>	<b>23</b>
<b>List of Abbreviations</b>	<b>27</b>
<b>Summary</b>	<b>31</b>
<b>Chapter 1 – Introduction</b>	<b>36</b>
<b>1.1 Background</b>	<b>37</b>
<b>1.2 Pathophysiology of microvascular obstruction in myocardial infarction</b>	
1.2.1 Background	41
1.2.2 Mechanical obstruction of the microcirculation	41
1.2.3 Functional obstruction of the microcirculation	43
1.2.4 Reperfusion injury	44

1.2.5 Pre-existing dysfunction of the myocardial microcirculation	45
1.2.6 Summary	46
<b>1.3 Current tools for assessment of the coronary microcirculation</b>	<b>48</b>
1.3.1 Electrocardiographic ST-segment resolution following reperfusion	48
1.3.2 TIMI myocardial blush grade	50
1.3.3 Corrected TIMI frame count	52
1.3.4 Assessment of microvascular integrity using myocardial contrast echocardiography	53
<b>1.4 Cardiac magnetic resonance imaging following acute myocardial infarction</b>	<b>57</b>
1.4.1 Background	57
1.4.2 Late gadolinium contrast enhancement CMR (ceCMR)	60
1.4.3 CMR for the assessment of MVO	62
1.4.4 CMR methodology for assessment of MVO	63
1.4.5 Clinical and prognostic implications of MVO as assessed by ceCMR	65

1.4.6 The optimal timing for CMR scanning following STEMI	67
<b>1.5 Novel invasive markers for microvascular dysfunction using a coronary temperature/pressure wire at the time of emergency PCI</b>	<b>69</b>
1.5.1 Coronary microvascular resistance	69
1.5.2 Thermodilution derived coronary flow reserve	70
1.5.3 The index of microcirculatory resistance	72
1.5.4 IMR in the presence of an epicardial stenosis	74
1.5.5 The clinical utility of IMR	77
1.5.6 IMR in STEMI	77
1.5.7 Pressure derived collateral flow index	78
<b>1.6 Aims of the thesis</b>	<b>80</b>
 <b>Chapter 2 - Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology</b>	 <b>84</b>
<b>2.1 Introduction</b>	<b>85</b>
<b>2.2 Fractional Flow Reserve</b>	<b>86</b>

<b>2.3 Adenosine</b>	87
2.3.1 Intracoronary adenosine	88
2.3.2 Practical considerations when using intracoronary adenosine	89
2.3.3 Intravenous adenosine	90
2.3.4 Practical considerations when using an intravenous adenosine infusion	91
2.3.5 The effects of methylxanthines on adenosine	92
2.3.6 Adenosine 5'-triphosphate (ATP)	92
<b>2.4 Other vasodilator agents</b>	93
2.4.1 Sodium nitroprusside	93
2.4.2 Dobutamine	95
2.4.3 Papaverine	96
2.4.4 Radiographic Contrast media	98
<b>2.5 The future of pharmacological stress</b>	98
<b>2.6 Conclusions</b>	100
 <b>Chapter 3 – Methods</b>	 102



<b>3.1 Study overview and recruitment</b>	103
3.1.1 Inclusion and exclusion criteria	103
3.1.2 Recruitment	104
3.1.3 Consent and ethics	105
3.1.4 Acute management of patients	105
3.1.5 Index event and hospital admission	107
3.1.6 Three month visit	108
<b>3.2 Invasive coronary physiological assessment protocols</b>	109
3.2.1 Pressure wire preparation	109
3.2.2 Hyperaemic agent used during pressure wire studies	110
3.2.3 Measurement of coronary wedge pressure (Pw)	111
3.2.4 Measurement of pressure derived collateral flow index (CFIp)	112
3.2.5 Measurement of the index of microcirculatory resistance (IMR)	112
3.2.6 Thermodilution derived mean transit times	113
<b>3.3 Assessment of angiographic Thrombolysis in Myocardial Infarction (TIMI) flow grade</b>	114
<b>3.4 ceCMR Protocols</b>	115

3.4.1 Preparation of patient for the scan	115
3.4.2 Clinical assessment prior to ceCMR scans	116
3.4.3 Left Ventricular structure and function	117
3.4.4 Cinematographic (cine) imaging	118
3.4.5 Short axis cine stack	118
<b>3.5 Contrast imaging</b>	122
3.5.1 First-pass perfusion imaging	122
3.5.2 Imaging of early microvascular obstruction	123
3.5.3 Late gadolinium-enhancement imaging	123
<b>3.6 CMR analysis methodology</b>	125
3.6.1 LV volumes and ejection fraction	125
3.6.2 “Early” Microvascular Obstruction	126
3.6.3 Infarct volumes and late/ persistent MVO	126
3.6.4 Site of myocardial infarction	128
3.6.5 Transmural extent of myocardial infarction	129
3.6.6 Assessment of LV remodelling	129
3.6.7 Timing of CMR scans	130

### **3.7 Assessment of “traditional” indices of microvascular and myocardial damage**

3.7.1 Electrocardiographic assessment	131
3.7.2 Assessment by corrected Thrombolysis in Myocardial Infarction Frame Count (cTFC)	131
3.7.3 Biochemical assessment	132
<b>3.8 Statistical methods</b>	132
<b>3.9 Funding of the study</b>	133
<b>3.10 Sponsoring of the study</b>	133

## **Chapter 4 - Demographics, admission data, angiographic**

### **and cardiac MRI results**

<b>4.1 Patient screening and recruitment</b>	135
<b>4.2 Demographics</b>	135
4.2.1 Index event	136
4.2.2 Admission blood results	137
4.2.3 Timescale of presentation and treatment	138
4.2.4 Angiographic and PCI data	138

4.2.5 Medication on discharge	139
<b>4.3 Physiological assessment using pressure wire at the time of PCI</b>	140
<b>4.4 CMR data and analysis</b>	141
4.4.1 Overview	141
4.4.2 Analysis of baseline and follow up ceCMR scans	142
<b>4.5 The influence of anatomical site of myocardial infarction and therapeutic interventions at the time of emergency PCI on coronary pressure wire derived indices of microvascular obstruction</b>	143
<b>4.6 A comparison of pressure wire data by primary operator's choice of treatment at the time of emergency PCI</b>	144
<b>4.7 Discussion - Demographics, admission data, angiographic and cardiac MRI results</b>	146
4.7.1 Demographics and patient characteristics	146
4.7.2 Pressure wire data in comparison with previous studies	147
4.7.3 CMR results in comparison with previous studies	149
<b>4.8 Conclusion</b>	151

<b>Chapter 5 - The relationship between coronary pressure wire derived indices of microvascular dysfunction at the time of emergency PCI with microvascular and myocardial damage on cardiac MRI</b>	<b>152</b>
<b>5.1 Introduction</b>	<b>153</b>
<b>5.2 Methods</b>	<b>154</b>
<b>5.3 A comparison of patients with and without microvascular obstruction on contrast enhanced cardiac MRI</b>	<b>155</b>
5.3.1 Demographics, cardiac risk factors, admission information and angiographic variables	155
<b>5.4 A comparison of pressure wire data in patients with and without MVO on ceCMR</b>	<b>156</b>
<b>5.5 Comparison “early” and “late” MVO volumes, mass and ratio</b>	<b>158</b>
<b>5.6 The relationship between pressure wire data and MVO volumes, mass and ratio on CMR scanning</b>	<b>160</b>
<b>5.7 The relationship between IMR and LVEF at baseline and follow up</b>	<b>160</b>
<b>5.8 The relationship between IMR and infarct volumes at baseline and follow up</b>	<b>164</b>
<b>5.9 The relationship between IMR and LV Volumes at baseline and follow up</b>	<b>166</b>

<b>5.10 The relationship between IMR and infarct transmurality at baseline and follow up</b>	170
<b>5.11 The relationship between IMR and LV remodeling</b>	174
<b>5.12 Discussion</b>	176
5.12.1 The comparison of different cardiac MRI methods of MVO assessment in AMI	176
5.12.2 The relationship between pressure wire indices of microvascular obstruction and CMR data at baseline and follow-up	177
<b>5.13 Limitations</b>	181
<b>5.14 Conclusions</b>	182
 <b>Chapter 6- A comparison of Index of Microcirculatory resistance prior to and following stent implantation in emergency PCI for STEMI</b>	183
<b>6.1 Introduction</b>	184
<b>6.2 Methods</b>	185
6.2.1 Physiological assessment	185
6.2.3 CMR protocol	187
6.2.3 CMR analysis	187

6.2.4 Angiographic analysis	187
6.2.5 Statistical analysis	187
<b>6.3 Results</b>	188
6.3.1 Patient characteristics	188
6.3.2 IMRtrue, IMRapp and TIMI flow grade pre and post stenting	189
6.3.3 The Influence of adjunctive therapy on change in IMR	190
6.3.4 The Influence of change in IMR on evidence of myocardial damage	190
6.3.5 The influence of angiographic no reflow on change in IMR	191
<b>6.4 Discussion</b>	192
<b>6.5 Limitations</b>	194
<b>6.6 Conclusions</b>	195

<b>Chapter 7 - The relationship between coronary pressure wire derived markers of microvascular obstruction and “traditional” indices of myocardial damage and microvascular obstruction in ST – elevation myocardial infarction</b>	196
<b>7.1 Background</b>	197

<b>7.2 Methods</b>	197
<b>7.3 Results</b>	197
7.3.1 A comparison of pressure wire data with TIMI flow grade prior to PCI	
7.3.2 A comparison between the invasive physiological indices of MVO and corrected TIMI frame count immediately after emergency PCI	198
7.3.3 A comparison of pressure wire data with ECG ST segment resolution index	199
7.3.4 Comparison between physiological assessment of MVO following PCI and peak troponin I	200
7.3.5 The influence on time to presentation and reperfusion on pressure wire Data	201
7.3.6 A comparison of pressure wire data with method of AMI reperfusion	201
<b>7.4 Discussion</b>	204
7.4.1 The relationship between IMR and other indices for microvascular damage available directly after emergency PCI	204
7.4.2 The relationship between IMR, time to reperfusion and method of reperfusion	205



7.4.3 The relationship between pressure wire derived indices of microvascular damage and peak troponin I	207
<b>7.5 Conclusions</b>	208
 <b>Chapter 8 - Advances in cardiac imaging in STEMI survivors: diagnostic utility of cardiac magnetic resonance</b>	209
<b>8.1 Introduction</b>	210
<b>8.2 Methods</b>	211
8.2.1 Patient population	211
8.2.2 Follow up	212
8.2.3 CMR scans	213
8.2.4 CMR analysis and reporting	213
8.2.5 Incidental findings	213
8.2.6 Biochemical assessment of infarct size	214
<b>8.3 Statistical analysis</b>	215
<b>8.4 Results</b>	215
8.4.1 CMR scans	218

8.4.2 Cardiac findings	219
8.4.3 Incidental findings	222
8.4.4 CMR findings are associated with early rehospitalisation for heart failure or ACS	225
<b>8.5 Discussion</b>	225
<b>8.6 Limitations</b>	229
<b>8.7 Conclusions</b>	230
<b>Chapter 9 - Conclusions and clinical implications</b>	231
<b>9.1 Postulated therapeutic interventions to minimize microvascular damage in STEMI</b>	231
<b>9.2 Clinical implications for use of IMR in STEMI</b>	233
<b>References</b>	235
<b>Appendix I</b>	273
<b>Appendix II</b>	276
<b>Appendix III</b>	277
<b>Appendix IV</b>	286
<b>Appendix V</b>	287

## **List of figures**

- Figure 1.1: Mechanisms Responsible for No-Reflow**
- Figure 3.1: Flow diagram of study**
- Figure 3.2: Outlines and timings of pressure wire readings**
- Figure 3.3: Thermodilution curves at baseline and hyperaemia with simultaneous Pa and Pd measurement as represented on the RADI analyser screen**
- Figure 3.4: Planning of cine CMR image acquisition**
- Figure 3.5: Mid-ventricular short-axis slices acquired using a contrast-sensitive segmented inversion recovery sequence 15 minutes after injection of gadolinium-DTPA, from two separate patients admitted with anterior STEMI.**
- Figure 3.6: The 17 segment American Heart Association model for anatomical assessment of myocardial infarction in the ventricular short axis CMR images**
- Figure 4.1: ECG defined site of MI.**
- Figure 5.1: IMR box-plots dichotomised according to presence or absence of MVO**
- Figure 5.2: Correlation of “early” MVO mass with “late” MVO mass**
- Figure 5.3: Scatterplot of IMR (log transformed) against left ventricular ejection fraction at 2 days**

- Figure 5.4:** Scatterplot of IMR (log transformed) and left ventricular ejection fraction at 3 months.
- Figure 5.5:** Scatterplot of IMR (log transformed) against left ventricular end systolic volume indexed for body surface area on ceCMR at 2 days
- Figure 5.6:** Scatterplot of IMR (log transformed) against transmural score at baseline ceCMR imaging at 2 days
- Figure 5.7:** Scatterplot of IMR (log transformed) against transmural score at baseline ceCMR imaging at 3 months
- Figure 7.1:** Scatterplot with regression of cTFC vs IMR.
- Figure 7.2:** Scatterplot of IMR vs peak troponin I
- Figure 7.3:** Median IMR and Pw in each of the PCI groups
- Figure 8.1:** Transmural inferior MI assessed by ceCMR
- Figure 8.2:** Incidental findings noted on ceCMR imaging

## **List of tables**

- Table 2.1:** Dosage table for IV adenosine at 140 micrograms/kg/min
- Table 2.2:** Dosage table for IV adenosine at 180 micrograms/kg/min
- Table 4.1:** Laboratory values on admission to hospital with index event
- Table 4.2:** Angiographic data for the study population
- Table 4.3:** Summary of standard cardiovascular secondary prevention medication at discharge from hospital in the study population
- Table 4.4:** A summary of pressure wire data pre and post stenting in the study population.
- Table 4.5:** Summary of CMR data at baseline and follow-up
- Table 4.6:** Comparison of pressure wire data post PCI by ECG
- Table 4.7:** Comparison of physiological indices for microvascular dysfunction
- Table 4.8:** Comparison median IMR in this study with contemporary work in this field
- Table 5.1:** Comparison of baseline characteristics of those with and without MVO
- Table 5.2:** Comparison of pressure wire data in the MVO present and MVO absent groups
- Table 5.3:** Correlations and P values of “early” and “late” MVO volumes, mass and ratio calculated using digital planimetry

- Table 5.4:** Results of multivariable regression analyses for left ventricular ejection fraction measured by ceCMR performed 2 days and 3 months post-MI
- Table 5.5:** Results of multivariable regression analyses for myocardial infarct volume measured by ceCMR performed 2 days and 3 months post-MI
- Table 5.6:** Results of multivariable regression analyses for increased left ventricular end systolic volume index measured by ceCMR performed 2 days
- Table 5.7:** Results of multivariable regression analyses for increased left ventricular end diastolic volume index measured by ceCMR performed 2 days
- Table 5.8:** Results of multivariable regression analyses for increased left ventricular end systolic volume index measured by ceCMR performed at 3 months
- Table 5.9:** Results of multivariable regression analyses for increased left ventricular end diastolic volume index measured by ceCMR performed at 3 months
- Table 5.10:** Results of univariate and multivariate regression predictive models for increased transmural score at 2 days post myocardial infarction
- Table 5.11:** Results of univariate and multivariate regression predictive models for increased transmural score at 2 months post myocardial infarction
- Table 5.12:** A comparison of  $\Delta$  LVESVI defined by pressure wire data

<b>Table 6.1:</b>	<b>Patient demographics in pre and post stenting patients</b>
<b>Table 6.2:</b>	<b>The comparison of pressure wire data and TIMI flow grade before and after stenting</b>
<b>Table 6.3:</b>	<b>The differences between indicators of myocardial damage grouped according to change in IMR following emergency PCI</b>
<b>Table 7.1:</b>	<b>Pressure wire indices following PCI grouped by TIMI flow grade prior to PCI</b>
<b>Table 7.2:</b>	<b>Pressure wire data assessed by ST segment resolution index</b>
<b>Table 7.3:</b>	<b>Median IMR and with mean infarct volumes at 48h by type of PCI</b>
<b>Table 8.1:</b>	<b>Clinical characteristics in patient population in the early MRI study</b>
<b>Table 8.2:</b>	<b>CMR results in early MRI study population</b>
<b>Table 8.3:</b>	<b>Incidental findings on CMR</b>

## **List of Presentations, Publications and Prizes**

### **Presentations**

McGeoch RJ, Watkins S, Good R, Berry C, Hogg KJ, Rae AP, Petrie M, Eteiba H, Lindsay MM, Robb SD, Hillis WS, Dargie HJ, Oldroyd KG. The relationship between index of microcirculatory resistance and LV volumes on CMR imaging in ST elevation myocardial infarction.

*Oral presentation, Scottish Cardiac Society, Nairn, September 2007*

McGeoch RJ, Watkins S, Berry C, Davie A, Byrne J, Hillis WS, Lindsay MM, Robb SD, Dargie HJ, Oldroyd KG. Index of Microcirculatory Resistance (IMR) could be used at the time of emergency PCI as a marker of microvascular obstruction (MVO) and myocardial damage in ST elevation myocardial infarction (STEMI).

*Oral presentation, Royal Medico-Chirurgical Society of Glasgow, Glasgow, March 2008*

McGeoch RJ, Watkins S, Berry C, Davie A, Byrne J, Hillis WS, Lindsay MM, Robb SD, Dargie HJ, Oldroyd KG. The Index of Microcirculatory Resistance (IMR) but not coronary collateral supply, is associated with Microvascular Obstruction (MVO) revealed by contrast enhanced magnetic resonance imaging (ceMRI).



*Moderated poster presentation, British Cardiovascular Society, June 2008*

McGeoch RJ, Watkins S, Berry C, Davie A, Byrne J, Hillis WS, Lindsay MM, Robb SD, Dargie HJ, Oldroyd KG. The index of microvascular resistance measured acutely predicts the severity and nature of myocardial infarction in patients with ST segment elevation myocardial infarction

*Poster Presentation, American Heart Association, New Orleans, December 2008*

McGeoch RJ, Watkins S, Berry C, Davie A, Byrne J, Hillis WS, Lindsay MM, Robb SD, Dargie HJ, Oldroyd KG. Acute invasive measures of microvascular function predicts early and long-term infarct size and left ventricular function revealed by magnetic resonance imaging in patients with ST segment elevation myocardial infarction.

*Poster Presentation, British Society of Cardiovascular Magnetic Resonance Imaging. Oxford, March 2009*

McGeoch RJ, Watkins S, Davie A, Byrne J, Hillis WS, Lindsay MM, Robb SD, Dargie HJ, Oldroyd KG, Berry C. Endogenous chemical and cellular repair responses are linked to the extent of cardiac injury in human myocardial infarction.

*Oral presentation, Molecular Regulation of Cardiac Disease Symposium, London, May 2009*

McGeoch RJ, Watkins S, Berry C, Davie A, Byrne J, Hillis WS, Lindsay MM, Robb SD, Dargie HJ, Oldroyd KG. The index of microvascular resistance measured acutely

predicts infarct severity and left ventricular function at 3 months in patients with ST segment elevation myocardial infarction

*Oral presentation, British Cardiovascular Society, London, June 2009*

McGeoch RJ, McGarrity A, Payne A, Watkins S, Steedman T, Davie A, Hillis WS, Lindsay MM, Robb SD, Tardif JC, Rheaume E, Oldroyd KG, Berry C. Circulating Chemical Cellular Injury/Repair Responses are linked to the extent of Heart Injury in Human Myocardial Infarction.

*Oral Presentation, American Heart Association, Orlando Nov 2009*

McGeoch RJ, Payne AR, Steedman T, Woodward R, Saul A, Foster J, Lindsay MM, Hood S, Petrie MC, Tzemos N, Oldroyd KG, Berry C

Advances in cardiac imaging in STEMI survivors: safety and clinical utility of cardiac magnetic resonance imaging

*Poster presentation, Royal College of Physicians and Surgeons of Glasgow Triennial Conference, Glasgow Nov 2011*

Prognostic Value of the Index of Microcirculatory Resistance after Primary Percutaneous Coronary Intervention

Yong ASC, Loh J, McGeoch RJ, Shah M, Ho M, Daniels D, Low A, Oldroyd KG, Fearon WF

*Oral Presentation. ACC, Chicago, March 2012*

## **Publications**

McGeoch RJ, Oldroyd KG. Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology.

*Catheterisation and cardiovascular interventions. Feb 2008 : 71(2); p198-204*

McGeoch RJ, Watkins S, Berry C, Davie A, Byrne J, Hillis WS, Lindsay MM, Robb SD, Dargie HJ, Oldroyd KG. The index of microcirculatory resistance measured acutely predicts the nature and severity of myocardial infarction in patients with ST segment elevation myocardial infarction

*JACC Cardiovasc Interv. 2010 Jul;3(7):715-22.*

## **Prizes**

British Cardiovascular Intervention Society Young Investigator Prize, *London, February 2009*

## **List of abbreviations**

ACC: American College of Cardiology

ACE: Angiotensin converting enzyme

ACS: Acute coronary syndrome

AHA: American Heart Association

AMI: Acute myocardial infarction

AMICI: Acute myocardial infarction contrast imaging

AP: Dr Alex Payne

BMI: Body mass index

BMS: Bare metal stent

CB: Professor Colin Berry

CFI<sub>p</sub>: Pressure derived collateral flow index

CFR: Coronary flow reserve

CHD: Coronary heart disease

CK: Creatine Kinase

ceCMR: Contrast enhanced cardiac magnetic resonance imaging

CMR: cardiac magnetic resonance imaging

CSO: Chief Scientists Office Scotland

cTFC: Thrombolysis in myocardial infarction flow count

Cx: Circumflex coronary artery

DEDICATION: Drug elution and distal protection during percutaneous intervention

DES: Drug eluting stent

DTPA: Diethylenetriaminepentaacetic acid

ECG: Electrocardiogram

eGFR: estimated glomerular filtration rate

ESC: European Society of Cardiology

FAME: Fractional flow reserve versus angiography for multi-vessel evaluation

FFR: Fractional flow reserve

GUSTO: Global utilisation of streptokinase and tissue plasminogen activator for occluded arteries

HASTE: Half Fourier Acquisition Single Shot Turbo Spin Echo

HF: Heart failure

HLA: Horizontal long axis

KGO: Professor Keith Oldroyd

IC: Intracoronary

IMR: Index of microcirculatory resistance

IRA: Infarct related artery

IQR: Inter-quartile range

IV: Intravenous

LAD: Left anterior descending coronary artery

LV: Left ventricle

LVEDV(I): left ventricular end-diastolic volume (index)

LVEF: left ventricular ejection fraction

LVESV(I):left ventricular end-systolic volume (index)

LVMI: left ventricular mass index

LVOT: left ventricular outflow tract

LVSD: left ventricular systolic dysfunction

MACE: Major adverse cardiac events

MBG: Myocardial blush grade

MCE: Myocardial contrast echocardiography

MCESI: Myocardial contrast echocardiography systolic index

MI: Myocardial infarction

MML: Dr Mitchell Lindsay

MRI: Magnetic resonance imaging

MVO: Microvascular obstruction

PCI: Percutaneous coronary intervention

POBA: Plain old balloon angioplasty

Pa: Aortic pressure

Pd: distal coronary pressure

PFO: patent foramen ovale

Pw: Distal coronary wedge pressure

RCA: Right coronary artery

RM: Ross McGeoch

SA: Short axis

SD: Standard deviation

SPECT: Single-photon emission computed tomography

SR: Dr Stephen Robb

STEMI: ST elevation myocardial infarction

TE: echo time (during CMR image acquisition)

TFC: Thrombolysis in myocardial infarction flow count

TFG: Thrombolysis in myocardial infarction flow grade

TI: time to inversion (during CMR image acquisition)

TIMI: Thrombolysis in myocardial infarction

TMR: True microvascular resistance

TnI: Troponin I

TR: repetition time (during CMR image acquisition)

TS: Tracey Steedman

TTE: Trans-thoracic echocardiography

turbo-FLASH: turbo fast low angle-shot

VALIANT: Valsartan an acute myocardial infarction study

VLA: Vertical long axis

WIG: Western infirmary general hospital

WMS: Wall motion score

WMSI: Wall motion score index

WSH: Professor Stewart Hillis

## Summary

Despite the interventional and pharmacological advances in treatment in ST elevation myocardial infarction in recent decades it continues to be a significant cause of morbidity and mortality in Scotland and around the world. The diagnosis and treatment of ST elevation myocardial infarction has been the subject of intense investigation and the focus of numerous randomised clinical trials over the past few decades. In an attempt to minimise adverse sequelae it is imperative that in patients with ST elevation myocardial infarction (STEMI) the immediate goal of therapy is to rapidly achieve patency of the epicardial infarct related artery (IRA) and consequently reperfusion of the affected myocardium.

Thrombolysis achieves normal flow (TIMI grade 3) in the IRA in around 50% of patients compared to around 90% with primary PCI (pPCI). The successful restoration of epicardial coronary artery patency with TIMI grade 3 flow, however, does not necessarily translate into adequate tissue level perfusion. Inadequate tissue level perfusion in ST – elevation myocardial infarction in the presence of a patent epicardial artery is characterised by myocardial microvascular dysfunction. Evidence of microvascular obstruction (MVO) regardless of how it is assessed is associated with adverse clinical outcomes in this patient group. A series of consistent data has clearly shown that MVO has a strong negative impact on outcome.



The index of microvascular resistance is a marker of myocardial microvascular resistance which be validated in vitro and in vivo and has been shown to be independent of variations in haemodynamic state. By incorporating collateral flow IMR has been validated in the presence of an epicardial stenosis and therefore can be calculated prior and and following stenting. Calculation of IMR at the time of emergency PCI for STEMI could potentially provide a marker of microvascular and myocardial injury in the very early post infarct period when further potential interventions would be most beneficial to the patient.

Cardiac MRI imaging is the current gold standard for assessment of left ventricular ejection fraction and infarct volumes. Using Gadolinium contrast agent CMR can characterise microvascular obstruction and calculate infarct volumes. This useful information is normally available at the time of emergency PCI.

The principle aim of this thesis is to compare pressure wire derived markers of microvascular obstruction, principally IMR, calculated at the time of emergency PCI for STEMI with evidence of microvascular and myocardial damage as assessed by ceCMR scanning at 2 days and 3 months post PCI. In particular I will look at whether IMR at the time of PCI for STEMI can be used as a predictor of myocardial damage on ceCMR.

I will also compare IMR the “traditional” indices currently used to assess microvascular perfusion and assess the impact that stenting itself has on the coronary microvasculature by comparing IMR prior and following PCI.

CMR imaging is not commonly available in the early post infarct period. I will therefore also look at the safety, feasibility and clinical utility of ceCMR imaging in the 24 to 48 hour period following PCI for STEMI.

Patients who were undergoing emergency PCI for STEMI were recruited. They underwent pressure wire assessment at the time of emergency PCI and had ceCMR scans at 2 days and 3 months following their myocardial infarction. A total of 77 patients were consented for the study between 04/01/2007 and 28/02/2008 and 69 patients had successful coronary physiological studies at the time of PCI. Two hundred patients in total underwent early ceCMR post STEMI over a longer time period. The funding for my study from the CSO Scotland allowed the evolved project to run for a further 18 months (and indeed still continues following further funding from the BHF) after I went back into clinical work therefore I was able to use extra patients whom underwent early CMR for that aspect of the thesis.

In summary the findings of this thesis are:

- IMR is significantly higher in patients in whom there is evidence of MVO in ceCMR scanning at 48h but does not predict the amount of MVO present.
- IMR is a strong independent predictor of LVEF, infarct volumes and LVESV on ceCMR imaging at 48h and 3 months.
- IMR was an independent predictor of transmural score on ceCMR
- IMR does not alter significantly following stenting in emergency PCI indicating that stenting itself does not significantly alter the coronary microvasculature.
- IMR correlates closely with the “traditional” markers of myocardial damage and myocardial infarction in ST – elevation myocardial infarction.
- Anatomical site of myocardial infarction and therapeutic interventions at the time of emergency PCI do not significantly influence coronary pressure wire derived markers of microvascular obstruction taken immediately post – procedure.

- There was a nearly exact relationship between the presence of “early” and “late” MVO assessed by ceCMR imaging 48h post STEMI
- CMR in the early post infarct period is safe, feasible and provides useful diagnostic information

This was the first study to directly compare IMR with ceCMR assessment of MVO and myocardial damage. I feel that my results complement the other work done in this field both in stable patients and in the STEMI population. I have shown that an elevated IMR is linked to microvascular and myocardial damage as revealed by ceCMR in the early post infarction period and at longer term follow up. Accordingly, I suggest measurement of IMR represents a new approach to risk assessment at the very earliest stage of acute MI management, and potentially, therefore enables triage of higher risk patients to more intensive therapy.

# **Chapter 1: Introduction**

## **1.1Background**

Improvements in the primary prevention of coronary artery disease, predominantly through more rigorous diagnosis and aggressive control of classical cardiac risk factors, have led to a decline in premature coronary heart disease in the Western world<sup>1</sup>. Despite this acute myocardial infarction (AMI) remains a significant problem at a local and national level as well as on a global scale.

In one Scottish study looking at patients presenting to their general practitioner with angina as a first manifestation of potential ischaemic heart disease the investigators found that of these 1785 patients, within the five years' follow-up, 152 (8.5%) patients underwent coronary artery bypass grafting, 108 (6.1%) underwent percutaneous coronary angioplasty, 116 (6.5%) had an acute myocardial infarction, 84 (4.8%) died from ischaemic heart disease, and 175 (9.8%) died from any cause.<sup>2</sup> In Scotland, although the age-standardised mortality rates following AMI have fallen between 1994 and 2004 (from 223 to 140 per 100 000), cardiovascular morbidity and mortality remain high.<sup>3</sup>

In the United Kingdom, based on incidence rates of AMI of 600 per 100 000 in men and 200 per 100 000 in women under the age of 70 years, an estimated 123 000 persons aged 75 or less will suffer an AMI per year.<sup>3</sup> These data are thought to be a under-representation given the relative young age of the patients involved.<sup>4</sup> The combined expense of direct treatment, loss of earnings by the workforce, and informal caring for

these patients is estimated at over £7.9 billion per annum to the United Kingdom economy.<sup>1</sup>

Coronary heart disease (CHD) caused about 1 of every 5 deaths in the United States in 2005. CHD mortality in 2005 was 445 687. Current estimates in America state that each year, an estimated 785 000 people will suffer a first AMI, and about 470 000 will have a recurrent attack. It is estimated that an additional 195 000 silent first myocardial infarctions occur each year. In addition, in 2005 1 in 8 death certificates (292 214 deaths) in the United States mentioned heart failure.<sup>5</sup>

The detrimental effect of heart failure after presenting with AMI is well established.<sup>6-8</sup> In an analysis of the VALsartan In Acute myocardial iNfarcTion study (VALIANT) of 11 040 post-MI patients deemed to be stable (no major non-fatal cardiovascular events or deaths within 45 days of randomization and without a prior history of HF), 1139 (10.3%) developed HF during the median 25-month follow-up at a rate of 3.4% per year.<sup>9</sup> United Kingdom data from a large, single centre that followed up AMI patients who had a first or recurrent myocardial infarction in 1998 reported that 63% developed heart failure over the subsequent 6 years. This group also reported 84% of those who died during follow-up first developed HF.<sup>10</sup>

A North American study which looked at population-based cohort of 7,733 patients  $\geq 65$  years of age hospitalized for a first MI between 1994 and 2000 in Alberta, Canada found that 2,831 (37%) MI patients were diagnosed with new HF and 1,024 (13%) died. Among

hospital survivors who did not have HF during their index hospitalization (n = 4,291), an additional 3,040 patients (71%) developed HF by 5 years, 64% of which occurred in the first year.<sup>11, 12</sup>

The diagnosis and treatment of ST elevation myocardial infarction has been the subject of intense investigation and the focus of numerous randomised clinical trials over the past few decades. In an attempt to minimise adverse sequelae it is imperative that in patients with ST elevation myocardial infarction (STEMI) the immediate goal of therapy is to rapidly achieve patency of the epicardial infarct related artery (IRA) and consequently reperfusion of the affected myocardium.

Thrombolysis achieves normal flow (TIMI grade 3) in the IRA in around 50% of patients compared to around 90% with primary PCI (pPCI). A meta-analysis of 23 randomised controlled trials has shown that primary PCI (pPCI) is superior to intravenous thrombolytic therapy for the prevention of death, stroke and reinfarction<sup>13</sup>. Evidence also states that in cases of failure to reperfuse following intravenous thrombolysis rescue percutaneous coronary intervention is the treatment of choice<sup>14</sup>. The successful restoration of epicardial coronary artery patency with TIMI grade 3 flow, however, does not necessarily translate into adequate tissue level perfusion.

Inadequate tissue level perfusion in ST – elevation myocardial infarction in the presence of a patent epicardial artery is characterised by myocardial microvascular dysfunction. Evidence of microvascular obstruction (MVO) regardless of how it is assessed is



associated with adverse clinical outcomes. A series of consistent data has clearly shown that MVO has a strong negative impact on outcome.<sup>15-21</sup> Indeed, patients with no-reflow exhibit a higher prevalence of: 1) early post-infarction complications (arrhythmias, pericardial effusion, cardiac tamponade, early congestive heart failure); 2) left ventricular impairment; 3) late repeat hospital stays for heart failure; and 4) mortality.<sup>22</sup>

As a consequence attention in recent years has shifted from merely achieving epicardial artery patency towards the status of the coronary microvasculature. Restoration of epicardial vessel patency does not mean complete perfusion recovery and perfusion of the microvasculature is an additional prerequisite for optimal recovery. However, there is not, as yet, a defined gold – standard for assessment of microvascular dysfunction in the cardiac catheterisation laboratory when intervention to minimise microvascular damage would be potentially of maximal benefit to the patient. Advances in the early identification of these patients and the pathophysiology of MVO in ST – elevation myocardial infarction could aid the development of preventative and therapeutic strategies.<sup>23</sup>

Hence, this thesis will concentrate on novel methods for early assessment of MVO using a coronary pressure wire at the time of emergency PCI for STEMI using contrast enhance cardiac magnetic resonance imaging (ceCMR) as the gold standard for assessment of left ventricular function and microvascular obstruction.

## **1.2 Pathophysiology of microvascular obstruction in myocardial infarction**

### **1.2.1 Background**

Myocardial microvascular obstruction was first described as no – reflow phenomenon in 1974<sup>24</sup>. In relation to this the working hypothesis is that ST elevation myocardial infarction is primarily an epicardial arterial event, with acute thrombus formation on the background of local atherosclerotic plaque rupture. This results in occlusion of the culprit vessel with subsequent downstream hypoxic myocardial damage and cell death.<sup>25</sup> The most prominent hypothesis is that coronary microvasculature damage is as a result of this acute insult secondary to mechanical and functional obstruction and reperfusion injury. However primary microvascular dysfunction must also be considered in this patient population.<sup>26</sup>

### **1.2.2 Mechanical obstruction of the microcirculation**

Distal embolisation of atherosclerotic material has been recognised as an important factor in decreased myocardial perfusion in the setting of ST elevation myocardial infarction. This has been shown by the injection of microspheres to represent atherosclerotic debris in the experimental canine setting<sup>27</sup> and was first noted in autopsy of 25 cases of sudden death due to acute coronary thrombosis. *Falk* noted that in 73% of cases there was

fragmentation of the proximal thrombus with peripheral embolisation causing micro-embolic occlusion of the small intra-myocardial arterioles associated with microinfarcts.<sup>28</sup> A further autopsy study confirmed this in patients who died within 30 days of thrombolysis or balloon angioplasty for treatment of ST – elevation myocardial infarction.<sup>29</sup>

Initial studies using a distal protection device confirmed a high number of patients in whom this was present and suggested improvement in surrogate markers of microvascular perfusion.<sup>30</sup> Systematic evaluation of angiographic evidence reveals distal embolisation to be in the region of 15% although due to the visual nature of assessment this number is thought to be artificially low.<sup>31</sup> In this same study, distal embolisation also carried an increased risk of poor clinical outcomes and was associated with an eight fold increase in 5 – year mortality. On the basis of these findings downstream embolisation of thrombus and plaque material is thought to be the major contributor to the mechanical element of microvascular obstruction in reperfused myocardial infarction. Hence, it was hypothesized the distal protection devices that prevent embolisation during primary PCI may improve distal perfusion.

This concept however has not been proven in the numerous randomised controlled trials which remained inconclusive despite capture of atheromatous material. The DEDICATION study further confirmed that the routine use of distal protection by a filterwire system during primary PCI did not seem to improve microvascular perfusion, limit infarct size, or reduce the occurrence of MACE.<sup>32-34</sup> A significant amount of distal

embolisation may occur prior to any medical or therapeutic intervention limiting the therapeutic benefits of distal protection devices. Therefore, although the presence of distal coronary embolisation is well documented its ultimate function and clinical significance remains to be further determined.

### **1.2.3 Functional obstruction of the microcirculation**

Distal embolisation of plaque material must not be taken in isolation and it must be remembered that these substances are potentially vasoactive and therefore not biologically inert. These bioactive materials have the potential to increase the functional impairment of the coronary circulation. Experimental models support the hypothesis that microcirculatory vasoconstriction plays a part.

The vasoconstricting peptide endothelin-1 is expressed in active plaque as a tissue factor which is shown to cause a significant reduction in coronary blood flow when released into the coronary circulation.<sup>26</sup> Moreover, ischaemia itself is known to reduce the bioavailability of nitric oxide further contributing to the dysfunction of the coronary microcirculation. However the extent to which these elements influence outcome in ST – elevation myocardial infarction is currently uncertain.

### **1.2.4 Reperfusion injury**

This is a controversial issue from a clinical standpoint if not an experimental one. This is defined as myocardial injury caused by the restoration of coronary blood flow after an ischaemic episode and can occur regardless of whether reperfusion is by medical or mechanical means. The coronary microcirculation is thought to be infiltrated by neutrophils and platelets at the time of reperfusion.<sup>35, 36</sup>

A number of pathophysiological mechanisms have been postulated with the major focus being on the central role of the microcirculation.<sup>37</sup> Histological studies have confirmed platelet as well as leukocyte accumulation and activation in the myocardial microcirculation, leading to vasoconstriction, thrombosis as well as the release of oxygen free radicals, proteases and pro-inflammatory mediators that can lead directly to tissue and endothelial damage. Neutrophils also form aggregates with platelets that plug capillaries, thus mechanically blocking flow.<sup>38</sup>

Increase in oxidative stress mediates a reduction in nitric oxide bioavailability as well as activation of the endogenous endothelin and the local renin-angiotensin system. At the time of myocardial reperfusion there is an increase in intracellular calcium and this induces cardiomyocyte death by causing hypercontracture of the heart cells and mitochondrial PTP opening. Consequently myocyte death is observed as is interstitial oedema and further leukocyte adherence.<sup>26, 36</sup>

The majority of the work relating to reperfusion injury is done in experimental models following acute occlusion of a previously normal epicardial artery. The disappointing

attempts to convert successful studies in animal experimental models into the clinical setting, has raised the question of the suitability of these animal models as representation of acute myocardial infarction in humans.

### **1.2.5 Pre-existing dysfunction of the myocardial microcirculation**

There is increasing evidence that pre-existing microvascular dysfunction may also part a part in outcomes following ST elevation myocardial infarction and in assessment of risk of myocardial infarction in patients with angiographically coronary arteries. Coronary flow reserve (CFR) is thought to be a marker of microvascular disease. One study that looked at 120 patients in whom the epicardial coronary vasculature was angiographically normal or mildly disease found that reduced coronary flow reserve was significantly associated with a poor long-term outcome. Cardiovascular events occurred in seven (18%) patients in the lowest tertile of coronary flow reserve compared with four patients in the middle tertile (10%) and two patients in the upper tertile (5%).<sup>39</sup> Hence there is evidence that myocardial microvascular obstruction could be a predictor of future coronary events in the absence of haemodynamically significant coronary artery disease. It is likely that in this setting this merely represents a marker of vascular disease which is yet to appear significant angiographically rather than an independent contributor towards risk of future vascular events.

The impact of pre-existing diabetes mellitus on myocardial perfusion following primary angioplasty has also been investigated. One study found that despite similar high rates of

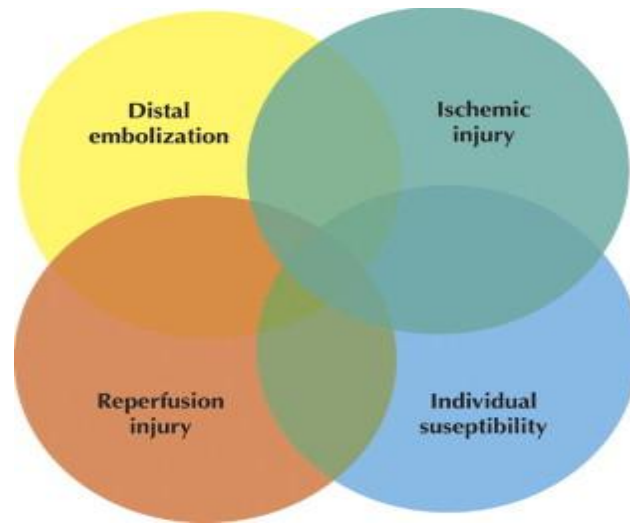
TIMI flow grade 3 after primary PCI in patients with and without diabetes, patients with diabetes are more likely to have abnormal myocardial perfusion as assessed by both incomplete ST segment resolution and reduced myocardial blush grade. Diminished microvascular perfusion in diabetics after primary PCI may contribute to adverse outcomes.<sup>40</sup>

A substudy of the EMERALD study confirmed this adverse prognosis in diabetic patients concluding that in patients with ST-segment elevation myocardial infarction undergoing primary PCI, diabetes is independently associated with decreased myocardial reperfusion, larger infarct, development of congestive heart failure, and decreased survival. In this study myocardial perfusion was again assessed using myocardial blush grade and ST segment resolution index and infarct size was assessed using technetium-99m single photon emission computed tomography measured between days 5 and 14 post reperfusion.<sup>41</sup>

### **1.2.6 Summary**

The pathophysiology of myocardial microvascular obstruction in the setting of myocardial infarction is multi-factorial, comprising of mechanical obstruction, functional obstruction, reperfusion injury and the elements comprising this as well as pre-existing microvascular disease in specific patient groups. The exact pathological mechanisms

remain to be determined and this may in part be due to the heterogeneous nature of the pathophysiological process.



**Figure 1.1: Mechanisms Responsible for No-Reflow** Four interacting mechanisms (distal embolisation, ischemia-related injury, reperfusion related injury, and individual susceptibility to microvascular injury) are responsible for no-reflow phenomenon. The individual contribution of these mechanisms to the pathogenesis of no-reflow is likely to vary in different patients.

### **1.3 Current tools for assessment of the coronary microcirculation**



As previously stated when treating ST – elevation myocardial infarction with primary or rescue angioplasty restoration of normal epicardial blood flow (TIMI 3) flow does not guarantee sufficient microvascular perfusion or optimal outcomes due to a combination of the factors. These patients would need to be identified at the earliest possible opportunity in order to maximize the impact of any potential future target therapies. A variety of methods ranging from electrocardiographic criteria to magnetic resonance imaging and intracoronary pressure assessment can be used for this purpose.

### **1.3.1 Electrocardiographic ST-segment resolution following reperfusion**

The measurement of the degree of resolution of ST segment elevation on the surface 12 lead ECG has long been used to assess success or failure of reperfusion therapy. It is well established that early and complete resolution of ST segment deviation is a powerful predictor of infarct-related artery patency, preserved microvascular integrity and low mortality in patients with STEMI. When assessed 90 – 180 minutes after the administration of thrombolytic therapy, complete resolution of ST segment elevation is associated with a very high (90 – 95%) probability of a patent infarct related artery, and around an 80% probability of TIMI (thrombolysis in myocardial infarction) grade 3 flow.

42, 43

In contrast, failure to completely resolve ST-segment elevation is not associated with a particularly high rate of occluded infarct related artery (around 50%). These patients are known to have an adverse prognosis <sup>44</sup> and a significant proportion of these patients are now known to have decreased microvascular perfusion.

Studies using contrast echocardiography, myocardial blush grade and intracoronary pressure assessment among patients with normal epicardial blood flow following STEMI have shown inconstant results when comparing persistent ST segment to other markers of persisting microvascular dysfunction. <sup>45-49</sup> Several studies have failed to show an association between ST-segment resolution and extent of microvascular obstruction assessed by cardiac magnetic resonance imaging. Furthermore, other published data have failed to show a definitive link between ST-segment resolution and infarct size measured by single photon emission computed tomography imaging. <sup>46, 50</sup>

The above has looked at ST-segment resolution index, however, there are now a variety of ways that the ECG can be assessed to provide further information about reperfusion. ST analysis may have a place as a surrogate marker of outcome in STEMI but the evidence shows that it cannot be used for accurate quantification of microvascular dysfunction. In addition, some patients with acute myocardial infarction have ECGs that cannot be interpreted such as left bundle branch block. Furthermore, if ST segment analysis is to be accepted as a surrogate measure of outcome in primary PCI studies a

consensus is needed about which measures to analyse, the optimal timing of ECG analysis and whether single ECGs or continuous ECG sampling is preferable.<sup>51</sup>

### **1.3.2 TIMI myocardial blush grade**

TIMI myocardial blush grade (MBG) is a semi-quantitative angiographic index of microvascular damage after recanalization of the infarct related artery.<sup>52</sup> This index is graded from 1 to 3, one being what appears to be no apparent myocardial perfusion and grade three being apparently normal myocardial perfusion in the context of TIMI grade 3 flow in the epicardial artery. MBG is a strong angiographic predictor of mortality in patients with TIMI 3 flow after primary angioplasty. Enzymatic infarct size was found to be larger and left ventricular ejection fraction was found to be lower in patients with MBG 0 or 1 compared with MBG 2 or 3.<sup>53, 54</sup>

MGB has also been shown to have an association with other potential markers of microvascular dysfunction such as ST segment resolution index, TIMI frame counting and coronary pressure wire derived markers.<sup>17, 47</sup>

However, MGB can be subjective and as such can be open to differing interpretation by different operators. Although MGB has been shown to be associated with enzymatic

markers of infarct size<sup>55</sup> recent studies comparing MBG with more accurate markers of myocardial damage post myocardial infarction such as contrast echocardiography, cardiac MRI imaging and SPECT scanning have raised doubts about its ability to accurately predict myocardial perfusion.<sup>16</sup>

In one study using SPECT scanning for assessment of myocardial viability in patients with TIMI 3 flow post angiography found that if MBG 0 and 1 were regarded as a sign of nonviable myocardium and MBG 2 and 3 were regarded as viable myocardium the sensitivity of MBG for the prediction of myocardial viability was 79%, specificity was 40%, positive predictive value was 88% and negative predictive value was 27%. This showing that although sensitivity is fairly good specificity is very low<sup>56</sup>.

*Porto et al* analysed the pathophysiological features underlying different blush grades using early CMR imaging and concluded that increased MBG was associated in a linear fashion with less microvascular obstruction on CMR imaging, concluding that the common practice of including MBG grades 2 and 3 into a single “patent microcirculation” category may not be justified.<sup>57</sup> In addition, *Fearon et al* concluded that MBG did not correlate with 3 month echocardiographic wall motion score in patients treated with primary PCI in the context of STEMI.<sup>47</sup>

TIMI myocardial blush grade is therefore known to be a useful angiographic predictor of outcome in STEMI although given its semi-quantitative nature there can be intra-operator variability in its interpretation. While it can serve as a marker of microvascular disease it cannot be used for accurate assessment of microvascular dysfunction and myocardial viability.

### **1.3.3 Corrected TIMI frame count**

The thrombolysis in myocardial infarction (TIMI) frame count (TFC) was developed as a simple objective, quantitative and reproducible method to assess coronary blood flow.<sup>58</sup> This method counts the number of cine-angiographic frames required for radio-opaque contrast to reach specified landmarks in each coronary artery. The TFC provides a more reproducible measurement of infarct-related artery blood flow than the TIMI flow grade. The TFC has also been shown to be associated with prognosis with one study finding that the corrected TIMI frame count (cTFC) three weeks after myocardial infarction was an independent predictor of five-year survival, but not 10-year survival in patients treated with thrombolysis for STEMI.<sup>59</sup> In the setting of percutaneous intervention for STEMI *Handama et al* found that lower cTFC of the infarct-related artery immediately after PCI was associated with greater functional recovery; and hence, cTFC could predict clinical and functional outcome in patients undergoing successful angioplasty.<sup>60</sup>

It has been postulated previously that in the setting of PCI for STEMI cTFC may be suitable to assess the degree of microvascular injury. However when *Ohara et al* investigated the relationship between cTFC and coronary blood flow velocity parameters (using a coronary Doppler wire) reflecting the degree of microvascular injury, in patients with acute myocardial infarction, they found that cTFC reflected epicardial coronary blood flow velocity but was not accurate to assess the degree of microvascular injury after primary coronary intervention.<sup>61</sup>

From a practical aspect these angiographic assessments can rely on performing very long acquisitions at high frame rates particularly if there is slow flow or no-flow and this generates technical problems for some catheter laboratory x-ray systems as well issues about radiation exposure.

#### **1.3.4 Assessment of microvascular integrity using myocardial contrast echocardiography**

Myocardial contrast echocardiography (MCE) is a technique that uses micro-bubbles during transthoracic echocardiography (TTE). These micro-bubbles (typically 2 to 6  $\mu\text{m}$  in diameter) remain exclusively within the intravascular space, and their status within any myocardial territory can be used to assess the status of microvascular perfusion within that area.<sup>62</sup> Micro-bubbles are biologically inert and purely act as tracer agents. They are

able to pass through an intact microcirculation. After bolus injection of micro-bubbles, contrast intensity seen within the myocardium reflects the concentration of bubbles. During a constant infusion of bubbles and resultant full saturation of the myocardium, the signal intensity represents the capillary blood volume. During high powered imaging, micro-bubbles are destroyed and the rate of replenishment can be measured. Myocardial blood flow at tissue level can thus be determined from the product of capillary blood volume and rate of micro-bubble replenishment after destruction by high powered imaging. Decreases in myocardial blood flow are associated with a proportionate prolongation of replenishment time<sup>63, 64</sup>.

*Ito et al* first described the significance of no reflow detected by intracoronary MCE despite apparently successful reperfusion therapy. In 39 patients with anterior STEMI treated with thrombolysis they found that patients demonstrating no-reflow had significantly reduced left ventricular ejection fraction and lower regional wall motion scores at 1 month follow-up.<sup>65</sup>

MCE was compared with corrected TIMI frame count, myocardial blush grade and percentage ST segment resolution at 90 and 180 minutes to predict left ventricular function assessed by regional wall motion score index (WMSI) at one month. In the small study (n=15) MCE was found to be the best predictor of improvement in LV function with sensitivity and specificity of 88 and 74% respectively.<sup>66</sup>

Intracoronary MCE can be performed at the time of emergency PCI by injection of contrast agent into the coronary ostium. Myocardial perfusion can be graded semi – quantitatively using an MCE score index (MCESI) from averaging the scores in each of the American Heart Association 16 segment model for myocardial perfusion (0 = not visible, 1 = patchy, 2 homogeneous contrast effect)<sup>16</sup>. In a study of 124 patients when  $MCESI \geq 1$  is considered adequate reperfusion, those with evidence of MVO defined by  $MCESI = 0$  had higher mean creatinine kinase, lower baseline ejection fraction on TTE and higher adverse remodeling at 6 month follow up.  $MCESI = 0$  patients also showed worse survival in terms of cardiac death ( $p < 0.0001$ ) and combined events ( $p < 0.0001$ )<sup>16</sup>.

The multicentre prospective cohort study AMICI (Acute Myocardial Infarction Contrast Imaging) evaluated the extent of microvascular damage assessed by MCE in comparison with tradition markers of microvascular damage in the prediction of LV remodeling after emergency PCI in ST elevation myocardial infarction. At multivariate analysis only TIMI grade  $< 3$  flow and endocardial length of contrast defect (expressed as a percentage of endocardial length) were independently associated with adverse LV remodeling. Among patents with TIMI grade 3 flow endocardial length of contrast defect was the only independent variable associated with adverse LV remodeling.<sup>49</sup> In this study MCE was performed 12-24 post PCI.



In the majority of studies MCE examination using intravenous contrast the first examination is performed between 12 – 24h following PCI. This could potentially result in a delay in identification of “at risk” patients. In addition some studies thus far in the field have concentrated on anterior myocardial infarction although not the case in the AMICI study. Inadequate echocardiographic image quality is another potential pitfall of this imaging modality especially in patients with inferior/posterior or apical myocardial infarction, patients with chronic lung disease or with a high body mass index (BMI). Of note, inadequate echocardiographic image quality was an exclusion from the AMICI study therefore it is not possible to tell how many patients were excluded on this basis.<sup>21</sup>

Intracoronary MCE has been used to assess microvascular perfusion in the early post intervention period (5 – 60 minutes). One study evaluated this in 199 patients following PCI however was limited to anterior myocardial infarction<sup>66</sup> The semi-quantitative nature of the indices used in these situations can also make interpretation open to observer variability and examinations require appropriate technical expertise especially in patients who are overweight.

Despite the evidence for MCE in the diagnostic assessment of microvascular damage and prediction of LV remodeling in some circumstances, currently available contrast agents are not yet approved for myocardial perfusion, only for LV opacification. Thus, their use is limited to clinical studies and consequently restricted in the clinical area.

## **1.4 Cardiac magnetic resonance imaging following acute myocardial infarction**

### **1.4.1 Background**

European and American guidelines recommend that all patients who have suffered AMI should undergo a formal evaluation of LV function, ideally pre-discharge. The exact means of LV assessment is not stipulated in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, while the European Society of Cardiology (ESC) guidelines recommend that TTE should be performed in all patients; other modalities may be used if available.<sup>67, 68</sup>

Unenhanced 2-dimensional (2-D) TTE is the most widely-used method of assessing LV function following AMI<sup>69</sup>. It is widely available and portable, but operator and acoustic window dependent. Even with a skilled operator and good acoustic windows a major limitation in LV function assessment in the post AMI period is the necessary geometrical assumptions required to produce volumes from two-dimensional echocardiography.<sup>70 71</sup> While subjective assessment of LVEF by an experienced operator is normally sufficient in clinical practice<sup>72</sup> there are potential pitfalls when accurate LV assessment is needed for research purposes.

ECG-gated myocardial perfusion tomography has been validated in the assessment of ventricular volumes. As with 2-D echocardiography, it is reasonably reliable in the normal heart but can be limited by low spatial and temporal resolution.<sup>73, 74</sup> The use of ionizing radiation limits the utility of nuclear techniques for serial follow up studies, especially in research.

Cardiac magnetic resonance imaging (CMR) has many advantages in the assessment of ventricular mass and function and has rapidly become the reference standard against which other techniques are measured.<sup>75</sup> CMR is non-invasive, uses no radiation, and has been shown to be safe early after AMI, although specific safety questionnaires must be completed prior to consenting to the investigation and entering the designated MRI scanning room. CMR scanning has also been shown to be safe in the early post infarct period.<sup>76</sup>

CMR scanning affords not only the gold-standard means of assessment of LV volumes and ejection fraction, but also allows assessment of myocardial viability, perfusion and regional function. Without any geometric assumptions, excellent accuracy can be maintained in abnormally shaped hearts, for example after myocardial infarction, where other techniques could be prone to error.<sup>77-82, 82-84</sup>

Excellent reproducibility is essential for follow up studies of patients, and especially in research as the better the inter-study reproducibility the smaller the sample size needed to detect a true clinical difference between patient populations. CMR has been shown to have the best inter-study reproducibility of any imaging technique for both mass and volumes of the left and right ventricles and specifically it is considered superior to two dimensional echocardiography.<sup>70, 85, 86</sup>

In summary, CMR is now considered the gold-standard means of measurement of LV mass, volumes and LVEF, particularly in patients with LVSD in whom the geometrical assumptions on which planar imaging techniques necessarily depend, fail to account for the changes that occur in LV morphology. Volumetric analysis is performed on CMR by dividing the LV into a stack of short-axis slices, which removes the need for any geometric assumption. In addition, the excellent spatial and temporal resolution afforded by CMR allows accurate delineation of endocardial and epicardial borders.

#### **1.4.2 Late gadolinium contrast enhancement CMR (ceCMR)**

Although several techniques CMR techniques can be used for the diagnosis of myocardial infarction, the most accurate and best validated is ceCMR. The technique involves inversion recovery imaging 5-10 minutes after administration of intravenous

gadolinium contrast agent. With appropriate settings the normal myocardium appears black or nulled, whereas the non-viable regions appears bright or hyper-enhanced.

The exact mechanism of hyper-enhancement has not as yet been clearly elucidated but the postulated theory is based on 2 principles. Myocytes in normal myocardium are densely packed and tissue volume is predominantly intracellular, therefore the predominantly extra-cellular gadolinium contrast agent cannot cross the intact myocytes cellular membranes. Consequently gadolinium distribution is small and the volume is low in an area of normal myocardium. In AMI there is membrane rupture which allows gadolinium to diffuse into the damaged myocytes, resulting in increased gadolinium concentration, shortened T1 relaxation and subsequent hyper-enhancement. In the chronic setting, scar has replaced necrotic tissue and the interstitial space has expanded again leading to increased gadolinium concentration and hyper-enhancement.

In animal models, numerous studies have shown an almost exact relationship between the size and shape of infarcted myocardium as assessed by ceCMR to that of histopathological examination.<sup>87-91</sup>

Studies in humans have shown that infarct size measured by ceCMR is closely associated with peak cardiac enzyme release and to measurements performed by positron emission tomography.<sup>92-95</sup> Furthermore, ceCMR appears to be superior to single photon emission computed tomography (SPECT) in detecting sub-endocardial infarcts and infarcts in non-

anterior locations.<sup>96, 97</sup> In humans with ischaemic LVSD, the transmural extent of the delayed enhanced region on ceCMR correlates inversely with improvement in regional contractility following revascularisation.<sup>94</sup> It should be stressed, however, that delayed enhancement on ceCMR is not a specific sign of infarction – it simply indicates that the normal fluid homeostasis within the abnormal segment has been disrupted. Delayed contrast enhancement has been reported in a variety of conditions including myopericarditis, hypertrophic and dilated cardiomyopathies, infiltrative cardiac disorders, cardiac neoplasia and in the transplanted heart.

A recent multi-centre international study assessed the performance of ceCMR. In total, 282 patients with acute and 284 with chronic first time MI were scanned in 26 centres. It concluded that when a dose of gadolinium of 0.2mmol/kg (the dose used in this study) or higher was used, when MI was identified, its location was correct in more than 97% of patients (the location of the hyper-enhancement matched the perfusion territory of the infarct related artery). Of note this study also looked at chronic MI a subset of patients on whom less data exists, and in whom infarcts are thought to be more difficult to detect given the shrinkage that can occur during healing.<sup>88</sup>

Therefore in summary, the data indicates that ceCMR is a well validated and robust technique, with an effectiveness that rivals (and many say surpasses) the current best available imaging techniques for the detection and assessment of MI.

### **1.4.3 CMR for the assessment of MVO**

In the 1990's MRI hardware improvement and pulse sequence advances allowed development of first pass and delayed enhancement contrast sequences which resulted in accurate assessment of tissue perfusion and necrosis. Early AMI studies using these techniques, principally in non reperfused infarcts, observed the heterogeneous nature of infarcted tissue. In particular areas of hypo-enhancement on contrast imaging were thought to represent diminished tissue perfusion. These areas were therefore thought to represent "no-reflow" also known as MVO. Further work in reperfused infarcts also suggested a relationship between this phenomenon and MVO.

*Judd et al* compared CMR findings with pathological assessment of infarcts in a two day old canine model. They correlated regional blood flow as assessed by microspheres in the hyper and hypoenhanced areas with pathological assessment of infarct using thioflavin-S staining. They found that hypoenhanced areas on CMR scanning had significantly reduced blood flow in comparison with remote areas and that the special location of these areas correlated closely with the pathological staining. These findings provided support for the concept that the hypo-enhanced core within the hyper-enhanced area following contrast injection represented MVO.<sup>98</sup>

In 1995 *Lima et al* reported two distinct infarct types in humans with reperfused myocardial infarctions, those with hypo-enhancement surrounded by hype-renhanced regions, and those with hyper-enhanced regions alone. By time intensity curve analysis the investigators found that these different areas of enhancement occurred secondary to

differences in wash in kinetics of gadolinium. The hypo-enhanced regions exhibited delayed contrast “wash-in” kinetics secondary to a delay and or absence of the contrast agent perfusing the affected tissue. These findings were consistent with what was postulated to be found in areas of microvascular damage.<sup>99</sup>

#### **1.4.4 CMR methodology for assessment of MVO**

The literature reveals that there is, as yet, no standard approach to imaging microvascular obstruction using MRI. The most commonly used methods are first pass perfusion techniques, early MVO assessment (normally 2 minutes following gadolinium injection) and late MVO assessment also known as late gadolinium enhancement from images acquired more than 10 minutes after gadolinium administration.<sup>15, 100-102</sup>

In theory, first pass perfusion should allow the most accurate assessment of MVO size as it allows less time than the other methods for diffusion of the gadolinium contrast agent to diminish the size of the defect. However, conventional first pass perfusion imaging affords significantly less spatial resolution than the other methods and typically does not cover the whole heart using only 3 slices the cover the left ventricle. In addition since first pass perfusion functions by highlighting differences in relative perfusion between areas of myocardium anything which causes a perfusion defect, for example a scar caused by a chronic infarct, could be interpreted as an area of MVO.<sup>103 104</sup>



A proportion of patients whom have a defect of first pass scanning do not have evidence of MVO on late gadolinium imaging. This ranges from 26% to 31%. It has been hypothesised that the reduction in the size of the hypo-enhanced area indicated that the edges of the perfusion defect were filled in over time by gadolinium through collateral flow or by slow diffusion. It was therefore suggested that MVO on late gadolinium images reflected the presence of extensive and severe myocardial damage. Perhaps unsurprisingly it is this method for assessment of MVO which is most strongly linked with prognosis.<sup>105, 106</sup>

Recently, high resolution first pass assessment has been shown to be potentially superior to early and late gadolinium enhancement and may in the future become the method of choice for assessment and quantification of MVO<sup>104</sup> however at the time of our study these sequences were not available and given the higher temporal resolution, particularly with delayed gadolinium enhancement we concentrated of assessment of MVO using “early” and “late” gadolinium enhancement also known as early and persistent MVO.

One study which compared first pass and persistent MVO found a good level of concordance between the two methods.<sup>107</sup> Furthermore this thesis will document the comparison of early and persistent assessment of MVO in my study population.

There are few papers directly comparing ceCMR assessment of MVO with other imaging modalities. One study, comparing MRI with <sup>201</sup>Tl SPECT for assessment of infarct size, found that those with MVO as assessed by ceCMR had larger infarcts on <sup>201</sup>Tl SPECT

imaging. There was no direct comparison between the 2 modalities for assessment of MVO.<sup>108</sup>

There has been a direct comparison between ceCMR and contrast echocardiography in a reperfused dog infarct model using thioflavin-S staining as the gold standard. They found a good correlation between the 2 methods. The threshold for detecting MVO as defined by microsphere flow was lower for ceCMR ( <40% of remote regions) than for contrast echocardiography ( <60% of remote regions) suggesting that ceCMR may be less sensitive but more specific than echocardiography for the detection of MVO.<sup>109</sup>

#### **1.4.5 Clinical and prognostic implications of MVO as assessed by ceCMR**

The presence of persistent MVO on ceCMR imaging in reperfused STEMI treated by primary angioplasty has been shown to be a significant factor on detrimental LV remodeling and ejection fraction at 6 months post reperfusion.<sup>110</sup>

*Wu et al* analysed early MVO defined as early hypo-enhancement, in 44 AMI patients (eight patients with primary PCI, 20 patients with elective PCI >48h). In patients with MVO, more cardiovascular events occurred than in those without MVO and microvascular status predicted the occurrence of cardiovascular complications. The combined cardiovascular risk of death, re-infarction, congestive cardiac failure or stroke increased with infarct extent (30%, 43% and 71% respectively) for small, medium and

large infarcts. Even if the analysis was adjusted for infarct size the presence of early MVO remained a prognostic marker for post MI complications.<sup>111</sup>

The first study to link persistent MVO to prognosis was published in the European Heart Journal in 2005 by *Hombach et al.* They found using Kaplan-Meier curves a significant event free survival for patients without persistent microvascular obstruction. At 100 days follow up, the difference in occurrence of major adverse cardiac events (MACE) between patients with and without MVO was 12.6% (95% confidence interval, 1.4% - 23.8%). Furthermore, they found that the presence of early MVO was a predictor for the occurrence of MACE.<sup>15</sup>

The largest and most recent study linking persistent MVO with prognostic impact in reperfused AMI was published by *Cochet et al.*<sup>106</sup> They looked at 190 patients whom underwent primary PCI for treatment of STEMI. They found that persistent MVO was relatively common, occurring in around 50% of reperfused infarcts, a finding in keeping with work from our own group.<sup>112</sup> In addition they compared MVO assessed by first pass and persistent MVO. They found that persistent MVO was associated with a dramatically higher risk of cardiovascular events, even when adjusted for major markers of prognosis after AMI. In addition their data suggested that the prognostic value of persistent MVO was superior to MVO determined by first pass images.

Therefore to summarise, MVO assessment by late gadolinium is thought to represent potentially severe cases with persistent contrast filling defects. It is also known to be

common in reperfused AMI and is linked with prognosis more strongly than the other methods for assessment of MVO. For these reasons I have chosen to look at persistent MVO primarily in my work but will also record early MVO and therefore also allow comparison between the two methods.

#### **1.4.6 The optimal timing for CMR scanning following STEMI**

Animal studies have shown that MVO whether early or late as assessed by ceCMR can increase in size up to 48 hours.<sup>113</sup> A further study in the canine model has shown that MVO remains essentially unchanged at 2 days and 9 days post infarct.<sup>114</sup> However further work by *Albert et al* revealed that in 96 patients imaged on different days following AMI, MVO prevalence fell dramatically beyond 48 hours from the recorded time of infarction (with a decrease in prevalence of greater than 50% within the first 7 days).<sup>107</sup> Therefore as can be seen there is as yet no consensus on the optimal timing for imaging in this patient group. Given the evidence available my aim was to perform all ceCMR scans at around 48h following reperfusion. This could not be done exactly given the 24 hours nature of recruitment in the study. I also felt that given average stay in hospital following STEMI is gradually decreasing this methodology did not result in ceCMR scanning delaying the patients discharge or transfer back to their base hospital.

Although important prognostic information can be gained from ceCMR scans performed after successful reperfusion this diagnostic tool is not available in the very early post infarct period for a variety of reasons, clinical, logistical and theoretical. The result is that

this useful information is not available at the time of emergency PCI when interventions in an “at risk” patient group would potentially be most beneficial. Therefore this thesis will look also at the feasibility, safety and clinical utility of ceCMR in the very early post infarct period.

## **1.5 Novel invasive markers for microvascular dysfunction using a coronary temperature/pressure wire at the time of emergency PCI**

### **1.5.1 Coronary microvascular resistance**

Resistance equals pressure gradient divided by flow. In the case of the coronary circulation, the mean aortic to distal coronary back pressure gradient divided by total sinus blood flow over time yields total coronary resistance (mmhg/ml/min). Under normal conditions the epicardial arteries which run over the surface of the heart do not create any significant resistance to blood flow. Even at high flow rates only a negligible pressure difference exists between the central aorta and the most distal part of the angiographically smooth epicardial artery.<sup>115</sup>

Under normal physiological conditions, resistance is principally determined by vasomotor regulation of the arterioles with a diameter of less than 400  $\mu\text{m}$  and flow is kept constant over a wide level of perfusion pressures by auto-regulation. The control mechanisms of auto-regulation are numerous and beyond the remit of this thesis.<sup>116-119</sup> Therefore, under baseline conditions the knowledge of coronary resistance reflects basal metabolism, but when auto-regulation is exhausted, as in under pharmacological hyperaemia, minimal resistance can be calculated.

Thus, in order to evaluate the performance of the microvascular bed and quantify microvascular resistance the following conditions should ideally be met: (1) exclude the presence of obstructive epicardial coronary artery disease or determine the pressure distal to the stenosis, (2) quantify flow, (3) induce maximal vasodilation while recording pressure and flow, and (4) correct for coronary back pressure.<sup>120</sup>

The difficulties involved in accurate quantification of coronary flow in vitro have given rise to the use of thermodilution as a surrogate marker. According to thermodilution theory<sup>121, 122</sup> flow equals  $V/Tmn$  where  $V$  represents the vascular volume between the injection site (the tip of the guiding catheter) and the location of the sensor, in the distal part of the RADI<sup>TM</sup> coronary pressure/temperature wire, and  $Tmn$  is the mean time taken from a bolus of saline to travel from the sensor in the proximal shaft of the guidewire to the distal sensor. Given that these measurements are taken under conditions of pharmacological induced maximal hyperaemia  $V$  should remain static while  $Tmn$  becomes representative of flow. Upon these principles the first coronary pressure/temperature wire based assessment of the coronary microcirculation was developed drawing on the previous Doppler wire experience.<sup>123</sup>

### **1.5.2 Thermodilution derived coronary flow reserve**

The validity of the thermodilution principle to demonstrate CFR on a commercially available guide-wire (PressureWire 3, Radi Medical Systems) was first validated in an

experimental dog model by *De Bruyne et al* in 2001<sup>124</sup>. In this in-vitro model, absolute flow was compared with the inverse mean transit time ( $1/T_{mn}$ ) of a thermodilution curve obtained after a bolus of 3ml saline at room temperature. A very close correlation ( $r>0.95$ ) was found between absolute flow and  $1/T_{mn}$ . In the canine model a significant correlation was found between CFR, calculated from the ratio of hyperaemic to resting flow velocities using a Doppler flow wire, and the CFR derived from the ratio of resting to hyperaemic  $T_{mn}$  ( $r=0.76$ ;  $p = <0.001$ )

Therefore thermodilution derived CRF is calculated as follows<sup>124</sup>. Coronary flow reserve (CFR) is defined as the ratio of peak hyperaemic to resting flow (F).<sup>123</sup>

1.  $CFR = F \text{ at hyperaemia} / F \text{ at rest}$

Flow is the ratio of the volume (V) divided by  $T_{mn}$ . Thus, CFR can be expressed as follows.

2.  $CFR = (V/T_{mn}) \text{ at hyperaemia} / (V/T_{mn}) \text{ at rest}$

Assuming the epicardial volume (V) remains unchanged, CFR can be calculated as follows.

3.  $CFR = T_{mn} \text{ at rest} / \text{at hyperaemia}$



This was then validated in humans by comparison with what was at the time the current gold standard for invasive CFR calculation, the Doppler flow wire. In 103 coronary artery territories in 50 patients, in a variety of angiographically normal and stenotic vessels the correlation between the two methods was close ( $r = 0.80$ ;  $P < 0.001$ ).<sup>125</sup>

However, rather than being simply a measure of microvascular resistance, CFR accounts for both epicardial and microvascular resistance. Fractional flow reserve (FFR) is derived from the ratio of distal coronary pressure (beyond the stenosis in question) to the pressure proximal to the stenosis (in most cases taken as the aortic pressure). FFR, therefore accounted for the contribution of the epicardial artery to the total coronary resistance. Initially when thermodilution derived CFR was validated it was thought that CFR and FFR could provide the clinician with complimentary data.<sup>115, 125, 126</sup>

Therefore, while FFR went onto everyday use in our catheter laboratories for the evaluation of epicardial stenoses<sup>127</sup> the limitation of CFR to independently assess the coronary microvasculature limited its clinical utility.<sup>128</sup> Furthermore CFR is limited by its dependence on heart rate and blood pressure, thereby calling into question its reproducibility.<sup>129, 130</sup>

### **1.5.3 The index of microcirculatory resistance**

*Fearon et al*<sup>131</sup> postulated that the calculation of the microvascular resistance by dividing the distal coronary pressure by absolute coronary blood flow would provide an independent assessment of microcirculatory function. Their theory was that a novel index of microcirculatory resistance (IMR), defined as a distal coronary pressure divided by the inverse of the hyperaemic mean transit time (a correlate to absolute flow), measured simultaneously with a coronary pressure wire would independently evaluate microvascular resistance. Or put more simply IMR would equal distal coronary pressure multiplied by the hyperaemic mean transit time.

$$\text{IMR} = \text{Pd} \cdot Tmn$$

A fundamental assumption in the theory is that *Tmn* is inversely proportional to hyperaemic blood flow. Because

$$F = V / Tmn$$

Where flow (F) equals the ratio of epicardial vascular volume (V) and mean transit time (*Tmn*). Because true microvascular resistance (TMR) equals distal perfusion pressure divided by flow:

$$\text{TMR} = \text{Pd} / F$$

And because the vascular volume (V) may be assumed to remain constant at maximal hyperaemia by combining equations 1 and 2, can be derived that TMR is proportional to the product of distal coronary pressure and *Tmn*:

$$\text{TMR} = \text{Pd} \cdot \text{Tmn}$$

Because both distal pressure and flow would drop in the presence of an epicardial stenosis, IMR should remain unaffected. The investigators validated IMR against true microvascular resistance (TMR) in an open chested porcine model using embolised microspheres for disruption of the microcirculation. They found that changes in IMR between various epicardial and microcirculatory conditions mirrored those of TMR, their gold standard reference for microvascular resistance.<sup>131</sup>

This work was further corroborated by *Aarnoudse et al*<sup>132</sup> who not only added to the weight of evidence of the close relationship between inverse *Tmn* and absolute coronary flow but further validated IMR as an independent marker of microvascular resistance in an in vitro physiological model. They found a close correlation between inverse *Tmn* and absolute blood flow ( $R^2 = 0.93$ ) and IMR and TMR ( $R^2 = 0.94$ )<sup>132</sup>

#### **1.5.4 IMR in the presence of an epicardial stenosis**

While the initial IMR ( $\text{IMR} = \text{Pd} \cdot \text{Tmn}$ ) validation had pointed to the fact that IMR was independent of an epicardial stenosis<sup>131, 132</sup> some subsequent studies suggested that the

minimum achievable myocardial resistance actually increased with the severity of the epicardial arterial stenosis.<sup>133-135</sup> Those studies calculated microvascular resistance using a coronary pressure wire to calculate distal pressure and a Doppler flow wire to estimate coronary flow. Resistance was calculated by dividing pressure by coronary flow. Of note however, changes in collateral flow, which may occur with increasing severity of stenosis and which may affect the calculation of resistance, were not incorporated into the formula.

By working on the basis that myocardial blood flow is the sum of antegrade coronary flow and collateral flow, with collateral flow increasing with the severity of an epicardial stenosis. As a result of collateral flow, the distal perfusion pressure will not reach zero but rather will approach the coronary wedge pressure as the epicardial stenosis reaches total occlusion at maximal hyperaemia. Therefore, the increase in collateral flow results in an increase in myocardial flow that is reflected in the distal pressure measurement (the numerator in the equation of resistance) but not incorporated into the previous method for assessment of flow (the denominator in the equation of resistance) resulting in an overestimation of microvascular resistance. Once the epicardial stenosis is removed and collateral flow is thought to diminish minimal vascular resistance will appear to decrease.

By measuring collateral flow by measuring distal coronary wedge pressure and incorporating it into the calculation *Fearon et al*<sup>136</sup> found no change in the minimal microvascular resistance with an increasing epicardial stenosis.

$$IMR = [(Pa - Pv) \times Tmn] \times [(Pd - Pw)/(Pa - Pw)]^{136}$$

Where Pd, Pa, Pw and Pv are distal coronary pressure, aortic pressure, distal coronary wedge pressure and central venous pressure respectively.

Assuming Pv is around 0 then,

$$\underline{IMR = Pa.Tmn \times [(Pd - Pw)/(Pa - Pw)]^{136}}$$

Concurrent work by *Aarnoudse et al*<sup>137</sup> tested this hypothesis in humans. They performed a total of 90 measurements in 30 patients whom were scheduled to undergo PCI. They found that when coronary wedge pressure (Pw) was appropriately accounted for microvascular resistance did not change significantly with the severity of the epicardial stenosis. Therefore, not only concluding that IMR was safe and feasible in humans with commercially available equipment, but that IMR was a specific index of microvascular resistance when collateral flow was properly taken into account.<sup>137</sup>

More recently IMR incorporating coronary wedge pressure has been termed  $IMR_{true}$  and IMR in the absence of an epicardial stenosis has been termed  $IMR_{app}$ .<sup>138</sup> I will use this terminology when directly comparing the two prior to and post stenting in chapter 6.

### **1.5.5 The clinical utility of IMR**

In comparison with CFR, IMR had been shown to be a specific index for microvascular resistance whereas CFR took into account epicardial and microvascular resistance. However, one of the other limitations of CFR was that it was shown to vary with haemodynamic conditions thereby limiting its reproducibility<sup>129</sup> and hence it's clinical utility.

*Ng et al*<sup>130</sup> compared the reproducibility and haemodynamic dependence of IMR, CFR and FFR in humans under different haemodynamic conditions, including baseline, right ventricular pacing at 110 beats per minute, nitroprusside infusion, and dobutamine infusion. In comparison with CFR, IMR and FFR values remained similar throughout all haemodynamic conditions suggesting that IMR provided a reproducible interrogation of microcirculatory resistance, which was independent of haemodynamic changes, suggesting therefore, that IMR could be used across a patient population rather than between two time-points in one patient.

### **1.5.6 IMR in STEMI**

As the last decade progressed the significance of the microcirculation in the context of reperfused STEMI became more topical.<sup>23, 139</sup> An editorial in the *New England Journal of Medicine* suggested the need for sensitive diagnostic techniques to evaluate the microcirculation in patients with acute myocardial infarction.<sup>140</sup>

*Fearon et al*<sup>47</sup> evaluated IMR in 29 patients undergoing primary PCI for STEMI. They compared IMR with other known markers of microvascular damage TIMI perfusion grade, TIMI frame count, CFR and ST – segment resolution index in their ability to predict peak creatinine kinase (CK) as a marker of infarct size and recovery in wall motion scoring (WMS) as assessed by echocardiography. On multivariate analysis IMR was the most significant predictor of peak CK and three month WMS. IMR was also the only significant predictor of recovery of left ventricular function on the basis of percentage change in WMS ( $R = 0.50$ ,  $p = <0.01$ )<sup>47</sup>

It had therefore been shown that IMR was a feasible and safe, specific assessment of the coronary microcirculation which could potentially be used as a marker for microvascular resistance at the time of STEMI.

### **1.5.7 Pressure derived collateral flow index**

Pressure derived collateral flow index (CFIp) can be quantified on a pressure wire. This can only be done in the setting of PCI as it requires knowledge of Pw. The ratio of Pw to Pa during balloon inflation is thought to represent CFIp.

$$\text{CFIp} = (\text{Pw} - \text{Pv}) / (\text{Pa} - \text{Pv})$$

In practice the measurement of Pv is not routinely taken and has been assumed to have been 0.<sup>141</sup>

CFIp is hypothesized to increase with collateral flow and has been shown in a prospective study to predict future ischaemic events after PCI in patients with stable angina and normal left ventricular function<sup>142</sup>. In the infarcted heart, however, CFIp is not thought to solely reflect collateral supply but is influenced by microvascular dysfunction. A higher CFIp has been linked to other surrogate markers of poor microvascular perfusion, being significantly higher when no reflow<sup>143</sup> is seen by contrast echocardiography and being associated with poor ST segment resolution<sup>144</sup>.

Previous work by our own group found that increased CFIp and Pw in the patient group TIMI grade 3 flow following rescue PCI for STEMI was associated with poor left ventricular function adding weight to the theory that raised CFIp and Pw in the setting of STEMI may reflect a dysfunctional microcirculation rather than good collateral protection.<sup>141</sup>



*Sezer et al* measured CFIP in patients whom underwent PCI a mean of 3.3 days following successful thrombolysis for STEMI. They found that raised CFIP was an independent predictor for left ventricular dilatation assessed one year following infarction by echocardiography.<sup>45</sup>

CFIP is therefore postulated to be a surrogate marker of MVO in STEMI<sup>23</sup> although as can be seen it does not have the physiological data behind it that IMR has. It does appear however, from the work done previously that it does have an effect of left ventricular function following rescue PCI<sup>141</sup>, successful thrombolysis<sup>145</sup> and primary PCI<sup>146</sup>, further strengthening this argument.

## **1.6 Aims of this thesis**

Microvascular dysfunction is a significant problem linked with increased morbidity and mortality despite patency of the infarct related artery in STEMI. Contrast enhanced CMR scanning in the post infarct period allows assessment of left ventricular injury, can determine and allows quantification of MVO and allows quantification of infarct volumes. Cardiac MRI is thought to be the current gold standard for assessment of these

measures following STEMI. This important prognostic information is not however available until around 48h following PCI.

IMR has been validated in vitro and in stable patients as a quantitative marker of myocardial resistance. It can be calculated as the time of PCI using a commercially available guidewire and software. IMR has been shown in a small study to be more predictive of peak CK rise (a biochemical marker for infarct size) and left ventricular damage by echocardiography than traditional markers for MVO at the time of emergency PCI.

The hypothesis that this thesis will test is whether pressure wire derived markers on microvascular dysfunction, principally IMR, measured at the time of emergency PCI for STEMI, are associated with MVO and can predict left ventricular damage and infarct volumes on subsequent ceCMR imaging. A full outline of the aims of this thesis are stated below

The aims of this thesis are:

- To assess the relationship between pressure wire derived markers microvascular resistance, principally IMR, and MVO assessed of ceCMR imaging at 48h post emergency PCI for STEMI.

- To assess the ability of pressure wire derived markers microvascular resistance, principally IMR, at the time of emergency PCI to predict LVEF, LVESV, LVEDV and infarct volumes on ceCMR imaging at 48h and 3 months.
- To assess the relationship between pressure wire derived markers microvascular resistance and adverse ventricular remodeling
- To assess the relationship between pressure wire derived markers microvascular resistance and transmural score on ceCMR
- To assess the influence of anatomical site of myocardial infarction and therapeutic interventions at the time of emergency PCI on coronary pressure wire derived indices of microvascular obstruction.
- To assess the relationship between coronary pressure wire derived markers of microvascular obstruction and “traditional” indices of myocardial damage and microvascular obstruction in ST – elevation myocardial infarction, in particular, TIMI flow grade, ST-segment resolution index, corrected TIMI frame count, peak troponin I and time to reperfusion.
- To assess the relationship between coronary pressure wire derived indices of microvascular dysfunction prior to and following stenting in emergency PCI for ST elevation myocardial infarction.
- The relationship between IMR, CFIP and Pw at the time of emergency PCI

- To assess the correlation between early and late/persistent MVO assessed by ceCMR scanning 48 following STEMI
- To assess the feasibility, safety and clinical utility of ceCMR in the early post infarct period
- To assess the impact of IMR measured at the time of STEMI on clinical outcomes (in collaboration with other groups) See Appendix V

# **Chapter 2: Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology**

## **2.1 Introduction**

The coronary pressure wire is used for physiological assessment of the coronary vasculature increasingly frequently in clinical practice. Fractional flow reserve can now be used to assess lesion severity in a variety of anatomical situations. Increasingly the coronary pressure wire is being used to interrogate the coronary microvasculature. Coronary flow reserve (CFR) and Index of microcirculatory resistance (IMR) require hyperaemia to accurately assess thermodilution – derived mean transit times, and pressure derived collateral flow index (CFI<sub>p</sub>) is calculated from coronary wedge pressure and aortic pressure at hyperaemia. In addition coronary flow velocity as assessed by a coronary Doppler flow wire needs appropriate induction of hyperaemia. However, the majority of this article will however focus on hyperaemia induction for pressure wire studies.

Significant clinical decisions are made as a result of fractional flow reserve readings therefore it is imperative that they are carried out correctly. Maximal coronary hyperaemia is essential in producing accurate, reproducible measurements. This article focuses on the pharmacological agents that can be used for this purpose, discusses which agents can be used in specific situations, and briefly addresses the future of pharmacological stress in the catheter laboratory.

## 2.2 Fractional Flow Reserve

Measurement of pressure derived fractional flow reserve (FFR) is a widely used technique in cardiac catheterisation laboratories to determine the functional significance of coronary artery stenoses<sup>127</sup>. FFR is defined as the ratio of the maximal blood flow achievable in a stenotic vessel to the theoretical maximal flow in the same vessel if no stenosis was present. In a normal coronary artery there should be no pressure gradient between the aorta and the distal artery resulting in a FFR value of 1. These simultaneous measurements can be made in a stenosed coronary artery using a pressure tipped coronary guide wire to record distal pressure and a guide catheter to record pressure in the aorta. Studies have shown that a  $FFR < 0.75$  reliably identifies a stenosis with the potential to induce reversible myocardial ischaemia. A multicentre registry study has also shown that post stenting FFR is a strong independent predictor of outcome at six months, the higher the post stenting FFR the lower the event rate.<sup>147</sup> Furthermore, in patients with multivessel disease FFR can be used as a reliable and lesion-specific index of stenosis severity.<sup>127</sup> Pullback of the pressure wire can be used to determine which of two or more serial stenosis is more functionally significant, Due to the interaction of serial stenosis determination of the exact FFR of distal lesions requires knowledge the coronary pressure proximal to that particular lesion and not the aortic pressure that is used in routine clinical practice. The FAME trial was a multicentre randomised study comparing FFR guided PCI with angiographically guided PCI in patients with multi-vessel disease and determined that an FFR guided strategy results in superior clinical outcomes.<sup>127</sup>

The achievement of maximal hyperaemia is a prerequisite for the accurate determination of all pressure wire derived markers of lesion severity and microvascular resistance.

The available pharmacological agents for inducing maximal coronary hyperaemia can be given by intracoronary injection (ic) or intravenous infusion (iv). The most commonly used agent in clinical practice is adenosine, both ic and iv and intracoronary papaverine. For the sake of completeness this article will also cover dobutamine, sodium nitroprusside and contrast media although these should not be viewed as routine, effective options for induction of hyperaemia for pressure wire studies.

### **2.3 Adenosine**

Adenosine was identified in the myocardium in 1929. It is synthesised in the myocardium and interstitial adenosine concentration rises as a result of increased metabolic oxygen requirements and ischaemia.<sup>148</sup> Exogenously administered adenosine causes profound microvascular dilatation mediated by an adenosine receptor (A<sub>2</sub>) on the cell membrane of resistance vessel myocytes. Therefore adenosine induces near-maximal coronary vasodilation primarily through activation of adenosine receptors in vascular smooth muscle and hyperaemia is independent of metabolic demand.<sup>149</sup> However the exact physiological role of adenosine in the regulation of coronary blood flow is as yet unknown. The pharmacological profiles of adenosine differ depending on the mode of administration.



### **2.3.1 Intracoronary adenosine**

Intracoronary adenosine is an extremely safe agent to induce maximal hyperaemia.<sup>150</sup> The peak effect occurs less than 10 seconds after administration but has a duration of action of less than 20 seconds. There have been numerous studies looking at the appropriate doses of intracoronary adenosine needed to achieve hyperaemia. Initial thinking that lower doses of the drug (15 – 20 micrograms in the right coronary artery and 18 – 24 micrograms in the left system)<sup>151</sup> have been superseded in recent years by evidence that administration at these levels may result in an overestimation of FFR in a significant number of patients, specifically those with an FFR between 0.75 and 0.80, the so called “grey area”. It has been shown that intracoronary doses of ic adenosine are safe at higher doses, with minimal side effects. While initial high doses of ic adenosine are not always necessary, incremental dose escalation is recommended in those with an intermediate FFR value of 0.75-0.80.<sup>151</sup> Current thinking is that to achieve optimal hyperaemia patients should be administered an intracoronary dose of 40 micrograms into the right coronary artery and 60 micrograms into the left coronary. This should be increased in 20-30mcg increments to a maximum of 150 micrograms if the FFR remains between 0.75 and 0.80.<sup>150</sup>

The main side effect associated with this method of administration is short lasting, transient atrio-ventricular block, which is understandably, most frequently noted after administration of the drug into the right coronary artery.

### **2.3.2 Practical considerations when using intracoronary adenosine**

Prior to administration of ic adenosine it is prudent to administer a standard dose of ic nitrate to decrease the possibility of arterial spasm influencing the FFR measurements. In order to achieve maximal drug delivery to the coronary artery and to obtain accurate measurements of the aortic pressure it is essential to use a guide catheter without side holes and to ensure co-axial engagement. For all pressure wire studies it is important not to use a guide catheter that is too large for the ostium of the artery as this may cause pressure damping to occur. This can be recognised by the presence of a ventricularised aortic pressure tracing.

The more specific limitations encountered when using ic adenosine relate to both its rapid onset of peak effect and the short duration of peak hyperaemia. It is not possible to make a pull back curve to assess the potential severity of serial stenosis in the same epicardial artery. Given the short time scale involved in taking these measurements it is important that the readings are measured on a beat to beat basis rather than from a mean, which is the default setting in some analysers. Mean readings are likely to result in an underestimation of the maximum gradient. A further point to ensure an accurate FFR measurement is that the interruption in aortic pressure (Pa) recorded from the guide catheter should be as short as possible after the ic injection. A significant delay may result in the period of peak hyperaemia being over by the time aortic pressure is read. The use of an ic bolus of adenosine does however allow repeated measurements to be made

over a short period provided enough time is taken between readings for the effects of the previous dose to have waned.

### **2.3.3 Intravenous adenosine**

In contrast with dosages used to achieve hyperaemia using ic adenosine there is widespread consensus regarding the appropriate dose of iv adenosine. When administered through the femoral vein or a large cubital vein the usual dose in clinical practice is *140/micrograms/kg/min*. This should achieve a peak effect in around 1 minute. Similarly the effect wears off approximately 1 minute after the infusion is stopped. In the case of an intermediate FFR measurement of 0.75-0.80 the dose of the IV infusion can be safely increased to 180micrograms/kg/min.<sup>115</sup>

AV block is much less common with a continuous infusion of iv adenosine than with ic adenosine and is rarely seen in clinical practice. Adenosine can provoke bronchoconstriction so the main contraindication to iv adenosine is significant bronchoconstrictive lung disease such as asthma or chronic obstructive pulmonary disease. Intravenous adenosine is frequently accompanied by an unpleasant angina like sensation in the chest and throat which can be associated with dyspnoea.<sup>149</sup> This sensation is harmless and does not indicate myocardial ischaemia. The patient should be suitably reassured prior to the procedure to prevent any undue alarm. This course of action should allow the vast majority of patients to tolerate the sensation. This feeling should pass quickly after ending the infusion. If the patient remains asymptomatic throughout the

administration of adenosine then the physician should question whether the drug is being appropriately delivered. Administration of the drug should also cause a decrease in blood pressure of around 10-20% and a similar increase in heart rate. These should also act as markers that the drug is being delivered effectively.

#### **2.3.4 Practical considerations when using an intravenous adenosine infusion**

General rules with regard to intravenous infusions should be followed to ensure the maximal amount of the pharmacological agent reaches the coronary vasculature. These include using a volume controlled infusion pump with sufficient capacity and ensuring the patient's arm is extended if a brachial vein is used for the infusion. As with ic adenosine it is prudent to administer an ic dose of nitrate prior to commencing the infusion. One of the main advantages of using an IV infusion of adenosine is that it produces a steady state hyperaemia, which allows a pullback curve to be recorded. This allows physiological assessment of the entire coronary artery and assessment of serial stenoses and/or stent placements. Due to the short half-life of adenosine it is essential that venous return to the heart should not be interrupted by valvula-like manoeuvres. This can result in significant pressure signal fluctuations, which in turn can cause an overestimation of fractional flow reserve. The patient should therefore be instructed to breathe normally.

### **2.3.5 The effects of methylxanthines on adenosine**

It is postulated that caffeine can blunt the hyperaemic response by blocking the A2a receptors. Caffeine is a competitive inhibitor of adenosine at cellular level. There is not, as yet, definitive evidence that caffeine intake prior to a procedure which requires hyperaemia alters the fractional flow reserve. One small study (n=10) concluded that fractional flow reserve was not affected by an intravenous caffeine infusion at doses comparable to oral consumption.<sup>152</sup> Until further work is published in this area it is prudent to advise patients against caffeine ingestion for 24h prior to any procedure. *Nahser et al* looked at changes in coronary flow velocity measured by intracoronary Doppler catheter receiving 140 mcg/kg/ml of adenosine before and after an intravenous infusion of aminophylline. Although the numbers were again small (n=12), they found that the coronary haemodynamic effects of adenosine were attenuated by aminophylline concluding that the utility of myocardial imaging techniques using coronary vasodilation by adenosine as a prerequisite may be reduced in those patients treated with theophylline containing preparations.<sup>153</sup>

### **2.3.6 Adenosine 5'-triphosphate (ATP)**

ATP has a short half-life in plasma and is rapidly degraded into adenosine diphosphate, adenosine monophosphate, and adenosine. Although the effects of ATP are proposed to depend on its degradation to adenosine, neither direct stimulation of adenosine receptors by ATP nor an endothelium-dependent vasodilatory action of ATP via a P2-purinoreceptor can be fully excluded.

*Yamada et al* reported that 50 mcg of ic ATP would induce the same amount of vasodilation as 10 mg of papaverine without any significant haemodynamic or electrocardiographic changes.<sup>154</sup>

Perhaps the most comprehensive study looking at this pharmacological agent was by *De Bruyne et al* when comparing intracoronary and intravenous ATP with adenosine, papaverine and contrast medium. Their data indicated an equipotency of ATP and adenosine with no difference in their times of onset or duration of effect. They recommended the use of this agent at the same doses as that of adenosine. Increasing the intravenous infusion to greater than 140mcg/kg/min did not induce a further decline of the resistance index but induced a marked decline in systemic blood pressure in some patients.<sup>155</sup>

## **2.4 Other vasodilator agents**

### **2.4.1 Sodium nitroprusside**

This pharmacological agent has been looked at primarily in respect to no reflow in the acute myocardial infarction setting rather than its ability to achieve hyperaemia capable of producing reproducible physiological measurements. Nitroprusside relaxes arterial and venous smooth muscle without effects on other types of smooth muscle or myocardial contractility. Although it is thought that its actions are in some way mediated through the sympathetic nervous system they are not dependent on any specific adrenergic receptor or ganglion. Therefore, unlike drugs acting through sympathetic blockade, regional distribution of blood is virtually unchanged by sodium nitroprusside. Nitroprusside

induces hyperaemia by its ability to preferentially vasodilate the coronary microcirculation.<sup>156</sup> *Amit et al* enrolled 98 patients into a randomized, double-blind, placebo controlled trial looking at whether intracoronary SNP injected into a coronary artery prior to percutaneous intervention affected vessel flow and myocardial perfusion. They found that selective intracoronary administration of a fixed dose of SNP failed to improve coronary flow and myocardial tissue reperfusion but improved clinical outcomes at 6 months.<sup>157</sup>

*Parham et al* compared the hyperaemic and haemodynamic responses of intracoronary nitroprusside to intracoronary adenosine in patients during cardiac catheterisation with normal left anterior descending arteries. Using a Doppler wire time to peak and average peak velocity were similar with SNP and adenosine with the three doses of intracoronary SNP that were administered. (0.3, 0.6, and 0.9 microgrammes/kg). The duration of coronary hyperaemia is approximately 25 % greater with intracoronary SNP in comparison with adenosine. Significantly when used for coronary lesion assessment they found that intracoronary SNP produced identical FFR values to those obtained with adenosine.<sup>158</sup>

The data, thus far, indicates that intracoronary administration of sodium nitroprusside is safe and effective for the induction of maximal coronary hyperaemia. It produces a slightly prolonged maximal hyperaemic effect, in comparison with adenosine, however

given the small body of evidence it is currently difficult to advocate its use in routine clinical practice as a viable alternative.

#### **2.4.2 Dobutamine**

Dobutamine is not commonly used as an agent to induce hyperaemia in the cardiac catheterisation laboratory but is used frequently as a stressor agent for SPECT and stress echocardiography. Dobutamine is a sympathomimetic amine that acts through alpha and beta adrenoceptors stimulating positive inotropic and chronotropic effects as well as enhancing myocardial blood flow principally through metabolic vasodilation.<sup>159, 160</sup>

In keeping with the clinical environment in which dobutamine is used the literature contains very little about its potential use in the cardiac catheterisation laboratory during invasive pressure wire measurements. *Meimoun P* et al compared dobutamine and adenosine in assessment of transthoracic coronary flow velocity reserve. They found in the 47 patients they studied that dobutamine could be a good alternative to adenosine in this setting, particularly if the patient has a contraindication to adenosine<sup>161</sup>. Numerous other papers on the topic of dobutamine stress echocardiography exist, however, given the lack of evidence for the accuracy of dobutamine with regard to coronary pressure wire physiological assessment, its relatively long half-life and other possible alternatives to adenosine it is difficult to advocate its use in the catheterisation laboratory.



### 2.4.3 Papaverine

Intracoronary papaverine induces maximal coronary vasodilation and has a short duration of action. Peak effect after administration is at 10-30 seconds and the duration of plateau is around 45-60 seconds. The recommended dosages for intracoronary papaverine are 12-16mg in the right coronary artery and 16-20 mg in the left system.<sup>155, 162</sup> Historically papaverine was the pharmacological agent of choice in the assessment of coronary flow reserve but has been superseded by adenosine because of concerns about complications. Specifically papaverine may induce Q-T prolongation which can lead to polymorphic ventricular tachycardia and ventricular fibrillation.<sup>163</sup> Correcting hypokalaemia pre-procedure and ensuring patients are not taking other drugs which cause Q-T prolongation (class I and III anti-arrhythmic drugs) can minimise the potential for this serious side effect. *Pijls NHJ and De Bruyne B* reported that in over 1000 patients whilst Q-T prolongation was common ventricular fibrillation occurred no more commonly than after contrast injection.<sup>155</sup> However, several studies have demonstrated that ic papaverine induces a significant increase in coronary venous lactate in both canine models and in patients with normal coronary arteries and these results suggest that papaverine may produce myocardial ischaemia.<sup>164, 165</sup>

*De Bruyne B et al* compared intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine and contrast medium to assess fractional flow reserve and found that only intracoronary papaverine (20mg) and intravenous adenosine (140mcg/kg/h) induce complete, true steady state hyperaemia to enable a pressure pullback curve. They

stated that the latter was the easiest means for this, especially in cases with diffuse disease.<sup>155</sup>

Papaverine is essentially the only intracoronary injection, which can allow production of a pressure pullback curve although it is not ideal given the time constraints. Its half-life also means that the operator should wait five minutes between successive measurements using ic papaverine and should limit the number of doses to three in any one patient to reduce the risk of side effects.

Over the years for both practical and safety issues intracoronary papaverine has been superseded by adenosine for the production of coronary hyperaemia in assessment of fractional flow reserve. However papaverine still has a place in the cardiac catheterisation lab in those in whom adenosine is contra-indicated when appropriate precautions are taken.

#### **2.4.4 Radiographic Contrast media**

Both ionic and non-ionic radiographic contrast media cause vasodilation and associated increases in coronary blood flow when injected into the coronary arteries at the time of angiography.<sup>166</sup> *Hodgson and Williams* compared ic papaverine to radiographic coronary flow reserve in patients with ischaemic heart disease and patients with normal coronary vasculature. They concluded that papaverine was superior to contrast media because of the greater degree of hyperaemia and the ability to more accurately differentiate non-

ischaemic from ischaemic vascular regions in individual patients.<sup>167</sup> Radiographic contrast media does not therefore produce sufficient coronary vasodilation for accurate assessment of fractional flow reserve.

## **2.5 The future of pharmacological stress**

Work in this field has concentrated on synthetic selective A<sub>2A</sub> receptor adenosine agonists. As well as stimulating the A<sub>2A</sub> receptor, adenosine itself also non-selectively activates A<sub>1</sub>, A<sub>2b</sub> and A<sub>3A</sub> receptor. Such nonselectivity is thought to contribute to the side effects that are seen during pharmacological stress testing (eg bronchospasm and A-V block). Theoretically selective A<sub>2A</sub> adenosine receptor agonists would provide selective coronary vasodilation, rapid onset and termination of action and bolus administration as well as being tolerated in those in whom adenosine is currently thought to be contra-indicated.<sup>168</sup>

Initial small studies looking at the selective A<sub>2A</sub> receptor agonist's binodenoson and regadenoson have been reasonably encouraging in the field of nuclear myocardial perfusion imaging. Both showed a reproducibility of results in patients receiving clinically indicated adenosine single-photon emission computed tomography scans (SPECT) and both were noted to have a reduced subjective side effect profile at lower doses.<sup>169, 170</sup>

On the basis of these and other studies three selective A<sub>2A</sub> receptor agonists, regadenoson, binodenoson and apadenoson are now in larger phase III clinical trials as pharmacological stress agents. Quite how these agents will be used in the future remains to be seen. The work so far has concentrated, predictably, on non-invasive nuclear perfusion imaging. Whether they can be useful in the cardiac catheterisation laboratory in the context of coronary pressure measurements will be decided in the future.

## **2.6 Conclusions**

In conclusion, adenosine whether used intravenously or intracoronary is a safe and reliable method for the induction of coronary hyperaemia. The context in which the study is performed as well as operator preference should determine the route through which the drug is delivered. The authors believe this should be the first choice vasodilator to be used in coronary physiological assessment using a pressure wire. Intracoronary papaverine is a viable alternative in those in whom adenosine is contra-indicated.

## Dosage tables

<i>Weight (lb)</i>	<i>Weight (kg)</i>	<i>Infusion (ml/hr)</i>
99	45	378
110	50	420
121	55	462
132	60	504
143	65	546
154	70	588
165	75	630
176	80	672
187	85	714
198	90	756
209	95	798
220	100	840
231	105	882
243	110	924
254	115	966
265	120	1008

Table 2.1: Dosage table for IV adenosine at 140 micrograms/kg/min

<i><b>Weight (lb)</b></i>	<i><b>Weight (kg)</b></i>	<i><b>Infusion (ml/hr)</b></i>
<b>99</b>	<b>45</b>	<b>486</b>
<b>110</b>	<b>50</b>	<b>540</b>
<b>121</b>	<b>55</b>	<b>594</b>
<b>132</b>	<b>60</b>	<b>648</b>
<b>143</b>	<b>65</b>	<b>702</b>
<b>154</b>	<b>70</b>	<b>756</b>
<b>165</b>	<b>75</b>	<b>810</b>
<b>176</b>	<b>80</b>	<b>864</b>
<b>187</b>	<b>85</b>	<b>918</b>
<b>198</b>	<b>90</b>	<b>972</b>
<b>209</b>	<b>95</b>	<b>1026</b>
<b>220</b>	<b>100</b>	<b>1080</b>
<b>231</b>	<b>105</b>	<b>1134</b>
<b>243</b>	<b>110</b>	<b>1188</b>
<b>254</b>	<b>115</b>	<b>1242</b>
<b>265</b>	<b>120</b>	<b>1296</b>

Table 2.2: Dosage table for IV adenosine at 180 micrograms/kg/min

## **Chapter 3: Methods**

### **3.1 Study overview and recruitment**

The principal techniques used for this thesis were intracoronary physiological assessment and contrast-enhanced cardiac magnetic resonance imaging (ceCMR). In this chapter the background, methods, apparatus and protocols for these techniques will be outlined.

#### **3.1.1 Inclusion and exclusion criteria**

Patients were prospectively enrolled when the following inclusion criteria were present:

- Age  $\geq 18$  years with ECG and symptomatic evidence of acute STEMI and in whom emergency PCI was intended
- Written informed consent.

Exclusion criteria were:

- Standard contraindications to MRI: pacemakers; cochlear implants; some types of prosthetic heart valves, surgical prostheses, or vascular clips; metal intraocular foreign bodies
- Contraindications to gadolinium: eGFR  $<30$  mL/min/1.73m<sup>2</sup>; sickle cell anaemia; haemolytic anaemia
- Contraindications to adenosine
- Cardiogenic shock
- Previous myocardial infarction
- Pregnant.



### **3.1.2 Recruitment**

STEMI patients referred to our institution within 12 hours of symptom onset for primary PCI or after failed intravenous thrombolytic therapy for rescue PCI, or who underwent cardiac catheterization within 24 h of successful thrombolytic therapy were considered for enrollment.

During the time of the study the Western Infirmary in Glasgow was a tertiary referral centre for coronary intervention for the West of Scotland. Patients were referred to the Western infirmary from other hospitals for emergency or urgent coronary angiography or referred to the cardiology department for assessment from the accident and emergency department. At the time of the study the hospital ran a 24h emergency percutaneous intervention (PCI) service for acute ST-elevation myocardial infarction (STEMI).

Only consultant interventional cardiologists from the Western Infirmary took part in the study (KGO, MML, SDR, WSH, CB). The West of Scotland emergency PCI rota at this time was also staffed by consultant cardiologists from Glasgow Royal Infirmary and Stobhill Hospital who did not participate. Accordingly we did not recruit consecutive patients. Patients were screened and consented by myself or by the Consultant cardiologist on-call who was performing the PCI if I was not in the hospital. The consultants were fully aware of the study protocols and procedures and were involved in the development of the study.

### **3.1.3 Consent and ethics**

The research protocol was approved by the West Glasgow Ethics committee and informed consent was obtained from each patient. Given the time constraints involved in recruiting patients in the acute setting a shortened patient information sheet was used for initial consent prior to PCI. (Appendix I) Patients who agreed to enter the study were then asked to sign consent form one. A member of on-site staff not involved in the study was also asked to sign this consent form. (Appendix II) Following emergency PCI and before cardiac magnetic resonance imaging (CMR) patients were then given a longer, more detailed patient information sheet. (Appendix III) If, after further consideration and discussion they agreed to continue in the study they were asked to sign consent form 2. (Appendix IV)

### **3.1.4 Acute management of patients**

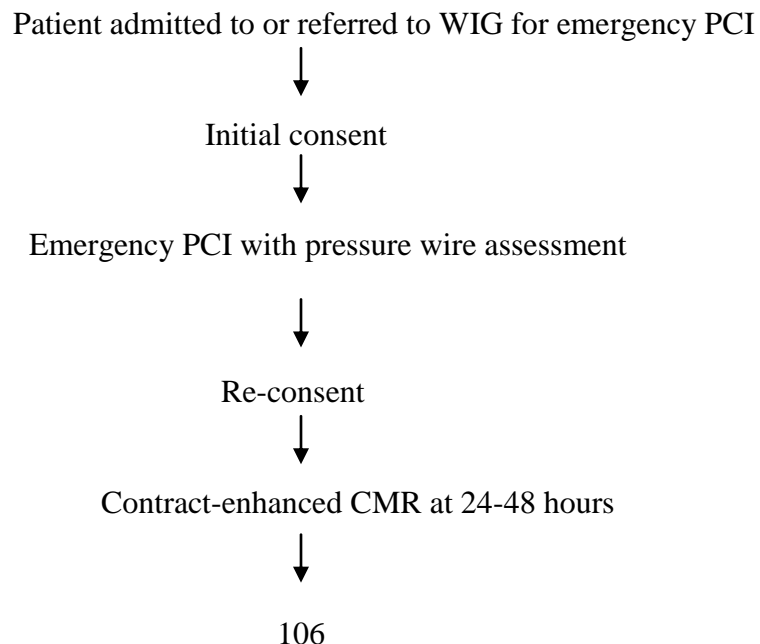
The trial did not interfere with routine patient management. Only patients in whom the decision for emergency coronary angiography had been made were considered for the study. If at the time of angiography the patient was deemed too unstable or had coronary artery disease not suitable for PCI by the operator the patient was excluded. The type and size of intracoronary balloons, type, size and number of stents and the use of thrombectomy catheters and glycoprotein 2b/3a inhibitors was at the discretion of the

primary operator. Vascular access route was also at the discretion of the primary operator although radial arterial access was the primary option of choice at our institution.

Following emergency PCI patients were managed in the coronary care unit in the Western Infirmary. Length of stay and the prescription of standard medical secondary prevention including ACE inhibitors and  $\beta$ -blockers were entirely at the discretion of the admitting consultant and their team.

If patients were deemed too unwell by myself or by the admitting consultant to tolerate a cardiac MRI scan or if it was thought unsafe for the patient to leave the coronary care unit the patient was excluded from the study.

**Flow diagram of study (Figure 3.1)**



Repeat Contrast-enhanced-CMR at 3 months

## **END OF TRIAL**

### **3.1.5 Index event and hospital admission**

After obtaining written, informed consent enrolled patients were assigned a unique study code number. They then underwent emergency PCI with physiological coronary pressure assessment. Thereafter they were re-consented and underwent ceCMR at 24-48h following re-perfusion.

In addition to coronary angiography, pressure wire assessment and ceCMR the following were performed and recorded during the patient's initial hospital admission:

- Physical examination, including measurement of height, weight and resting haemodynamics prior to ceCMR scan
- Retrieval and photocopying of diagnostic ECG (acute MI), post reperfusion ECG/90 minute ECG
- Recording of baseline blood results on admission
- 12h troponin I
- Patient demographics, past medical history, cardiac risk factors, admission and discharge medication

- Accurate recording of timings in the patient journey from onset of pain to reperfusion

The above information and was recorded for each patient in the study on paper and electronically on a Microsoft Access database on a secure computer.

### **3.1.6 Three month visit**

This consisted of a two hour visit to the Glasgow Cardiac MRI Unit at the Western Infirmary.

Physical examination, including measurement of height, weight and resting haemodynamics prior to ceCMR scan

- 12 lead ECG recording
- Contrast enhanced cardiac MRI scan with simultaneous electrocardiographic recording.

### **3.2 Invasive coronary physiological assessment protocols**

PCI was performed in line with current international guidelines. Glycoprotein IIb/IIIa inhibitors and thrombectomy catheters were used at the discretion of the primary operator.

In this study, a commercially available 0.014-inch floppy pressure guide wire (PressureWire-6, RADI Medical Systems) was used with the appropriate software and interface (Radi-Analyzer, RADI Medical Systems). This wire has a micro-sensor at a location 3 cm from the floppy tip, which enables simultaneous recording of coronary pressure measurement as well as temperature measurement at the location of that sensor, with an accuracy of 0.02°C. The shaft of this wire, acting as an additional electric resistance, can be used as a second thermistor, providing the input signal at the coronary ostium of any fluid injection with a temperature different from blood. All signals can be displayed and recorded on the commercially available analyser for future off-line analysis.

#### **3.2.1 Pressure wire preparation**

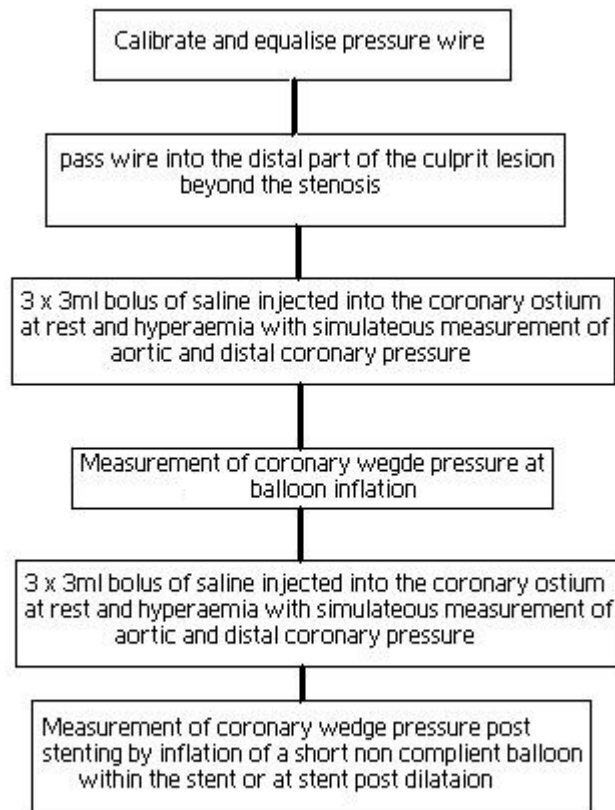
In the majority of cases the coronary pressure/temperature sensitive guidewire was used as the primary guide-wire. The guide-wire was calibrated outside the body, equalised within the guide catheter, with the pressure sensor positioned at the ostium of the guide catheter, and then advanced into the distal segment of the culprit artery. Meticulous

attention was taken to ensure appropriate catheter engagement and only guide catheters without side holes were used in the study. Patient details were entered into the analyser unit which allowed recording and storage of coronary physiological data.

### **3.2.2 Hyperaemic agent used during pressure wire studies**

Adenosine induces near-maximal coronary vasodilation primarily through activation of adenosine receptors in vascular smooth muscle.<sup>171</sup> In this study we used intravenous adenosine administered through an anti-cubital vein at a dose of *140/micrograms/kg/min* via a volume controlled infusion pump. The patient was then assessed for a symptomatic and physiological response to adenosine. When this occurred the physiological measurements were taken. This route of adenosine administration was chosen to allow a hyperaemic “steady state” to occur allowing time to take the appropriate measurements. Prior to administration of the intravenous infusion we administered a bolus of intracoronary glyceryl tri-nitrate into the coronary artery to minimise the potential effects of arterial spasm on the readings.

### **Outline and timings of pressure wire readings (Figure 3.2)**



### 3.2.3 Measurement of coronary wedge pressure (Pw)

This was measure by balloon inflation prior to stenting within the area of the stented segment. When the delivery balloon was inflated, occluding antegrade flow, mean pressure distal to the stenosis was recorded as the coronary wedge pressure (Pw) in millimetres of mercury (mmHg). Post stenting Pw was recorded with a short non-compliant balloon inflated within the stented segment to occlude antegrade flow.



### **3.2.4 Measurement of pressure derived collateral flow index (CFIp)**

The pressure derived coronary collateral flow index (CFIp) can be obtained from the Mean Pw, mean aortic pressure (Pa), and mean central venous pressure (Pv):

$$\text{CFIp} = \text{Pw} - \text{Pv} / \text{Pa} - \text{Pv}$$

Maximal hyperaemia and Pw were achieved as discussed previously. Distal coronary pressure (Pd) was obtained from the pressure wire and aortic pressure was recorded at the tip of the guide catheter using a fluid filled system. CFIp (units) was calculated from the ratio of mean Pw (Pd during balloon inflation and complete coronary occlusion) and mean Pa under conditions of maximal hyperaemia ( $\text{CFIp} = \text{Pw}/\text{Pa}$ ). Pv was not routinely recorded. However, patients who were haemodynamically compromised and likely to have increased Pv (cardiogenic shock, right ventricular infarction) were excluded

### **3.2.5 Measurement of the index of microcirculatory resistance (IMR)**

IMR is calculated as the product of simultaneously measured distal coronary pressure (Pd) and thermodilution-derived mean transit time (Tmn) of a bolus of Saline injected at room temperature into the coronary artery during maximal hyperaemia induced by continuous intravenous infusion of adenosine (140mcg/kg/min). The inverse of Tmn has been shown to correlate with absolute coronary blood flow. In the absence of any stenosis

in the epicardial artery IMR is equal to  $P_d \times T_{mn}$  at maximal hyperaemia. When an epicardial stenosis is present accurate determination of IMR requires knowledge of coronary wedge pressure and can be represented by the following equation:

$$IMR = P_a \cdot T_{mn} [(P_d - P_w) / (P_a - P_w)]$$

where  $P_a$  represents the aortic pressure measured by the guiding catheter and  $P_w$  is the coronary wedge pressure measured by the pressure wire during balloon occlusion as described previously.

### **3.2.6 Thermodilution derived mean transit times**

Thermodilution curves were generated prior to and following stenting in the infarct related artery. We used guide catheters without side holes to allow accurate delivery of a saline bolus into the coronary ostium. Care was also taken to flush the catheter with saline thereby removing contrast which could potentially interfere with the measurements. Thermodilution curves in the culprit coronary artery were obtained by short manual injections of 3 ml of Saline at room temperature into the coronary ostium as described previously. Measurements were performed in triplicate at baseline and at hyperaemia. Care was taken not to advance or pull back the wire during these measurements and meticulous attention was paid to guide catheter engagement.. Simultaneous measurement of mean  $P_a$  and  $P_d$  in combination with  $P_w$  as described previously allowed off-line calculation of IMR using both methods.

**Figure 3.3 – Thermodilution curves at baseline and hyperaemia with simultaneous Pa and Pd measurement as represented on the RADI analyser screen**



### **3.3 Assessment of angiographic Thrombolysis In Myocardial Infarction (TIMI) flow grade**

This was recorded by the primary operator prior to and following PCI and was based on the following visual analysis of the coronary vascular anatomy:

0, no perfusion, no antegrade flow beyond the point of occlusion;

- 1, penetration of the occlusion but no perfusion of the coronary bed distal to the obstruction;
- 2, partial perfusion of the distal coronary bed;
- 3, complete perfusion of the distal coronary bed.

### **3.4 ceCMR Protocols**

CMR scanning was performed using a Siemens Sonata 1.5 Tesla (Erlangen, Germany) scanner using a six channel anterior chest coil and spinal coils within the gantry table, during breath-hold, and gated to the ECG. Each scan was performed by one of two experienced operators (RM, TS), both of whom are Advanced Life Support-qualified. RM was present throughout all scans thereby providing constant medical cover. Prior to entering the controlled zone, an MRI safety checklist was performed and signed by both patient and qualified MRI personnel. The importance of keeping as still as possible, and maintaining adequate breath-holds, was reinforced verbally prior to commencement of the scan. End-expiration is optimal for consistent breath-holding and was preferred.

#### **3.4.1 Preparation of patient for the scan**

The following steps were performed in all cases:

- Patient demographic details entered on scanner database
- The power injector (Medrad Spectris, Volkach, Germany) for administration of the contrast agent (gadolinium diethylenetriaminepentaacetic acid, DTPA, GE Healthcare) was prepared. The Medrad injector contains two quick-fit syringes connected by a Y-tubed delivery set. Into syringe A, gadolinium-DTPA was drawn at a dose of 0.1mmol/kg. Syringe B contained 50ml 0.9% sodium chloride
- Patient placed on table
- Siemens active Brooker ECG electrodes placed on patient's anterior chest wall, and position varied to obtain an optimal R wave
- A 20G IV cannula was placed in a peripheral vein, and connected to the Medrad injector.
- The six channel phased-array chest coil (Siemens CP body array flex) was applied and aligned
- Patient, wearing ear protectors or headphones, enters scanner
- Medrad power injector armed

### **3.4.2 Clinical assessment prior to ceCMR scan**

As part of the larger study assessing safety and feasibility of CMR scanning following STEMI, each patient underwent an ECG to assess cardiac rhythm recorded, pulse and blood pressure taken and clinically assessed for evidence of heart failure and scored according to the Killip classification.<sup>172</sup>

### **3.4.3 Left Ventricular structure and function**

All CMR scans commenced with a multi-slice breath-hold localiser. Each of the localisers described in this section used the same protocol:

Protocol: Multi-slice single-shot breath-hold true fast imaging with steady-state precession (trueFISP) localiser with transverse, Sagittal and coronal slices. Settings: field of view = 360mm, field of view phase = 81.3%, slice thickness = 6mm, repetition time (TR) = 3.41ms, echo time (TE) = 1.71ms, flip angle = 60°, averages = 1, phase resolution = 80%, phase oversampling = 0%

From these images, the best axial image depicting the LV and septum was selected (Figure 3.4 A). If no suitable image was produced by the initial localiser, a second axial localiser was performed using the coronal images until the closest match to Figure 3.4 A was obtained. This was used to plan 3 vertical long axis (VLA) parallel localisers along the long axis of the LV from the mid-point of the mitral valve to the apex.

From the resulting VLA scan, 3 horizontal long axis (HLA) localisers were then planned, using the mid-point of the mitral valve and the LV apex to prescribe the orientation (Figure 3.4 B). This resulted in 3 HLA slices (Figure 3.4 C). Using the atrioventricular groove as a landmark, 3 short axis (SA) localiser slices were planned, with the most basal slice positioned in the atria to depict the left ventricular outflow (Figure 3.4 C). From the

resulting SA images, 3 long axis views can be prescribed – the 4-chamber, 2-chamber and left ventricular outflow tract (LVOT) views (Figure 3.4 D).

#### **3.4.4 Cinematographic (cine) imaging**

Having thus acquired 3 orthogonal long axis views, cine studies were acquired in each of these 3 orientations, as follows:

Protocol: trueFISP breath-hold cine. Settings: field of view = 360mm, field of view phase = 81.3%, slice thickness = 8mm, TR = 47.4ms, TE = 1.58ms, flip angle =  $60^{\circ}$ , averages = 1, measurements = 1, phase resolution = 65%, phase overSampling = 20%, segments = 15.

These images were used for visual analysis of structure and long axis function.

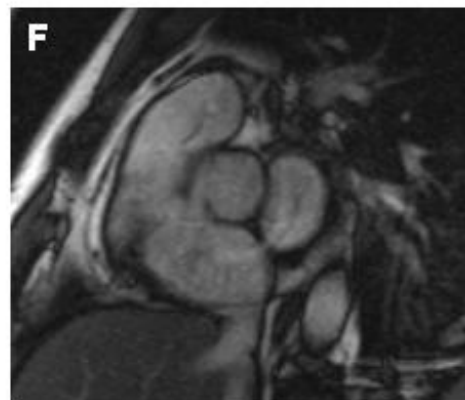
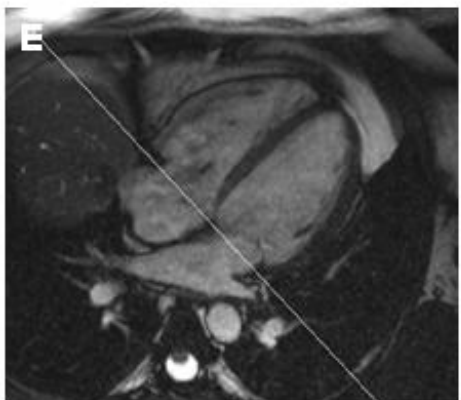
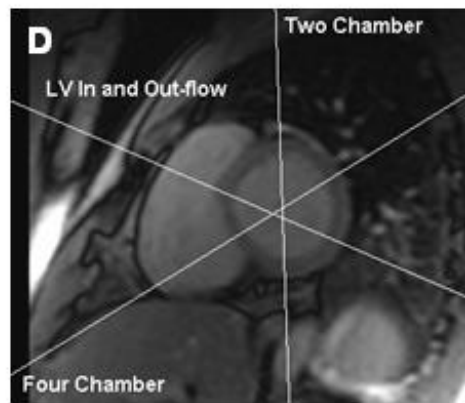
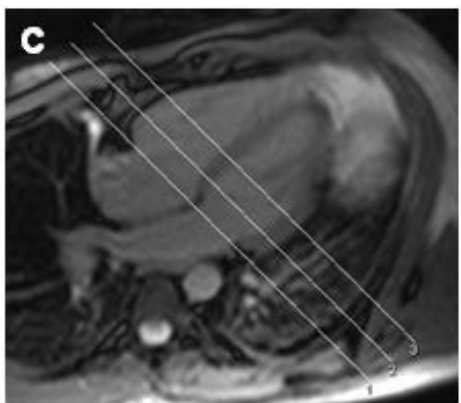
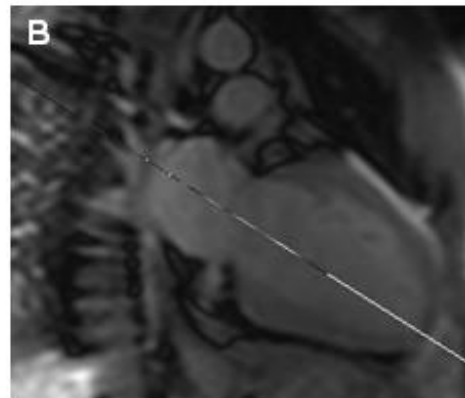
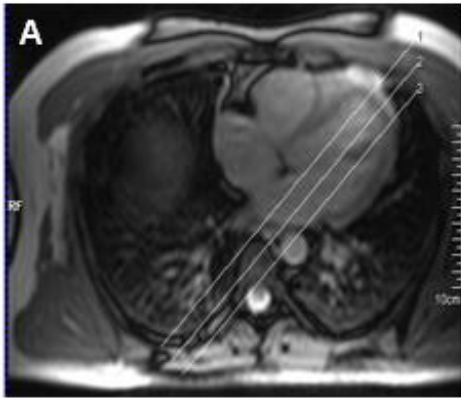
#### **3.4.5 Short axis cine stack**

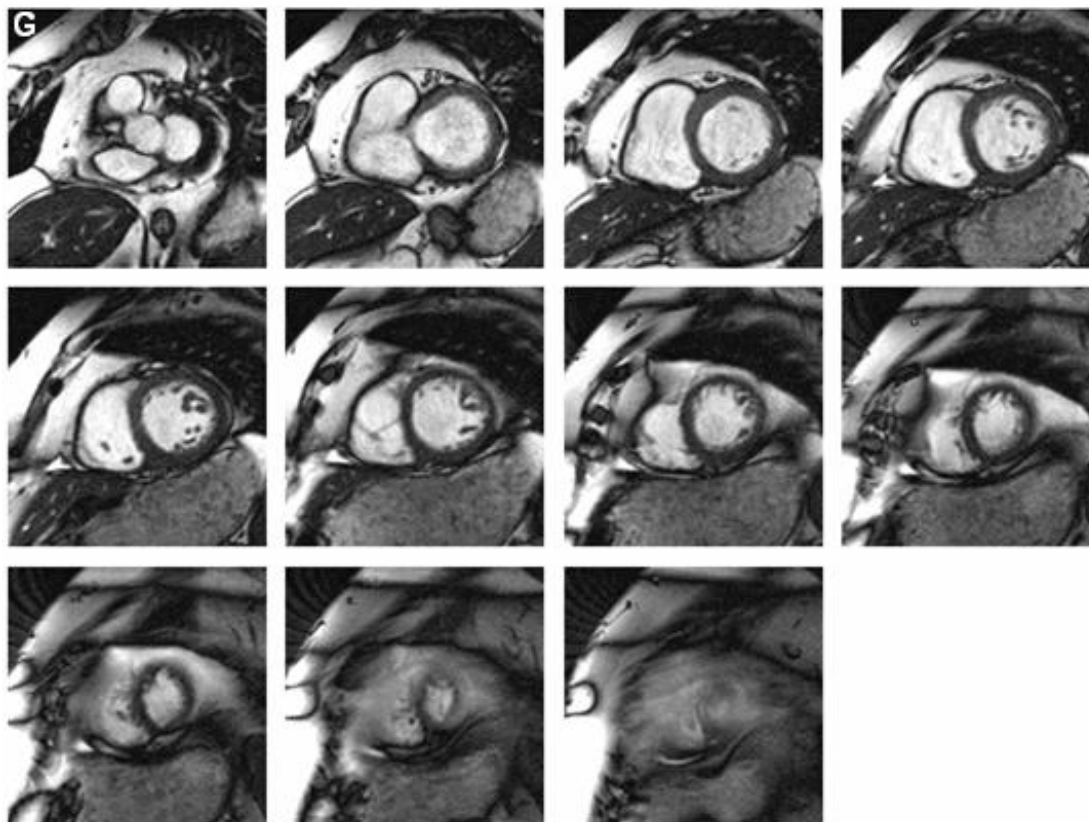
Quantitative volumetric assessment of ventricular function requires that the LV be divided into a stack of short axis (SA) slices from base to apex. Measurements from each slice are then summed to provide overall ventricular mass and volumes, from which LVEF can be calculated. The SA stack was prescribed from the 4-chamber HLA cine already acquired. Using the end-diastolic image from this view, the cursor was positioned in an orientation across the mitral valve plane through the atrioventricular groove (as a marker of the most basal SA slice) as in Figure 3.4 E. The most basal slice that results is depicted in Figure 3.4 F. The slice position was then incremented by 10mm moving

towards the apex of the LV and repeated until the LV was completely covered; inter-slice gaps of 2 mm were used. A representation of the final SA cine stack is shown in Figure 3.4 G. The Same protocol was used for all SA cine slices:

Protocol: trueFISP breath-hold cine. Settings: field of view = 340mm, field of view phase = 81.3%, slice thickness = 8mm, interslice gap = 2mm, TR = 47.4ms, TE = 1.58ms, flip angle =  $60^{\circ}$ , averages = 1, measurements = 1, phase resolution = 65%, phase over sampling = 20%, segments = 15







**Figure 3.4 Planning of cine CMR image acquisition.** From transverse, Sagittal and coronal scout images, the best image of the LV and septum is selected (A) and then used to produce a vertical long-axis (VLA) localiser (B). Orientating the next scan through the apex and mid-point of the mitral valve (B – orientation line) creates a horizontal long-axis (HLA) localiser (C). Using the atrioventricular grooves as landmarks (C), a perpendicular plane to this HLA localiser is prescribed (D), based on which three orthogonal long-axis planes can be planned (2-chamber, 4-chamber and LV outflow tract views). Cine images are acquired for each of these three long-axis orientations. Finally a short-axis cine stack is planned on the 4-chamber HLA cine image (E). A short-axis image is acquired of the base of the LV (F), from which slice position is advanced at 10mm intervals from base to apex, creating a short-axis cine stack (G).

## **3.5 Contrast imaging**

### **3.5.1 First-pass perfusion imaging**

The visualisation of first-pass myocardial perfusion following bolus contrast injection requires ultra-high speed MR imaging. A balanced single-shot turbo fast low angle-shot (FLASH) sequence with a saturation recovery pre-pulse before each slice was employed. This typically allowed 3 SA slices (copied from the cine SA stack) to be acquired per heart-beat. No breath-hold was required. The weight-adjusted dose of gadolinium-DTPA was delivered into a peripheral vein via the Medrad power injector at a constant rate of 6ml/s, followed by 0.9% sodium chloride flush. The first-pass protocol was as follows:

Protocol: first-pass single-shot turbo-FLASH sequence with Saturation recovery preparation, 3 slices per heartbeat. Non-breath-hold, controlled respiration. Settings: field of view = 340mm, field of view phase = 81.3%, slice thickness = 8mm, TR = 183ms, TE = 0.99ms, flip angle = 8°, averages = 1, measurements = 60, time to inversion (TI) = 100ms

### **3.5.2 Imaging of early microvascular obstruction**

At 2 to 5 minutes after contrast injection, images were acquired for the determination of “early” MVO. This required a single-shot steady-state free precession sequence with a

non-selective inversion pulse. No breath-hold was required. Typically three to five SA slices per heartbeat were acquired, copied from the SA cine stack. A single-shot sequence was acquired at each of four time-points: 2, 3, 4 and 5 minutes after contrast injection.

The protocol for early MVO imaging was as follows:

Protocol: ECG trigger, 100 lines field of view = 270 x 360, slice thickness = 8mm, interslice gap = 2mm, flip angle 30°, TE 1.2ms, TR 2.7ms, TI 200-350ms, bandwidth/pixel = 980 Hz, matrix 256.

### **3.5.3 Late gadolinium-enhancement imaging**

15 minutes after bolus contrast injection in all scans, ceCMR images were acquired. This utilised a contrast-sensitive segmented inversion recovery sequence to acquire a second stack of SA images (positions copied from the SA cine stack). Images were also acquired in three long axis views, with orientations copied from the cine 4-chamber, 2-chamber and LVOT views. Adequate breath-holding was essential for each acquisition. The protocol was as follows:

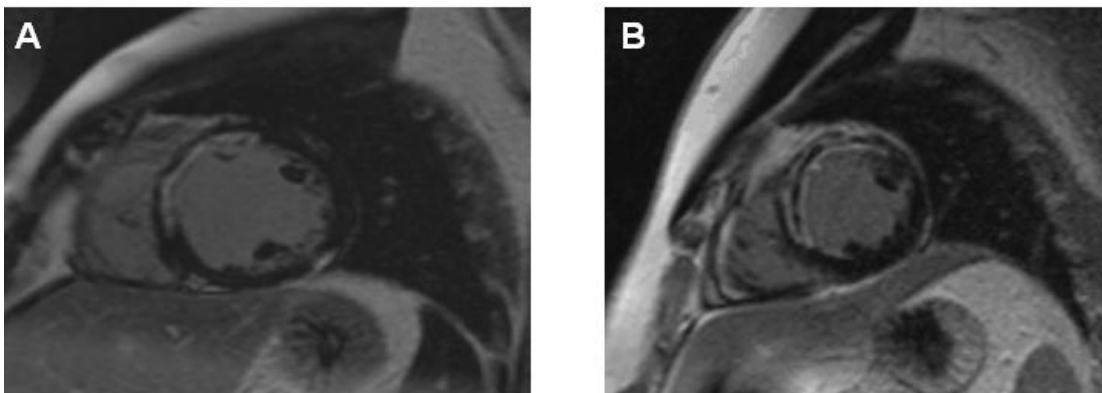
Protocol: Breath-hold segmented re-phased Turbo-FLASH sequence with non-selective inversion pulse with non-slice selective inversion-recovery.

Constant settings: field of view = 340mm, field of view phase = 81.3%, slice thickness = 8mm, interslice gap = 2mm, TE = 4.3ms, flip angle = 30°, averages = 2, segments = 25,

phase resolution = 65%, trigger delay = 0, trigger pulse = 2 (but dependent to an extent on heart-rate: trigger on pulse 1 if bradycardic, or pulse >2 if tachycardic).

#### *Variable settings*

The acquisition window was set greater than RR-interval and TR just under to allow for diastolic imaging. TI was 220ms (for initial scan) and adjusted according to image quality by 10ms steps within the range 200-300ms to optimise image quality. The TI was often varied between image acquisitions, and if the quality of the preceding image was poor it was repeated until an image of adequate quality was obtained. Optimal TI and TR produced a diastolic image with black (nulled) myocardium and bright late enhancement area (Figure 3.5 A). If late MVO was present, it appeared as a dark hypoenhanced core within the bright hyperenhanced area (Figure 3.5 B).



**Figure 3.5** Mid-ventricular short-axis slices acquired using a contrast-sensitive segmented inversion recovery sequence 15 minutes after injection of gadolinium-DTPA, from two separate patients admitted with anterior STEMI. (A) Subendocardial region of hyperenhancement affecting the anteroseptal wall of the LV, surrounded by normal (nulled, dark) myocardium; there is no MVO present.

**(B) Full-thickness infarction of the anteroseptal wall of the LV reveals hyperenhancement throughout wall, from endocardium to epicardium, with a hypoenhanced core – this core represents (late) MVO.**

### **3.6 CMR analysis methodology**

#### **3.6.1 LV volumes and ejection fraction**

Post-processing was performed using commercially-available Argus software (Siemens, Erlangen). The number of slices required to cover the LV in end-diastole and end-systole varied from scan to scan dependent on the long axis diameter of the LV. End-systole was chosen as the point where the total LV blood pool was smallest and end-diastole as the point where it was largest. The most basal LV slice at both end-systole and end-diastole was defined as that in which the blood pool was surrounded by 50% or more of ventricular myocardium; papillary muscles were excluded from the LV volumes and included in the LV mass. Manual digital planimetry was performed on endocardial and epicardial contours using the short axis cine images at both end diastole and end systole in random order by a single observer (RM) blinded to the pressure wire results. The scans were anonymised and randomised prior to analysis. Simple addition of the individual slice volumes in this stack of contiguous slices covering the entire LV allowed calculation of LVESV and LVEDV (ml), therefore allowing the calculation of LV ejection fraction (LVEF). LV myocardial mass (LVM) was estimated to be the mean of the total difference between the inner and outer circumferences of the LV myocardium in

end-diastole and end-systole, multiplied by the myocardial density (taken as  $1.05 \text{ g/cm}^3$ ). All CMR measurements were adjusted for total body surface area.

### **3.6.2 “Early” Microvascular Obstruction**

“Early” MVO previously known as simply microvascular obstruction “MO” is the term used for assessment of MVO in the early stage following gadolinium-DTPA injection. Quantitative analysis of the size and extent of both the first-pass defect and early MVO can be imprecise as it requires multiple geometric assumptions due to the limited number of SA slices acquired during ultra-fast imaging. However although less evidence is available regarding this the mass of hypo-enhanced tissue could be calculated by multiplication of the volume following digital planimetry by the myocardial density factor ( $1.05 \text{ g/cm}^3$ ). Early MVO was also graded as present or absent.

More recently literature comparing “early” MVO with “late” or persistent MVO has emerged suggesting that in contrast to early MVO, the presence and extent of late MVO is a strong independent predictor for the occurrence of death, non-fatal MI, myocardial reinfarction and congestive heart failure after STEMI.<sup>106, 173</sup>

### **3.6.3 Late gadolinium enhancement, infarct volumes and late/ persistent MVO**

Analysis of the delayed enhancement images was also performed using Argus software (Siemens, Erlangen). Again the scans were anonymised and randomised and the

perimeter of the hyper-enhanced region on each SA slice was traced by a single observer (RM) blinded to the pressure wire results. Acute infarction was considered present only if LGE was confirmed on both the short and long axis acquisitions and corresponded with a wall motion abnormality on cine imaging. The myocardial mass of LGE (grams) was quantified by a semi-automatic detection method using a signal intensity threshold of  $>2$  SD above a remote reference region. Argus software also facilitated summation of the volume of enhanced tissue from each slice, producing a measure of infarct volume (ml). The mass of hyper-enhanced tissue could be calculated by multiplication of the volume by the myocardial density factor ( $1.05\text{g/cm}^3$ ).

One major issue relevant to analysis of late hyper-enhanced images pertains to partial volume effect. The thickness of each slice is 8mm, but within this the pattern of late hyper-enhancement is not necessarily homogeneous. This irregularity can result in blurring of the infarct border. In some slices, towards the periphery of the hyper-enhanced area, regions are occasionally seen wherein the brightness level is intermediate between normal (black, nulled) myocardium and bright, hyper-enhanced myocardium. There is a lack of universal consensus on whether (and how) to account for this partial volume effect in the quantitative measurement of late hyper-enhanced tissue. In this study, in order to maintain consistency in our results, we decided to include everything that was hyper-enhanced, taking no account of partial volume effects.

Late MVO was defined as an area of hypo - enhancement (black) within the area of hyper-enhanced (bright) infarcted tissue. The perimeter of the dark area within the hyper-

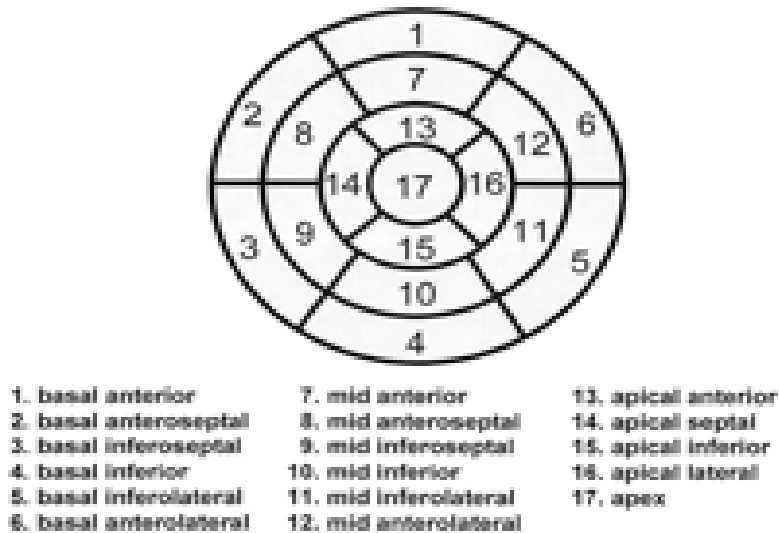


enhanced was traced using digital planimetry on each short axis slice using the same method as described above for infarct volumes. In cases of doubt about the nature of the hypo-enhanced area on short axis slices, the long axis slices were used, to differentiate late MVO from partial volume effects. The mass of hypo-enhanced tissue could be calculated by multiplication of the volume by the myocardial density factor ( $1.05\text{g/cm}^3$ ). Evidence thus far has simply indicated that the presence of MVO is associated with adverse outcomes therefore<sup>15</sup>, as with early MVO the presence or absence of MVO was also recorded. The presence of MVO was recorded by two experienced and blinded observers (AP, RM). When there was disagreement between the two observers a third experienced observer (CB) had the final say. As stated above late or persistent MVO is now associated with adverse clinical outcomes and is becoming the method of choice for assessment of MVO in this patient group given that it also allows further characterisation of the infarct with the images being coincident late gadolinium images.<sup>174</sup>

#### **3.6.4 Site of myocardial infarction**

The anatomical location of the infarct was based on the AHA standardised 17-segment model. Site of myocardial infarction was defined as anterior, inferior or lateral depending on the area in which the highest percent of infarcted tissue was visualised. The right ventricular insertion points were used as anatomical markers.

## Left Ventricular Segmentation



**Figure 3.6: The 17 segment American Heart Association model for anatomical assessment of myocardial infarction in the ventricular short axis CMR images**

### 3.6.5 Transmural extent of myocardial infarction

This was visually graded on a segmental basis of transmural extent of hyperenhanced tissue according to the following scheme: 0, no infarction; 1, 1% to 25% of LV wall thickness; 2, 26% to 50% of LV wall thickness; 3, 51% to 75% of LV wall thickness; and 4, 76% to 100% of LV wall thickness. This number was then divided by the number of affected segments to give a mean, or transmural score.<sup>175, 176</sup>

### 3.6.6 Assessment of LV remodelling

LV remodelling is defined as the change in left ventricular end systolic volume, indexed to body surface area (LVESVI), over time. An increase in LVESVI over time is termed adverse ventricular remodelling.<sup>100</sup>

### **3.6.7 Timing of CMR scans**

Animal studies have shown that MVO whether early or late as assessed by CMR can increase in size up to 48 hours.<sup>113</sup> A further study in the canine model has shown that MVO remains essentially unchanged at 2 days and 9 days post infarct.<sup>114</sup> However further work by *Albert et al* revealed that in 96 patients imaged on different days following acute MI, MVO prevalence fell dramatically beyond 48 hours from the infarct (with a decrease in prevalence of greater than 50% within the first 7 days).<sup>174</sup> Therefore there is as yet no consensus on the optimal timing for imaging in this patient group. Given the evidence available our aim was to perform all ceCMR scans at around 48h following reperfusion.

### **3.7 Assessment of “traditional” indices of microvascular and myocardial damage**

#### **3.7.1 Electrocardiographic assessment**

ST segment resolution (STR) was calculated as the percent resolution in the single lead with the maximum baseline ST segment elevation in the pre and post reperfusion ECGs.<sup>43</sup> If thrombolysis was achieved successful ECG and symptomatic reperfusion the diagnostic ECG and the 90 minute ECG were used. If rescue or primary PCI was needed the diagnostic and post catheter laboratory ECGs were used.

#### **3.7.2 Assessment by corrected Thrombolysis In Myocardial Infarction Frame Count (cTFC)**

Corrected TIMI frame count was calculated as the number of frames for dye to reach a standardised distal landmark in each angiographic territory. The first frame taken for the measurement was the frame in which dye touched both borders of the coronary artery in question and moved forward with at least 70% of the vessel lumen opacified. The standardised distal landmarks were taken as the first branch of the postero-lateral artery for the right coronary artery, the most distal branch of the obtuse marginal for the circumflex, and the distal bifurcation of the LAD. The number of frames from the first

frame to the last frame when the dye entered the standardised distal landmark was counted.

A standard image acquisition speed of 30 frames per second was used. The correction factor used to account for the increased length of the LAD compared to the right and circumflex arteries was 1.7 thereby giving a “corrected TIMI frame count”.

### **3.7.3 Biochemical assessment**

Troponin I concentration in cubital venous blood was measured 12 - 24 h post-MI using an automated analyser (Advia Centaur, Bayer Diagnostics). The limit of detection was  $<0.2 \mu\text{g/L}$

## **3.8 Statistical methods**

A sample size of 50 patients was calculated to have a power of (1-beta) 0.90 to detect a minimally significant correlation coefficient (R) of 0.45 between IMR and infarct size by ceCMR with a type 1 error rate of 0.05.

Invasive markers of microvascular function (coronary wedge pressure, fractional coronary collateral supply and the index of microcirculatory resistance) were non-normally distributed and are summarised with the median value and inter-quartile range (IQR). The Mann Whitney test was used to compare these data between patients with or

without MVO as revealed by ceCMR. An elevated IMR was defined as > than the median value.

Log transformed invasive markers of microvascular function and other clinical features were compared to ceCMR outcomes using univariate regression analysis. The variance in each model was expressed using the coefficient of determination,  $r^2$ . The univariable predictors with a p value of less than 0.1 were entered into a multivariate model. Since our focus was to evaluate the predictive value of IMR compared to other clinical characteristics which were available at the time of primary PCI, only variables which were clinically available at that time, such as time-to-reperfusion but not troponin concentration, were included in the multivariable models. A p value <0.05 was considered statistically significant. Statistical analyses were performed on MINITAB 14 software and NCSS 2007.

### **3.9 Funding of the study**

This work was funded by a project grant from the Chief Scientists Office Scotland (CZB/4/572).

### **3.10 Sponsoring of the study**

The trial was sponsored by the North Glasgow University Hospitals NHS Trust.

**Chapter 4: Demographics, admission  
data, angiographic  
and cardiac MRI results**

## **4.1 Patient screening and recruitment**

A total of 77 patients were consented for the study between 04/01/2007 and 28/02/2008. Of these 8 patients were deemed not suitable for pressure wire study, in each case because no percutaneous coronary intervention was needed or possible. (3 patients with severe 3 vessel disease, 2 patients with small side branch occlusion only and 1 with calcified vessels unable to wire and 2 with no overt coronary artery disease). Therefore 69 patients had successful coronary physiological studies at the time of PCI. Of these 12 patients did not have cardiac MRI imaging. Five patients refused and did not give a reason, 4 were stated they were claustrophobic and 3 were deemed to be unstable due to runs of non-sustained ventricular tachycardia.

This left 57 patients with successful physiological assessment and a baseline cardiac MRI scan. Of these, 47 had complete follow up scans. In addition a total of 47 patients had complete pre and post stenting physiological assessment.

## **4.2 Demographics**

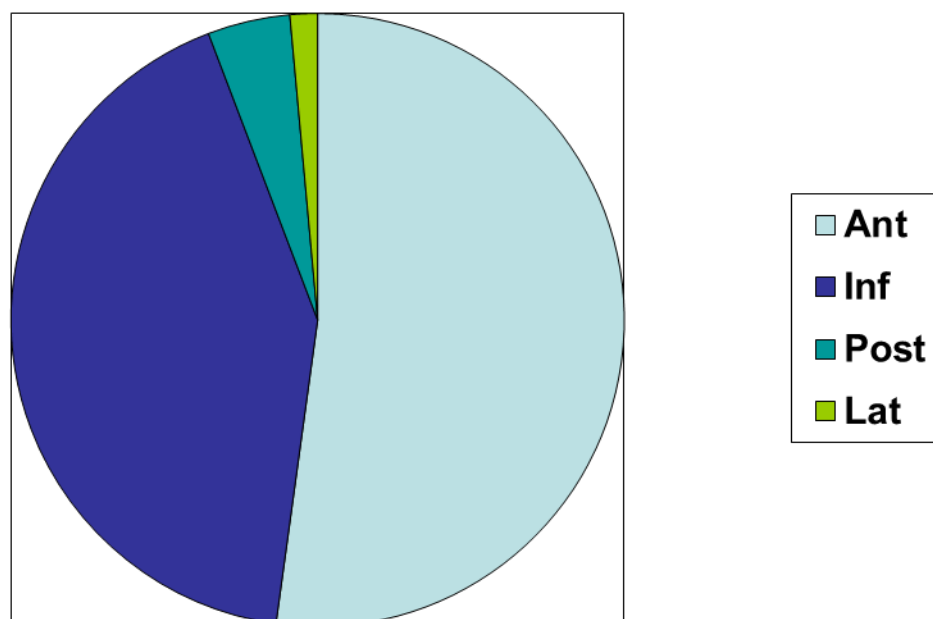
Of the 69 patients who underwent physiological assessment with pressure wire at the time of PCI, 60 (87%) were male and the mean (standard deviation [SD]) age was 58 (10.6). The majority (97%) were of Caucasian origin.



Within the study population cardiovascular risk profile included hypertension in 20 (29%), dyslipidaemia (defined as serum total cholesterol >5mmol/l and/or on lipid-lowering therapy prior to admission) in 17 (25%), current smoking at the time of admission in 36 (52%) and a family history of premature coronary artery disease (defined as a myocardial infarction in a first degree relative <60 years) in 10 (14%) of patients. Past medical history included myocardial infarction in 5 (7%), angina in 6 (9%), previous PCI in 4 (6%), cerebrovascular disease in 4 (6%), diabetes (type 2) in 4 (6%) and peripheral vascular disease in 1 patient. No patients in the study had previously documented left ventricular systolic dysfunction.

#### **4.2.1 Index event**

The reason for PCI in the study population (n=69) was primary PCI in 32 (46%) patients, rescue in 21 (31%) and prognostic (defined as PCI within 24 hours of successful reperfusion by thrombolysis) in 16 (23%). In total 37 patients received thrombolysis, with tenecteplase being used in every instance.



**Figure 4.1: ECG defined site of MI. Anterior = 36, inferior = 29, posterior = 3, lateral = 1 (n=69).**

#### 4.2.2 Admission blood results

	<i>Mean (Standard deviation)</i>
<b>Haematology (n=69)</b>	
Haemoglobin (g/dl)	14.1 (1.4)
White cell count x 10 <sup>3</sup> /μL	11.5 (2.8)
Platelets x 10 <sup>3</sup> /μL	251 (82)
<b>Biochemistry (n=69)</b>	
Sodium (mmol/l)	138 (2.8)
Potassium (mmol/l)	4.0 (0.4)
Urea (mmol/l)	5.4 (1.5)
Creatinine (μmol/l)	92.4 (15.9)
Glucose (mg/dl)	7.2 (2.1)
C – Reactive Protein (mg/dl)	21.1 (24.1)

**Table 4.1: Laboratory values on admission to hospital with index event**

#### **4.2.3 Timescale of presentation and treatment**

The median [interquartile range] time from symptom onset to presentation was 120 [66 – 240] minutes and the range within the study population was 0 minutes (for a patient who was already an inpatient) to 1620 minutes. The median [interquartile range] time from symptom onset to reperfusion by thrombolysis or PCI was 300 minutes [150 – 438] with the range being 30 minutes to 1740 minutes.

#### **4.2.4 Angiographic and PCI data**

The culprit artery as defined by the primary operator at the time of PCI was the left anterior descending (LAD) in 37 (54%) cases, the right coronary artery (RCA) in 28 (40%) and the circumflex (Cx) in 4 (6%) of patients.

<b>Culprit artery</b> *	<b>n (%)</b>
LAD	37 (54%)
RCA	28 (40%)
LCx	4 (6%)
<b>Stent type</b>	<b>n (%)</b>
Bare metal	45 (69%)
Drug eluting	19 (28%)
Balloon angioplasty	5 (7%)
<b>Stent data</b>	<b>mean (SD)<sup>†</sup></b>
Number of stents	1.4 (0.74)

Stent diameter (mm)	3.2 (0.45)
Stent length (mm)	26.9 (16)
<b>Adjunctive therapy</b>	<b>n (%)</b>
Aspirin (300mg)	69 (100%)
Clopidogrel (300mg)	69(100%)
Glycoprotein 2b3a inhibitor	52(75%)
Aspiration thrombectomy	31(45%)

**Table 4.2: Angiographic data for the study population. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables. \* Branch artery occlusions ie diagonal/obtuse marginal were categorised with the main epicardial artery. † n=64**

#### **4.2.5 Medication on discharge**

The discharge medication of the study population is outlined in the table below.

	n (%)
Aspirin	69 (100%)
Clopidogrel	69 (100%)
Beta Blocker	58 (84%)
ACE - Inhibitor	66 (96%)
Statin	69 (100%)

**Table 4.3: Summary of standard cardiovascular secondary prevention medication at discharge from hospital in the study population.**

### 4.3 Physiological assessment using pressure wire at the time of PCI

The protocols and timings of these measurements are described in the chapter 3. All patients had measurements taken at the end of the procedure and 47 (69%) patients also had pre stenting measurements. In one patient the distal coronary wedge pressure tracing was unsuitable for analysis and was not included. As this patient was treated only with balloon angioplasty we did not feel it was appropriate to perform a further balloon inflation in an attempt to re-record the coronary wedge pressure. A summary of the pressure wire data is detailed below:

	Pre-stenting (n=47)	Post-stenting (n=69)
Pw* (mmHg)	21 (15–26.3)	23 (16.3–30)
Mean transit time at rest (s)	0.95 (0.63–1.60)	0.73 (0.45–1.22)
Mean transit time at hyperaemia (s)	0.71 (0.47–1.02)	0.47 (0.33–0.70)
FFR (units)	0.79 (0.73–0.86)	0.89 (0.79–0.94)
CFR (units)	1.3 (1.11–1.45)	1.55 (1.31–1.72)
CFIp* (units)	0.25 (0.2–0.31)	0.27 (0.2–0.34)
IMR inc Pw* (units)	36.55 (24.7–62.6)	32.0 (22.3–52.3)
IMR (units)	41.3 (28.3–66.9)	34.8 (22.9–53.8)

**Table 4.4. A summary of pressure wire data pre and post stenting in the study population. All data are expressed as median (intra-quartile range). IMR inc Pw was calculated from the following equation “ $\text{Pa.Tmn} [(\text{Pd-Pw})/(\text{Pa-Pw})]$ ” and IMR was calculated using Pd.Tmn as mentioned previously. \* n=68.**

## **4.4 CMR data and analysis**

### **4.4.1 Overview**

Of the study population 57(83%) patients in total consented for CMR imaging. Of these 54 patients had complete scans as per protocol described in the methods section. Scanning was stopped early in 4 patients as these patients felt they were no longer able to tolerate the examination. Of these 4 patients, complete cine images were taken in all allowing analysis for LV volumes and ejection fraction. Gadolinium was administered in only one of these patients and “early MVO” images were taken prior to the patient requesting to finish the examination.

In summary 57 had complete cine images, 54 had “early MVO” sequences taken and 53 had “late gadolinium” sequences allowing assessment of infarct volume and “late MVO”

All patients were invited back for the follow up scan at 3 months. Fifty (88% of the initial CMR group) attended. Of these one gentleman was under the influence of alcohol on attendance and was therefore excluded from the study on safety grounds. Forty nine patients (87% of the CMR group) underwent a further ceCMR examination, all completing cine sequences. Two patients did not receive gadolinium, one as a consequence of a deterioration in renal function post MI and one because they felt unable to continue with the scan.

The mean (SD) time from PCI to scan one was 34 (16.1) hours. The mean (SD) time between the baseline scan and the follow up scan was 91.3 (5.4) days. The mean (SD) time for scan 1 was 41 (10.7) minutes and for scan 2 39.3 (9.4) minutes. Forty four patients were deemed to by Killip score 1 and the remaining 13 were Killip score 2 at the time of the initial CMR scan.

#### **4.4.2 Analysis of baseline and follow up ceCMR scans**

All scans were analysed as described in the chapter 3. The results are summarised in the table below

<i><b>CMR variables</b></i>	<i><b>2 days post-MI</b></i>	<i><b>3 months post-MI</b></i>
LV ejection fraction (%)	55.2 (11.9)	61.9 (10.8)
LV end-diastolic volume (ml)	130 .5 (29.3)	147.1 (32.9)
LV end-systolic volume (ml)	58.1 (21.0)	57.1 (24.4)
LV mass (g)	133.1 (32.8)	136 (29.7)
LV end-diastolic volume index (ml/m <sup>2</sup> )	68.2 (13.6)	74.3 (17.8)
LV end-systolic volume index (ml/m <sup>2</sup> )	30.5 (10.8)	28.9 (12.4)
LV infarct volume (ml)	23.1 (22.6)	12.1 (11.2)
LV infarct mass (g)	24 .2 (23.7)	12.4 (11.7)

LV mass/infarct ratio (%)	17.3 (14.8)	9.16 (8.94)
Transmurality score	2.25 (0.86)	1.89 (0.74)
“Early” MVO; n (%)	27 (50)	-
“Early” MVO volume (ml)	9.2 (7.4)	
“Early” MVO mass (g)	9.6 (7.8)	
LV mass/ “early” MVO ratio (%)	6.7 (4.9)	
“Late” MVO; n (%)	27 (51)	-
“Late” MVO volume (ml)	6.6 (7)	-
“Late” MVO mass (g)	6.8 (7.1)	-
LV mass/ “late” MVO ratio (%)	4.7 (4.5)	-

**Table 4.5. Summary of CMR data at baseline and follow-up. Data are expressed as mean (standard deviation).**



#### **4.5 The influence of anatomical site of myocardial infarction and therapeutic interventions at the time of emergency PCI on coronary pressure wire derived indices of microvascular obstruction.**

Following electrocardiographic analysis 32 infarcts were defined as inferior/posterior and 37 as anterior/lateral at the time of presentation. Pressure wire data following PCI were grouped by these criteria and compared in the table below.

	Inf/post STEMI	Ant/lat STEMI	P value
Median IMR [IQR]	29.2 [22.7-52.6]	37.8 [26.4-54.6]	0.43
Median CFIP [IQR]	0.30 [0.22-0.36]	0.26 [0.19-0.31]*	0.13
Median Pw [IQR]	24.0 [17.0-30.8]	22.5 [16.0-26.8]*	0.47

**Table 4.6: Comparison of pressure wire data post PCI by ECG site of STEMI at presentation. Non-normal data compared using the Mann Whitney test. \* (n=36)**

There was no significant difference in the pressure wire data post PCI by site of STEMI.

#### **4.6 A comparison of pressure wire data by primary operator's choice of treatment at the time of emergency PCI.**

All patients in the study were loaded with 300 mg aspirin and 300mg of Clopidogrel prior to emergency PCI. It was the primary operator's preference whether to use a glycoprotein 2b3a inhibitor in the peri-procedural period, to use aspiration thrombectomy or to use

drug eluting stents at the time of PCI. These are compared in the table below.

	n	Median IMR [IQR]	Median CFIp [IQR]	Median Pw [IQR]
GP2b3a	52	<b>36.1</b> [23.4-54.2]	0.28 [0.2-0.33]	22 [16-30]
No GP2b3a	17	<b>34.1</b> [17.4-52.2]	0.28 [0.21-0.34]	24.5 [17.3-30.5]
P value		0.46	0.99	0.61
Aspiration	31	<b>30.6</b> [23.1–41.5]	0.27 [0.19-0.34]	22 [16-30]
No aspiration	38	<b>37.3</b> [22.8-54.7]	0.29 [0.22-0.34] <sup>*</sup>	23 [16.5-29.5] <sup>*</sup>
P value		0.55	0.75	0.81
DES	19	<b>34.3</b> [20.1-47.8]	0.27 [0.23-0.35]	25 [20-32]
BMS/POBA	50	<b>35.2</b> [23.2 56.6]	0.28 [0.19-0.33] <sup>†</sup>	25 [20-32] <sup>†</sup>
P value		0.39	0.61	0.25

**Table 4.7: Comparison of physiological indices for microvascular dysfunction taken following PCI by primary operator's therapeutic choices in the peri-procedural period. The Mann Whitney test was used for comparison of non-normal data.**

<sup>\*</sup>(n=37) <sup>†</sup>(n=49)

## **4.7 Discussion - Demographics, admission data, angiographic and cardiac MRI results**

### **4.7.1 Demographics and patient characteristics**

In any study looking at STEMI it's useful to put the patient population into the context of historical and contemporary work. The mean age of patients in this study was just under 60 and the overwhelming majority were male, findings consistent with contemporary AMI studies.<sup>177</sup> Furthermore the demographics are in keeping with the Scottish STEMI population.<sup>3</sup> The patient population in this study was therefore in keeping with the study population in wider international AMI studies as well as being representation of the STEMI population in a national basis.

Although only a small number of previous studies have taken coronary physiological assessment using pressure wire in the AMI population, the patient population in this study is in keeping with these.<sup>45</sup> In particular, *Fearon et al* reporting a mean age of 62 and the majority of subjects male although the small numbers in this patient population contained a larger proportion of patients with hypertension and dyslipidaemia and a lower number of tobacco smokers. Broadly speaking the patient population in this study was similar to others in this field.<sup>47</sup>

Again small numbers of studies using the pressure wire at the time of STEMI had been done by the time of this work but again the proportion of successful physiological measurements was in keeping with previous work in this area.<sup>47, 141</sup>

I am not aware, at this point, of any previous studies which have enrolled patients prior to emergency PCI and then re-consented the patients after physiological assessment but prior to CMR scanning. Given the clinical uncertainties within this patient group I feel that 57 patient undergoing baseline MRI scan is satisfactory from 69 whom had given initial consent. A successful follow up MRI scan rate of around 80% is also in keeping with previous MRI studies with the AMI population.<sup>15</sup>

The study population were discharged from hospital with high levels of uptake of secondary preventative medications, with 100% on statin therapy, 84% on beta-blockers and 96% on ACE – inhibitors. Given that all of the study patients had underwent emergency PCI in the context of STEMI then anti-platelet therapy uptake of 100% on discharge is to be expected.

The study population under investigation in this thesis therefore represents a very well-treated cohort whose demographics, successful pressure wire and MRI scan rates are in keeping with previous studies within these fields.

#### **4.7.2 Pressure wire data in comparison with previous studies**

There have been increasing numbers of studies published looking at pressure wire indices for microvascular dysfunction, principally IMR, in recent years and to a lesser extent CFIp.

One study in which CFIp was performed in 28 patients a mean of 3.3 days following first acute myocardial infarction treated with thrombolysis the mean value was 0.17 units.<sup>145</sup> Previous work performed by *Balachandran et al* in the West of Scotland found a mean CFIp of 0.25 units when performed during rescue PCI following failed thrombolysis.<sup>141</sup> The median value in my mixed (primary, rescue and prognostic) study was 0.27 units following PCI and 0.25 units prior to PCI. This is in keeping with the limited body of work in this area. CFIp in my study is higher than in the work by *Sezer et al* but this could be explained by the 3.3 day time lapse between thrombolysis and pressure wire study in the Turkish group's study.<sup>145</sup>

There are more studies in the literature looking at IMR in acute myocardial infarction. Within these there are variations in the timing of the pressure wire studies in relation to emergency PCI. Furthermore some studies are limited to looking only at anterior myocardial infarctions. I have summarised these in the table below including my own data.

Authors	Year	Number of patients	Site of MI	Timing	Median IMR
Fearon et al <sup>47</sup>	2007	29	All	At PCI	<b>32</b>
Ito et al <sup>137</sup>	2009	40	All	At PCI	<b>26</b>
Sezer et al <sup>178</sup>	2010	35	All	48h post PCI	<b>29</b>
Lim et al <sup>179</sup>	2009	40	Anterior only	At PCI	<b>33</b>
McGeoch et al <sup>180</sup>	2010	57	All	At PCI	<b>35</b>

**Table 4.8: Comparison median IMR in this study with contemporary work in this field.**

The median IMR in my study was slightly higher than those in previous work in the field. It is not surprising that it is higher than the study by *Sezer et al* as you may expect IMR to decrease in the days following the acute event. I also included a significant proportion of patients whom had underwent rescue PCI and this increased the median IMR.

Overall I feel that the invasive coronary physiological measurements in my study were similar the contemporary work in this field.

#### **4.7.3 CMR results in comparison with previous studies**

As discussed previously contrast enhanced CMR is a well validated and robust technique for assessment of left ventricular ejection fraction, MVO and infarct sizes following myocardial infarction. In order to improve the validity of my work it is however important that my study is not taken in isolation and that my CMR analysis was in keeping with contemporary CMR studies in this area.

One of the landmark studies linking CMR findings with prognosis following myocardial infarction was the work by *Hombach et al*<sup>15</sup> published in 2005. They studied 110 patients a mean of 6.2 days after AMI. Infarct size was 12% of total LV muscle mass and MVO was detected in 47% of patients. I think that these results are in keeping with my own work, infarct size of 17% and MVO in 51% of patients. I think that the differences between the two studies can be explained by the time differences between myocardial infarction and scanning.

Infarct size shrank from 12% to 7.8% at follow up (mean 225 days) and no MVO was seen at follow up. Again this is similar to the decrease in infarct size in my study which fell to 9% at follow up, with no MVO found. In addition similar to my own work LVEF and LVEDV increased and LVESV decreased during follow up.

A more recent study by *Cochet et al* published in 2009 which again looked at the prognostic significance of MVO following re-perfused myocardial infarction found the aforementioned present in 47% of patients.<sup>106</sup>

*Wu et al*<sup>181</sup> studied 122 patients whom underwent CMR scanning within 1 week of myocardial infarction and follow up at 3 months. Similar to this work the mean age was 57 and 83% were male. In this patient population the mean infarct size was 22% of the LV mass and the mean ejection fraction was 41%. They found that follow up infarct size

decreased by 22%. They also noticed an increase in LVEF and LVEDV and a decrease in LVESV.

It can therefore be seen that although natural variations will apply, the CMR analysis data for my study cohort is in keeping with contemporary work in this area.

## **4.8 Conclusion**

The raw data on which this thesis is based, patient population, coronary physiological data and CMR analysis is in keeping with contemporary work in each of these areas.



**Chapter 5: The relationship between  
coronary pressure wire derived indices of  
microvascular dysfunction at the time of  
emergency PCI with microvascular and  
myocardial damage on cardiac MRI**

## 5.1 Introduction

Emergency percutaneous coronary intervention (PCI) is the established treatment for ST elevation myocardial infarction (STEMI). Despite achieving normal epicardial artery flow in the majority of patients up to one third of patients do not achieve myocardial microvascular reperfusion.<sup>26, 182</sup> Microvascular dysfunction in this setting is associated with an adverse prognosis.<sup>15, 16, 54</sup> However, there is no established method for evaluating the coronary microcirculation in STEMI patients in the cardiac catheterisation laboratory.

The index of microcirculatory resistance (IMR) is a novel pressure/temperature tipped guide-wire based quantitative measure of coronary microvasculature function. IMR has been validated in animal models and tested in stable patients,<sup>130, 131, 137</sup> and in a recent study of acute STEMI patients, IMR was a better predictor of left ventricular function 3 months post-MI than current standard methods for evaluating the microcirculation.<sup>47</sup>

Contrast enhanced cardiac magnetic resonance imaging (ceCMR) is the gold standard non-invasive technique for assessment of the coronary microcirculation.<sup>183</sup> Microvascular obstruction (MVO) on ceCMR following STEMI is associated with an adverse prognosis.<sup>111, 184</sup> However, for safety reasons, ceCMR is generally not performed until 2 or more days after hospital admission, limiting its clinical utility in the initial post-MI period.

In a broad range of STEMI patients, we aimed to determine whether IMR and other invasive physiological markers of microvascular dysfunction acquired immediately after stent deployment in emergency PCI for STEMI might predict the nature and severity of myocardial injury using ceCMR as the gold standard comparison. Specifically, we first hypothesized that an elevated IMR at the time of reperfusion would be associated with the nature of MI, as revealed by the occurrence of MVO on ceCMR. Secondly, we hypothesized that IMR would be independently predictive of the severity of MI, as subsequently revealed by infarct size and LV function on ceCMR during long term follow-up.

## **5.2 Methods**

Patients who met the pre-specific criteria and gave informed consent were included. During emergency PCI, a coronary pressure/temperature sensitive guidewire was advanced into the culprit artery and baseline means transit times (Tmn) were obtained following bolus intra-coronary injection of 3 ml of saline. Tmn and distal coronary pressure (Pd) were obtained under conditions of peak hyperaemia achieved by intravenous adenosine infusion (140 mcg/kg/min). IMR was calculated as  $Pd \times Tmn$ . Patients underwent baseline ceCMR 24-48h later and at 3 months follow up. Left ventricular dimensions were assessed using retro-gated (trueFISP) cinematographic breath-hold sequences and MVO was defined as a dark core of hypoenhancement within the area of hyperenhanced infarcted tissue using breath hold turboFLASH sequences following an intravenous bolus of gadolinium (0.1mmol/kg).

## **5.3 A comparison of patients with and without microvascular obstruction on contrast enhanced cardiac MRI**

### **5.3.1 Demographics, cardiac risk factors, admission information and angiographic variables**

As stated above there are two CMR sequences following gadolinium injection which can be used to elucidate the presence of microvascular obstruction. Fifty four patients had “early MVO” sequences taken and 53 had “late gadolinium” sequences allowing assessment of infarct volume and “late MVO”. Microvascular obstruction was noted on blinded analysis in 27 (51%) of 53 patients. This number is in keeping with previous MRI studies. There was no MVO noted on follow up CMR scanning. The breakdown of demographics and patient characteristics are noted in the table below.

	MVO present (n=27)	MVO absent (n=26)
Age (years[SD])	56.9 (10.2)	58.6 (11.7)
Male (%)	89	88
Smoker (%)	56	46
Hypertensive (%)	30	19
Dyslipidaemia (%)	37	12
Diabetes (%)	4	4
Haemoglobin (g/dl)[SD]	13.9(1.7)	14.3(1.1)
White cell count x 10 <sup>3</sup> /μL	11.7 (2.4)	11.5(3.6)

Platelet count x 10 <sup>3</sup> /μL	260.3 (107.3)	249.3(55.3)
Troponin I ng/ml	79.1 (113.9)	26.1 (18.1)
Time to reperfusion (h)	8.03 (6.8)	4.39 (3.3)
Aspirin (%)	100	100
Clopidogrel (%)	100	100
GP2b3a inhibitor (%)	89	62
Aspiration thrombectomy (%)	41	50
Drug eluting stent use (%)	19	38

**Table 5.1: Comparison of demographic data, cardiac risk factors, admission blood results, time to reperfusion and peri-procedural therapy in each group.**

There was no significant difference in age and gender between the two groups. The MVO group contained significantly more patients with a history of dyslipidaemia and hypertension. Peak troponin I was significantly elevated in the patients with MVO vs those without MVO: 79.1 (113.9) vs 26.1(18.1); p=0.024. Time from symptom onset to reperfusion was also longer in those in whom MVO was present: 8.03 (6.8) vs 4.39(3.3); p=0.018.

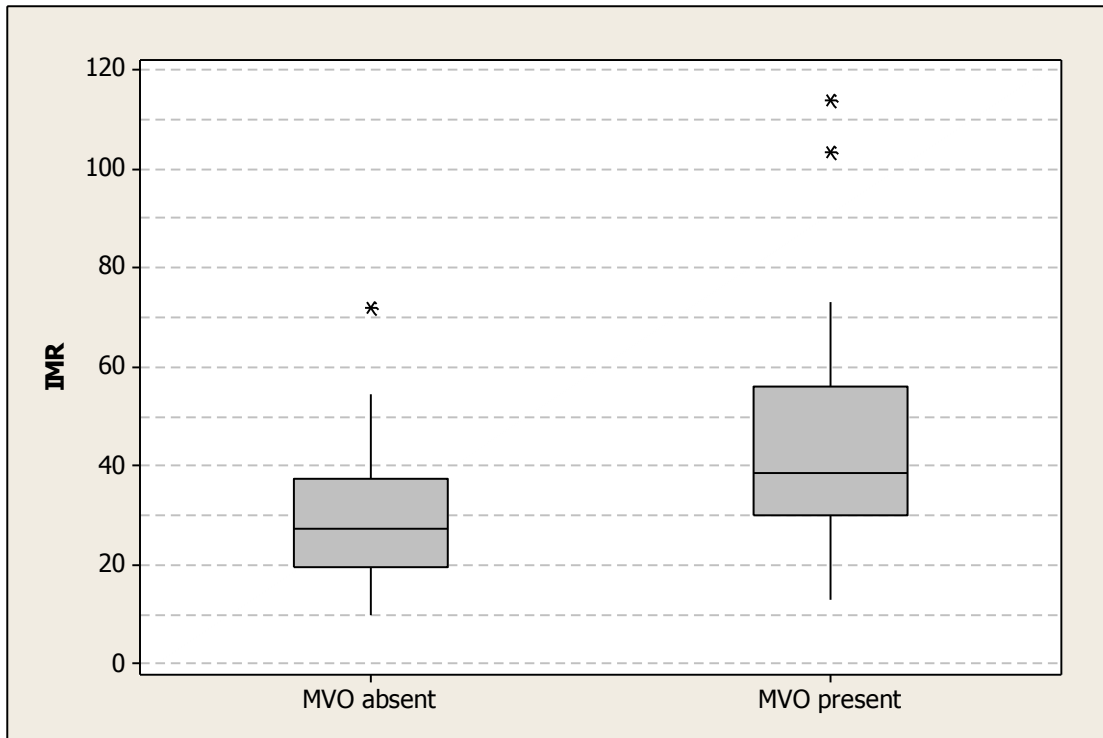
There were no significant differences in the peri-procedural therapy initiated in each group.

#### **5.4 A comparison of pressure wire data in patients with and without MVO on ceCMR**

The median IMR (IQR) in patients with MVO was higher (38.1 (29.4 – 54.6) units) compared to in patients without MVO (26.9 (18.9 – 36.9) units;  $p = 0.003$ , Figure 5.1). The pressure-derived collateral flow index and distal coronary wedge pressure were similar in both groups. The full results are outlined in the table below.

	MVO present (n=27)	MVO absent (n=26)	p value
Median Pw (IQR)	25 (17-32)	21 (15.5-25)	0.14
Median CFIp (IQR)	0.28 (0.2-0.35)	0.26 (0.19-0.34)*	0.41
median IMR(IQR)	38.1 (29.4-54.6)	26.9 (18.9-36.9)*	0.003

**Table 5.2: Comparison of pressure wire data in the MVO present and MVO absent groups. \* n=25**



**Figure 5.1: IMR box-plots dichotomised according to presence or absence of MVO**

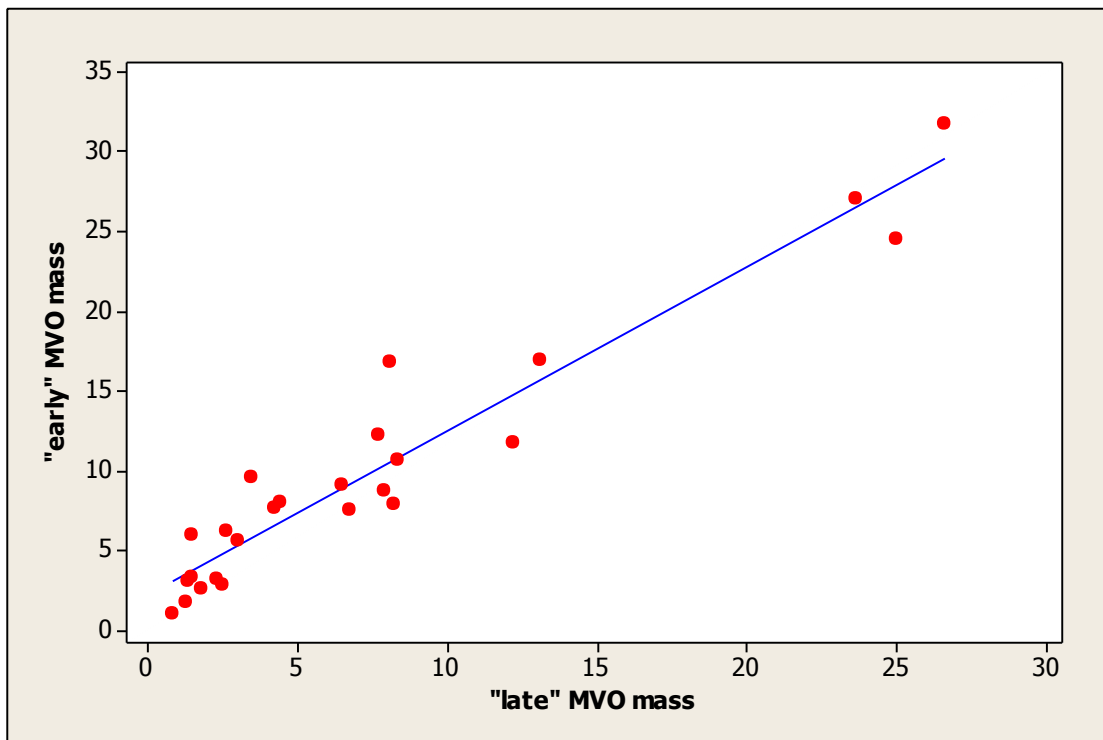
### **5.5 Comparison “early” and “late” MVO volumes, mass and ratio**

Twenty five patients were noted to have both “early” and “late” MVO on blinded analysis. One patient was noted to have “early” MVO but did not have “late” gadolinium sequences taken due to claustrophobia. One patient was thought to have “early” MVO but no “late” MVO and two patients were thought to have “late” MVO but no “early” MVO. In these 25 patients the mean (SD) “early” MVO volume was 9.4 (7.6) ml, the mean (SD) mass was 9.8 (8.0) grams and the ratio of MVO mass the left ventricular mass was 6.8% (4.9). The mean (SD) “late” MVO volume was 7.1 (7.1) ml, the mean (SD) mass was 7.4 (7.5) grams and the ratio of MVO mass the left ventricular mass was 5.1% (4.7). The

correlation between calculation of MVO volumes, mass and ratio was very close as can be seen in the table and graph below.

	R value	P value
MVO volume	0.96	<b>&lt;0.001</b>
MVO mass	0.96	<b>&lt;0.001</b>
MVO/LV mass ratio	0.95	<b>&lt;0.001</b>

**Table 5.3: Correlations and P values of “early” and “late” MVO volumes, mass and ratio calculated using digital planimetry. (n=25)**





**Figure 5.2: Correlation of “early” MVO mass with “late” MVO mass.  $R=0.96$ ;  
 $p<0.001$**

## **5.6 The relationship between pressure wire data and MVO volumes, mass and ratio on CMR scanning**

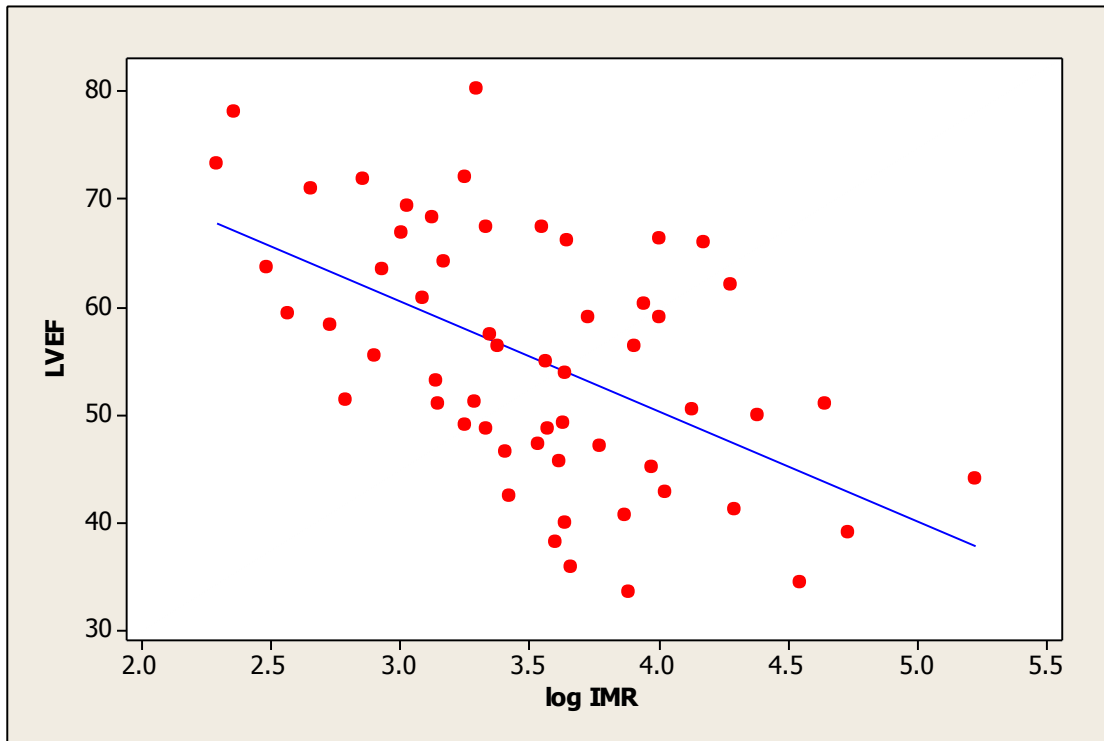
Given the very close correlation between the results for “early” and “late” MVO, I have compared the invasive physiological data taken following PCI with the “late” MVO data as only “late” MVO has been shown to be an adverse prognostic indicator.

Twenty seven patients were found to have “late” MVO and the volumes, mass and ratio to left ventricular mass were calculated as described previously. The demographics of these patients are as described above. There was no correlation between the invasive pressure wire measurements and either MVO volumes, mass or ratio to left ventricular mass.

## **5.7 The relationship between IMR and LVEF at baseline and follow up**

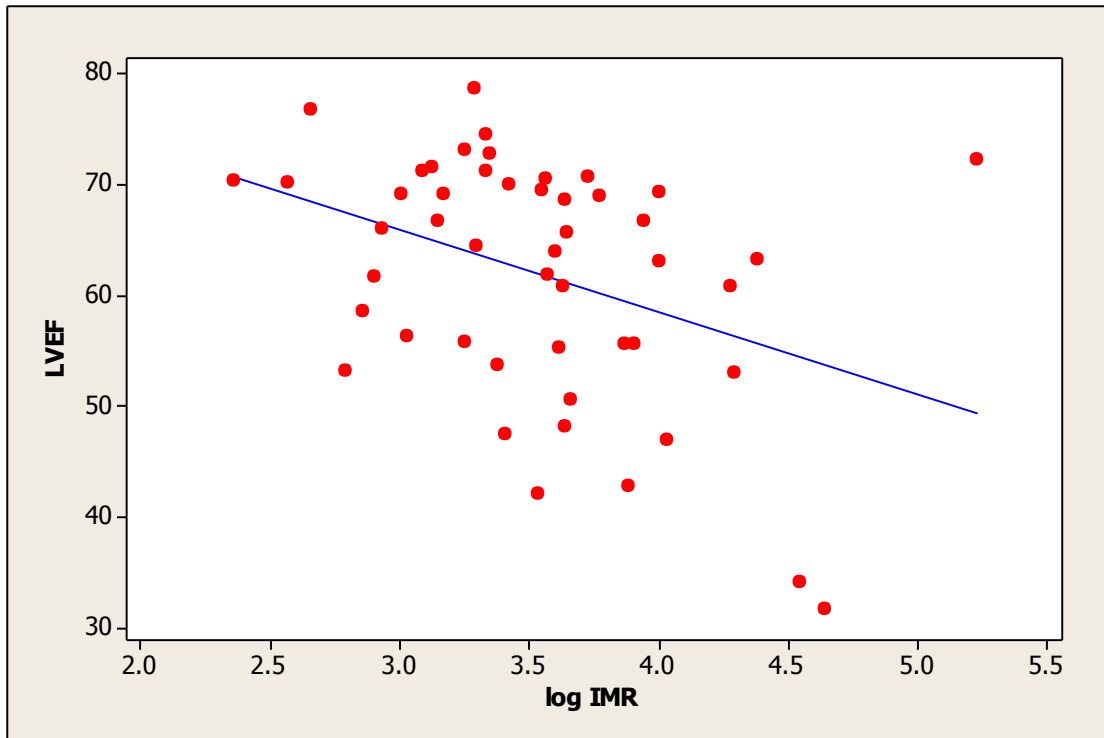
In univariable analyses, an elevated IMR was a negative predictor of left ventricular ejection fraction ( $p<0.001$ ) [figure 5.3] and a positive predictor of left ventricular end-systolic volume index (LVESVI,  $p=0.035$ ) at 2 days. IMR was the most significant

independent predictor of left ventricular ejection fraction at 2 days ( $<0.001$ ) Full results of the multivariate analysis are shown in table 5.4.



**Figure 5.3: Scatterplot of IMR (log transformed) against left ventricular ejection fraction at 2 days as assessed by ceCMR. In univariable analyses, an elevated IMR was a negative predictor of left ventricular ejection fraction ( $P<0.001$ )**

IMR continued to be a univariate predictor of ejection fraction at 3 month ( $p = 0.007$ , Figure 5.4]. CFIP and Pw were not found to predict ejection fraction at 3 months. IMR was a significant predictor of ejection fraction a 3 months in the multivariate model ( $p = 0.028$ ). (see table 5.4)



**Figure 5.4: Scatterplot of IMR (log transformed) and left ventricular ejection fraction at 3 months. Index of microcirculatory resistance continued to be a predictor of ejection fraction at 3 month ( $p = 0.007$ )**

	Univariate R <sup>2</sup> (%)	Univariate P value	Multivariate P value
<i>Predictors of LVEF at day 2</i>			
Cigarette smoking	5.4	0.08	0.37
Diabetes	12.1	0.008	0.025
IMR	29.1	<0.001	<0.001
Time to reperfusion	9.5	0.02	0.096
ST segment resolution > 70%	7.7	0.037	0.21
<i>Predictors of LVEF at 3 months</i>			
Glycoprotein IIb/IIIa inhibitor	10.8	0.02	0.031
IMR	14.5	0.007	0.028
Time to reperfusion	9.1	0.035	0.446
ST segment resolution > 70%	12.3	0.013	0.175
Culprit artery	16.8	0.003	0.039

**Table 5.4: Results of multivariable regression analyses for left ventricular ejection fraction measured by ceCMR performed 2 days and 3 months post-MI.**

The P values for the univariable models for LVEF measured by ceCMR at 2 days and 3 months follow-up respectively were: age (P=0.23; P=0.97); male gender (P=0.23; P=0.34); cigarette smoking (P=0.08; P=0.37), dyslipidaemia (P=0.94; P=0.34), hypertension (P=0.63; P=0.56), diabetes (P=0.008; P=0.34), glycoprotein IIb/IIIa inhibitor therapy (P=0.15; P=0.02), aspiration thrombectomy (P=0.31; P=0.22), IMR (P<0.001; P=0.007), CFIp (P=0.54; P=0.81), Pw (P=0.93; P=0.95), location of culprit artery

(P=0.19; P=0.003) time to reperfusion (P=0.02; P=0.035), ST-segment resolution > 70% (P=0.037; P=0.013), and cTFC (P=0.26;P=0.13). The strongest univariate predictors with a P value less the 0.1 were entered into the multivariate model to determine independent predictors. The rise in  $R^2$  value for each multivariate model including IMR as compared to all other variables was 37.1% to 50.8% at 2 days and 54.5% to 58% at 3 months.

## **5.8 The relationship between IMR and infarct volumes at baseline and follow up**

In univariate analysis IMR is a predictor of infarct mass ( $R^2=18.6\%$ ;  $P<0.001$ ) at 2 days . The other physiological markers of microvascular dysfunction were not predictors of infarct size. In the multivariate model IMR was the most significant independent predictor of infarct size at 2 days ( $P = 0.01$ ). Full results of the multivariate analysis are found below in table 5.5. At 3 months IMR remained an independent predictor of infarct volume on univariate analysis (  $R^2 = 15.6\%$ ;  $P = 0.006$ ). Again CFIP and Pw were not predictors of infarct volumes. In the multivariate regression model IMR was again a significant predictor of infarct volumes however culprit artery (LAD) was the most significant predictor. (table 5.5)

	Univariate R <sup>2</sup> (%)	Univariate P value	Multivariate P value
<i>Predictors of infarct volume at day 2</i>			
Glycoprotein IIb/IIIa inhibitor	5.3	0.09	0.29
IMR	18.6	<0.001	0.01
Time to reperfusion	11.1	0.016	0.32
ST-segment resolution > 70%	14.7	0.005	0.06
Culprit artery	14.2	0.006	0.03
<i>Predictors of infarct volume at 3 months</i>			
Dyslipidaemia	9.1	0.04	0.112
IMR	15.6	0.006	0.048
ST-segment resolution > 70%	9.9	0.031	0.384
Time to reperfusion	6.0	0.097	0.545
Culprit artery	21.3	0.001	0.021

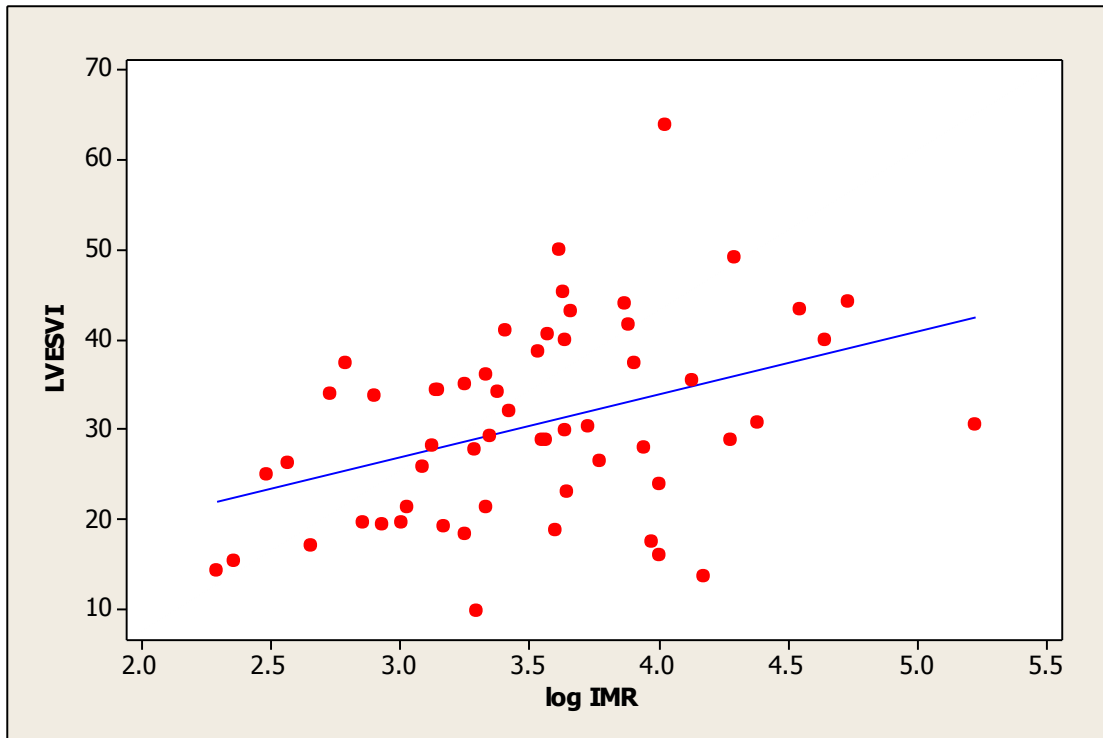
**Table 5.5: Results of multivariable regression analyses for myocardial infarct volume measured by ceCMR performed 2 days and 3 months post-MI.**

The P values for the univariable models for myocardial infarct volumes measured by ceCMR 2 days and 3 months post-MI, respectively, were: age (P=0.87; P=0.84); male gender (P=0.62; P=0.49); cigarette smoking (P=0.33; P=0.52), hypercholesterolaemia (P=0.18; P=0.04), hypertension (P=0.25; P=0.55), diabetes (P=0.77; P=0.52), glycoprotein IIb/IIIa inhibitor therapy (P=0.09; P=0.11), aspiration thrombectomy (P=0.43; P=0.26), IMR (P<0.001; P=0.006), CFIp p=0.53, p=0.67), Pw (P=0.82; P=0.72), time to reperfusion (P=0.016 ; P=0.097), ST-resolution >70% (P=0.005; P=0.031), culprit

artery ( $P=0.006$ ;  $P=0.001$ ) and cTFC ( $P=0.19$ ;  $P=0.23$ ). The strongest univariate predictors with a  $P$  value less than 0.1 were entered into a multivariate model to determine independent predictors. The rise in  $R^2$  value for each multivariate model including IMR as compared to all other variables was 51.3% to 53.9% at 2 days and 40.7% to 45.1% at 3 months.

## **5.9 The relationship between IMR and LV Volumes at baseline and follow up**

In univariate regression analysis IMR was the strongest predictor of LVESVI in the ceCMR scan 2 days following myocardial infarction ( $R^2 = 15.5\%$ ;  $p = 0.002$ ) [see figure 5.5]. Pw and CFIp were not predictors of LVESVI ( $R^2 = 1.3\%$ ;  $p = 0.4$ ) ( $R^2 = 2.0\%$ ;  $p = 0.29$ ) respectively. The 4 other most significant predictors of LVESVI on univariate analysis were entered into the multivariate model (see table 5.6).



**Figure 5.5: Scatterplot of IMR (log transformed) against left ventricular end systolic volume indexed for body surface area on ceCMR at 2 days.**

In univariate regression analysis IMR was the strongest predictor of high LVESVI in the ceCMR scan 2 days following myocardial infarction ( $R^2 = 15.5\%$ ;  $p = 0.002$ )

	Univariate $R^2$ (%)	Univariate P value	Multivariate P value
<i>LVESVI at day 2</i>			
IMR	15.5	0.002	0.009
Culprit artery	15.1	0.003	0.02
ST segment resolution < 70%	9.8	0.01	0.12
Time to reperfusion	4.5	0.11	0.78
Hypertension	4.3	0.12	0.16



**Table 5.6: Results of multivariable regression analyses for increased left ventricular end systolic volume index measured by ceCMR performed 2 days**

The following variables which did not reach significance when entered into the univariate model were not included in the multivariate model: age, gender, smoking, hypercholesterolaemia, diabetes, glycoprotein 2b3a use, aspiration thrombectomy at the time of PCI, CFIP, and Pw.

Using the same variables as above the five most significant predictors of left ventricular end diastolic volume corrected for body surface area (LVEDVI) were age, hypercholesterolaemia, CFIP, Pw and culprit artery. None of these variables reached statistical significance on the multivariate model (see table 5.7).

	Univariate R <sup>2</sup> (%)	Univariate P value	Multivariate P value
<i>LVEDVI at day 2</i>			
Age	5.7	0.07	0.12
Hypercholesterolaemia	4.9	0.99	0.09
CFIP	11.3	0.01	0.16
Pw	5.9	0.07	0.81
Culprit artery	8.6	0.03	0.09

**Table 5.7: Results of multivariable regression analyses for increased left ventricular**

### end diastolic volume index measured by ceCMR performed 2 days

The only significant univariate predictors of increased LVESVI on follow up ceCMR were electrocardiographic ST segment resolution of less than 70% (  $R^2 = 14.4\%$  ;  $p = 0.007$ ) and culprit artery location (  $R^2 = 20.9\%$  ;  $p = 0.001$ ). On entering the five most significant variables into the multivariate model the strongest predictor of LVESVI was culprit artery location (LAD).

	Univariate $R^2$ (%)	Univariate P value	Multivariate P value
<i>LVESVI at 3 months</i>			
GP2b3a	6.3	0.08	0.009
No aspiration thrombectomy	4.0	0.17	0.013
IMR	6.8	0.07	0.49
ST segment resolution < 70%	14.4	0.007	0.027
Culprit artery	20.9	0.001	0.005

**Table 5.8: Results of multivariable regression analyses for increased left ventricular end systolic volume index measured by ceCMR performed at 3 months**

The following variables were also entered in the univariate model but were less significant predictors than those about hence not entered into the multivariate model ; age, gender, smoking, dyslipidaemia, hypertension, diabetes, CFIp, Pw and time to reperfusion.

On univariate analysis for predictors of LVEDVI at 3 months of the variables stated above only the culprit artery was a predictor of increased volume (  $R^2 = 8.2\%$ ,  $P = 0.05$ ).

On entering the four other most significant predictors of increased LVEDVI into the multivariate model none were significant (table 5.9)

	Univariate R <sup>2</sup> (%)	Univariate P value	Multivariate P value
<i>LVEDVI at 3 months</i>			
Age	5.3	0.11	0.15
Gender	2.4	0.28	0.14
Diabetes	3.5	0.19	0.96
ST segment resolution < 70%	7.3	0.06	0.2
Culprit artery	8.2	0.05	0.12

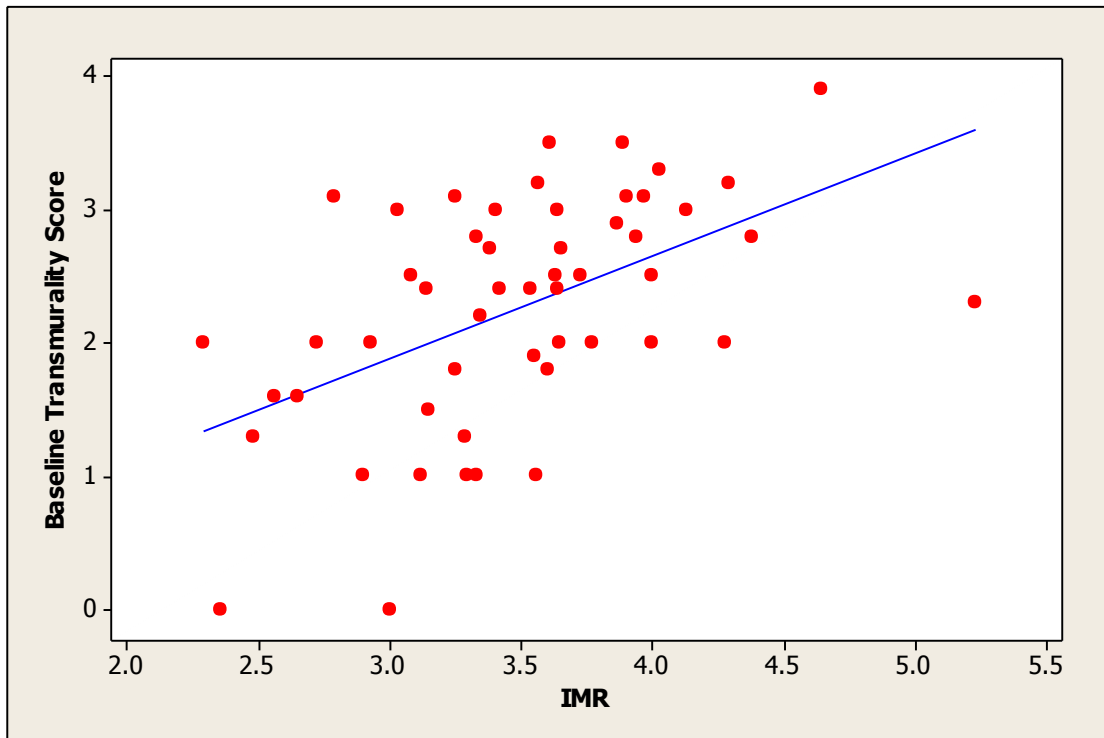
**Table 5.9: Results of multivariable regression analyses for increased left ventricular end diastolic volume index measured by ceCMR performed at 3 months**

The following variables were entered into the univariate analysis model but were less statistically significant for increased LVEDVI than those above; smoking, dyslipidaemia, hypertension, CFIP, Pw, IMR and time to reperfusion.

## **5.10 The relationship between IMR and infarct transmurality at baseline and follow up**

Fifty three patients had transmurality scores calculated as described in chapter 3. The mean (SD) value was 2.25 (0.86) with arrange of 0 to 3.9. Forty seven patients had transmuraity score calculated from the follow up CMR scans. The mean (SD) was 1.89 (0.74) and the range was 0 – 3.3. On univariate analysis using the various variables

mentioned above as predictors for increased transmural score at baseline the significant predictors were IMR ( $R^2 = 26.7\%$  ;  $p = < 0.001$ ) [see figure 5.6], electrocardiographic ST segment resolution  $> 70\%$  ( $R^2 = 22.1\%$  ;  $p = < 0.001$ ), time to reperfusion ( $R^2 = 22.1\%$  ;  $p = 0.004$ ), use of GP2b3a inhibitor ( $R^2 = 10.1\%$  ;  $p = 0.02$ ) and culprit artery ( $R^2 = 7.5\%$  ;  $p = 0.047$ ).



**Figure 5.6 : Scatterplot of IMR (log transformed) against transmural score at baseline ceCMR imaging at 2 days. IMR was the most significant predictor of increased transmural score at baseline ( $R^2 = 26.7\%$  ;  $p = < 0.001$ ).**

The five most significant univariate predictors for increased transmural score were entered in to the multivariate analysis model. IMR was again the most significant predictor of increased transmural score at baseline ( $p = 0.001$ ). Electrocardiographic

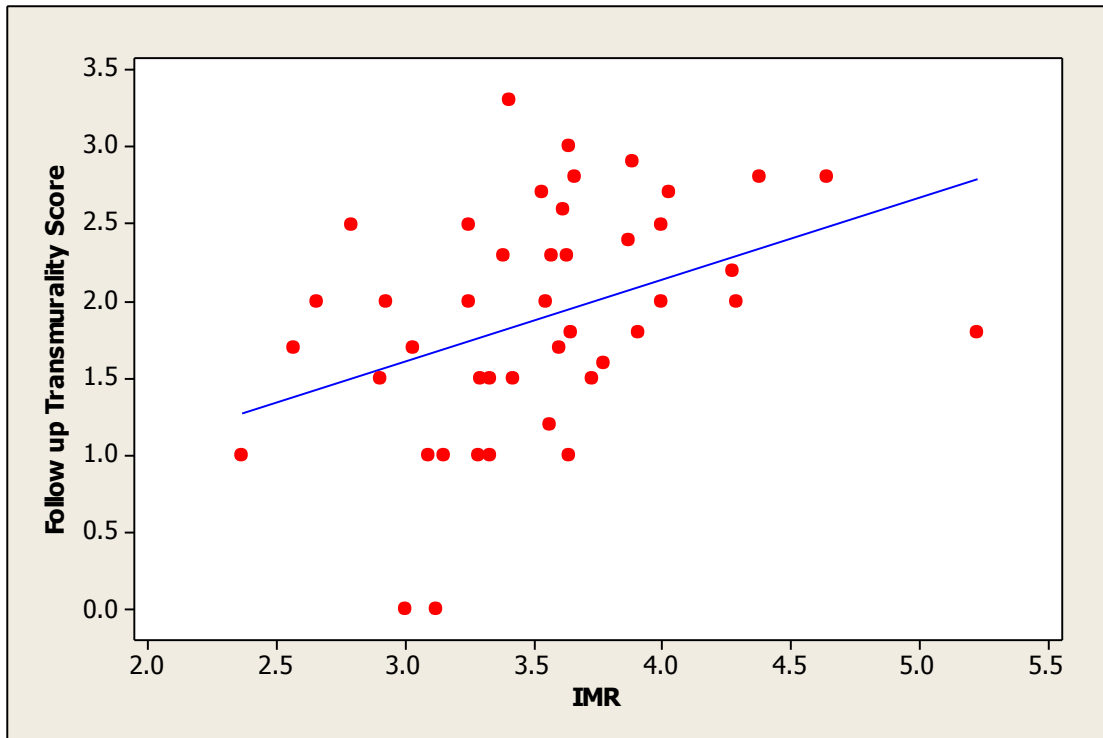
ST segment resolution index > 70% was also statistically significant ( $p = 0.006$ ). The complete results are seen in table 5.10.

	Univariate $R^2$ (%)	Univariate P value	Multivariate P value
<i>Transmurality score at baseline</i>			
GP 2b3a	10.1	0.02	0.08
IMR	26.7	< 0.001	0.001
Time to reperfusion	15.3	0.004	0.14
STR > 70%	22.1	< 0.001	0.006
Culprit artery	7.5	0.047	0.22

**Table 5.10: Results of univariate and multivariate regression predictive models for increased transmurality score at 2 days post myocardial infarction**

The following variables were entered into the univariate analysis model but were less significant than those above: age, male gender, cigarette smoking, dyslipidaemia, hypertension, diabetes, aspiration thrombectomy, CFIp, distal coronary wedge pressure, corrected TIMI frame count.

On univariate analysis using the various variables described as predictors for increased transmurality score at baseline the significant predictors were IMR ( $R^2 = 15.2\%$  ;  $p = <0.009$ ) [see figure 5.7], electrocardiographic ST segment resolution > 70% ( $R^2 = 14.8\%$  ;  $p = 0.008$ ), time to reperfusion ( $R^2 = 21.7\%$  ;  $p = 0.001$ ), use of GP2b3a inhibitor ( $R^2 = 17.2\%$  ;  $p = 0.004$ ) and culprit artery ( $R^2 = 5.8\%$  ;  $p = 0.005$ ).



**Figure 5.7: Scatterplot of IMR (log transformed) against transmurality score at baseline ceCMR imaging at 3 months. IMR was a significant predictor of increased transmurality score at baseline ( $R^2 = 15.2\%$ ;  $p = 0.004$ ).**

In the multivariate model GP2b3a use was the most significant predictor of transmurality score at 3 months ( $p = 0.007$ ). Electrocardiographic ST segment resolution  $> 70\%$  and increased IMR were also significant predictors ( $p = 0.008$  and  $p = 0.01$  respectively). See table 5.11 below.

	Univariate R <sup>2</sup> (%)	Univariate P value	Multivariate P value
<i>Transmurality score at follow up</i>			
GP 2b3a	17.2	0.004	0.007
IMR	15.2	0.009	0.015
Time to reperfusion	21.7	0.001	0.115
STR > 70%	14.8	0.008	0.008
Culprit artery	16.3	0.005	0.073

**Table 5.11: Results of univariate and multivariate regression predictive models for increased transmurality score at 2 months post myocardial infarction**

The following variables were entered into the univariate analysis model but were less significant than those above: age, male gender, cigarette smoking, dyslipidaemia, hypertension, diabetes, aspiration thrombectomy, CFIP, distal coronary wedge pressure, corrected TIMI frame count.

### **5.11 The relationship between IMR and LV remodeling**

The mean LVESVI (SD) decreased from 30.5 (10.8) ml/m<sup>2</sup> to 28.9 (12.4) ml/m<sup>2</sup> during the three month follow up period in the larger patient group. Forty nine patients had complete ceCMR scans at baseline and follow up and pressure wire studies performed at the time of PCI. In these patients the mean left ventricular end systolic volume index

(SD) decreased from 31.0 (10.7) ml/m<sup>2</sup> to 28.0 (12.4) ml/m<sup>2</sup> over the three month follow up period.

In the patient group with an IMR value greater than or equal to the median (35 units) the mean (SD) decrease in LVESVI was 3.04 (8.8) ml/m<sup>2</sup> vs 1.2 (9.7) ml/m<sup>2</sup> in those with an IMR of less than the median (p = 0.49).

In the patient group with a CFIP value of greater than or equal to the median (0.28 units) the mean decrease in LVESVI was 3.83 (8.7) ml/m<sup>2</sup> vs 0.4 (10.1) ml/m<sup>2</sup> in those with CFIP less than the median (p = 0.2).

In the patient group with a Pw of greater than or equal to the median (23 mmHg) the mean decrease in LVESVI was 0.31 (9.3) ml/m<sup>2</sup> vs 4.13 (8.7) ml/m<sup>2</sup> in those with Pw less than the median (p = 0.15).

	$\Delta$ LVESVI (SD) $\geq$ median (ml/m <sup>2</sup> )	$\Delta$ LVESVI (SD) < median (ml/m <sup>2</sup> )	P value
IMR	- 3.04 (8.8)	- 1.2 (9.7)	0.49
CFIP	- 3.83 (8.7)	- 0.4 (10.1)	0.2
Pw	- 0.31 (9.3)	- 4.13 (8.7)	0.15

**Table 5.12 : A comparison of  $\Delta$  LVESVI defined by pressure wire data. There is no significant difference between the groups.**



## **5.12 Discussion**

### **5.12.1 The comparison of different cardiac MRI methods of MVO assessment in AMI**

Researchers have commonly used different CMR methods for assessment of MVO. I compared the presence and extent of “early” MVO with “late” MVO. MVO can also be assessed by gadolinium enhanced first pass perfusion sequences. The conventional sequence for this affords only about half of the spacial resolution of the other methods available at the time of my work. It typically does not cover the entire heart but transects the LV on three predefined perpendicular planes. For this reason I did not include this in this thesis, although since my work has finished, a higher resolution first pass sequence has been developed.<sup>104</sup>

I found a very close correlation between “early” and “late” MVO. The fact that the LV mass/MVO ratio decreases between “early” and “late” MVO supports the suggestion that gadolinium passively diffuses into areas of microvascular damage over time following gadolinium injection and that the apparent size of MVO may decrease over a relatively short time period. However the differences between the two are minimal and indeed I think my work could help to refute the suggestion that localised areas of MVO may be missed by “late” MVO in comparison with “early”.

Given that the majority of the previous work linking prognosis with MVO has looked at “late” MVO<sup>15, 106</sup> and given the minimal differences between the two groups in my own study I think my work supports the assessment that the most appropriate method for assessment of MVO at the time of this thesis was the “late” MVO method. Furthermore I feel this supports the use of this method in this thesis.

#### **5.12.2 The relationship between pressure wire indices of microvascular obstruction and CMR data at baseline and follow-up**

Microcirculatory injury is a determinant of left ventricular function<sup>16, 185</sup> and prognosis following acute MI.<sup>15, 111</sup> While emergency PCI represents one of the first opportunities to evaluate and treat an acute MI patient the optimal method for evaluating the microcirculation in this setting is uncertain.<sup>23</sup>

The key findings in this aspect of my thesis are as follows:

Firstly, in a broad range of STEMI patients undergoing emergency PCI, an invasive measure of microvascular function, the IMR calculated immediately after PCI, was linked with the pathological nature of MI, since IMR was higher in patients with “late” MVO compared to those without “late” MVO, as revealed by ceCMR.

Secondly, IMR independently predicted the severity of MI as revealed by infarct volume and left ventricular function 2 days and 3 months post-MI.

Thirdly, IMR, but not coronary wedge pressure or pressure derived collateral flow index, independently predicted infarct size 2 days and 3 months post MI.

Fourthly, IMR, but not coronary wedge pressure or pressure derived collateral flow index independently predicted transmural score at baseline and follow up.

Finally, no pressure wire indices of microvascular injury were associated with adverse ventricular remodeling.

As discussed previously IMR has been subject to preclinical and clinical validation, and these studies have demonstrated that IMR measurement is largely independent of variations in haemodynamic state.<sup>130, 131, 137</sup> The seminal study by *Fearon et al*<sup>47</sup> confirmed the IMR to be superior to other commonly used clinical markers of microvascular dysfunction for predicting left ventricular function assessed by echocardiography.

This study is the first to compare invasively acquired measurements of microvascular injury using the coronary pressure wire with left ventricular function and MVO assessed by paired ceCMR studies obtained acutely and after longer-term follow-up.

Contrast enhanced CMR is recognized as the current non-invasive gold standard for assessment of coronary microvascular damage and left ventricular function and

dimensions.<sup>183</sup> A more recent study by *Hirsch et al*<sup>186</sup> quantified coronary blood flow characteristics using an intracoronary Doppler wire and related these findings to microvascular injury assessed by ceCMR. Twenty-seven anterior STEMI patients underwent repeat cardiac catheterization 4 - 8 days post primary PCI with ceCMR performed the preceding day. This study demonstrated that the extent of MVO was a multivariable predictor of abnormal coronary flow velocity characteristics, providing further functional evidence of the validity of ceCMR as a non-invasive tool to assess microcirculatory function. These observations complement those in the current study.

My findings complement those of the other previously published studies in this field in a number of important ways. My study had a larger sample size and included patients with a broader range of acute MI types (e.g. non-anterior STEMI). The time to presentation from the onset of symptoms for patients in our study was less restricted than in previous studies which excluded patients with symptoms > 12 h.<sup>47, 141, 187</sup>

This work is also the first to compare the pressure wire indices of microvascular dysfunction with myocardial damage at two distinct time points using ceCMR as the gold standard reference point. That IMR remained a significant independent predictor of decreased ejection fraction and increased infarct volume out to 3 months follow up further adds weight to the validity of the measurement.

This is the first study to compare pressure wire indices of microvascular damage with transmural score assessed by ceCMR. Given that IMR is an independent predictor of

infarct volumes at baseline and follow up. Again I feel that the relationship of IMR, but not distal coronary wedge pressure or pressure derived collateral flow index, to transmural score strengthens the case that IMR is a potential marker of subsequent myocardial injury which is available at the time of emergency PCI.

The pressure wire indices of microvascular dysfunction showed no relationship with adverse ventricular remodeling as assessed by ceCMR. The study was however powered to assess a difference in each MVO group and to look principally at the relationship between the pressure wire indices of microvascular dysfunction with ejection fraction and infarct volumes at baseline and follow up. There is nothing in the published literature about the relationship of IMR with adverse ventricular remodeling. The majority of patients in this study as with the other published literature had an improvement in their left ventricular systolic volume index. Therefore, given the small numbers of patients whom developed adverse ventricular remodeling, it is perhaps predictable that there was no relationship. I feel that a much larger patient population would be needed to try and exhibit such a finding.

Overall I think that these results extend the potential clinical relevance of IMR measurement to a larger group of patients with myocardial infarction and compliment the work that has gone before looking at IMR in the STEMI population. The median IMR in my study population was 35 units which is similar to that reported by *Fearon et al* (median IMR 32 units). My findings are consistent with and extend the results of these earlier studies and support the notion that standardized measurement of IMR may be

valid in clinical practice. Consequently, my results support the notion that invasive measures of microvascular function, specifically IMR, may be useful clinical tools to predict the initial severity of myocardial injury.

Only a minority of patients had a history of hypertension or diabetes and patients with previous MI in the culprit artery territory were not included. Therefore, the microvascular dysfunction observed in our patients was most likely influenced by the effects of acute coronary thrombosis and reperfusion, rather than the effects of chronic microvascular disease related to pre-existing cardiac disease.

### **5.13 Limitations**

There are also some important limitations in this aspect of the study. MVO is a dynamic phenomenon following coronary reperfusion and MVO which may be apparent on ceCMR initially may resolve by 48 h. In fact, MVO which is detectable 2 days post-MI is more correctly termed ‘persistent’ MVO. The dynamic nature of MVO may in part explain why elevated IMR values  $>35$  may occur in some patients with no visible MVO on ceCMR scanning two days later.<sup>188</sup> Serial ceCMR up to 48 h post-MI would be required to answer this question. The time point used to assess MVO by ceCMR is consistent with other studies in this subject and MVO measured at this time-point is an adverse prognostic marker.<sup>15</sup>

The study is limited by its small sample size, however IMR remains a significant predictor of myocardial damage. A larger sample size may have resulted in other predictors becoming significant. Larger studies will be needed to determine whether IMR can predict clinical outcomes (see Appendix V).

## **5.14 Conclusions**

The IMR is a simple wire based technique that can provide a quantitative assessment of microvascular function at the time of emergency PCI. We have shown that an elevated IMR is linked to MVO as revealed by ceCMR. MVO independently predicts long term prognosis following myocardial infarction. Accordingly we suggest measurement of IMR represents a new approach to risk assessment at the very earliest stage of acute MI management, and potentially, therefore enables triage of higher risk patients to more intensive therapy.

**Chapter 6: A comparison of Index of  
Microcirculatory resistance prior to and  
following stent implantation in emergency  
PCI for STEMI**



## 6.1 Introduction

Emergency percutaneous coronary intervention (PCI) is established as the treatment of choice in patients with ST segment elevation myocardial infarction (STEMI). Restoration of epicardial arterial flow and tissue level perfusion are the twin goals of this treatment. However despite achieving epicardial arterial patency in the majority of patients a significant proportion do not achieve complete myocardial reperfusion<sup>26, 182</sup>. The coronary microvasculature has been recognised as an important determinant of myocardial perfusion in the setting of STEMI. A variety of pathophysiological factors are thought to contribute to coronary microvasculature injury,<sup>25, 36</sup> including downstream microembolization of plaque material and thrombus at the time of balloon angioplasty or stenting, which if severe can lead to the phenomenon of no reflow. Autopsy studies have suggested that “clogging” of the microvasculature does occur during PCI as a result of downstream embolisation.<sup>29, 182</sup>

The status of the coronary microvasculature at the time of emergency PCI for STEMI can be assessed by measuring the index of microcirculatory resistance (IMR) using a pressure and temperature sensing coronary guidewire. IMR measured at the time of emergency PCI has been shown to be a predictor of the extent of subsequent myocardial damage.<sup>180</sup> When coronary wedge pressure is included in the calculation of IMR, accounting for collateral flow, it has been shown to be independent of any residual epicardial stenosis<sup>137</sup>. Accordingly any change in IMR pre and post stenting will reflect changes in microcirculatory resistance rather than any effect of stenting on the target epicardial

artery stenosis. For example, an increase in IMR post stenting could potentially result from downstream embolisation. We therefore investigated whether stent implantation at the time of emergency PCI for STEMI altered IMR and whether any changes in IMR pre and post stenting correlated with the extent of myocardial damage assessed using biomarkers and cardiac MRI.

## **6.2 Methods**

The study population included patients with STEMI referred to our institution for either primary PCI or rescue PCI after failed thrombolytic therapy or convalescent PCI within 24 h of successful thrombolytic therapy. Patients were prospectively enrolled when the following inclusion criteria were present: (1) age  $\geq 18$  years with electrocardiographic and symptomatic evidence of acute STEMI and in whom emergency stenting was intended, (2) written informed consent. Exclusion criteria were: (1) contraindications to adenosine, (2) cardiogenic shock. (3) Previous MI in the index territory (4) pregnancy. The research protocol was approved by the Institutional Review Board and informed consent was obtained from each patient.

### **6.2.1 Physiological assessment**

PCI was performed in line with current international guidelines with glycoprotein IIb/IIIa inhibitors and aspiration thrombectomy used at the discretion of the primary operator. In the majority of cases the coronary pressure/temperature sensitive guidewire was used as

the primary guide-wire. The guide-wire was calibrated outside the body, equalized within the guide catheter with the pressure sensor positioned at the ostium of the guide catheter, and then advanced into the distal third of the culprit artery. When indicated the guide-wire was disconnected from the analyser to allow the delivery of the various catheter devices used during the PCI and wiped with a damp sterile swab before reconnection.

After successful guide-wire passage into the infarct related artery beyond the stenosis/occlusion either balloon angioplasty or aspiration thrombectomy was performed as indicated. If the operating cardiologist did not think aspiration thrombectomy was indicated Pw was recorded during balloon pre-dilatation. If aspiration thrombectomy was performed Pw was recorded immediately following this by occlusive balloon inflation within the vessel at the site of proposed stenting. Immediately thereafter and before stenting thermodilution derived mean transit times were recorded at hyperaemia as previously described <sup>131</sup>. Adenosine 140 µg/kg/min was used to induce maximal hyperaemia via a large peripheral vein. Meticulous attention was paid to guide catheter engagement. Mean aortic pressure (Pa) and mean distal coronary pressure (Pd) were measured simultaneously during hyperaemia.

Ten minutes following stent delivery thermodilution derived mean transit times were measured again, Pa and Pd were recorded and Pw was obtained following inflation of a non-compliant balloon within the stented segment.

IMR was calculated using the following equations;

$$1. \text{ IMR}_{\text{true}} = \text{Pa} \cdot Tmn \cdot [(\text{Pd} - \text{Pw}) / (\text{Pa} - \text{Pw})]^{137}$$

$$2. \text{ IMR}_{\text{app}} = \text{Pd} \cdot Tmn^{130}$$

### **6.2.3 CMR protocol**

As described in the chapter 3.

### **6.2.3 CMR analysis**

Left ventricular mass, volume and function analyses were performed by a cardiologist experienced in CMR who was blinded to all clinical and pressure wire data. Results were obtained using Argus Dynamic Signal software (Siemens, Erlangen, Germany) as previously described.

### **6.2.4 Angiographic analysis**

TIMI flow grade was recorded pre and post stenting and corrected TIMI frame count (cTFC) after stenting by an experienced independent observer(JL).

### **6.2.5 Statistical analysis**

Statistical analysis was performed on MINITAB 16 software. The IMR data was non-normally distributed therefore is expressed as median [IQR] and was log transformed prior to statistical comparison. FFR, cTFC, TIMI flow grade, peak troponin I and LVEF were normally distributed and described as mean (standard deviation). The paired t test and the two sample t test were used to test for differences in the normally distributed data. A p value of less the 0.05 was taken as significant.

## 6.3 Results

### 6.3.1 Patient characteristics

Forty seven patients were enrolled in this study and their demographics and clinical characteristics are presented in Table 6.1. Successful physiological measurements were made all patients.

Variable	
Mean Age (SD)	58.7 (10.5)
Male Gender <sup>*</sup> (%)	44 (88)
Smoker <sup>*</sup> (%)	28 (56)
Hypertension <sup>*</sup> (%)	15 (30)
Dyslipidaemia <sup>*</sup> (%)	14 (28)
Diabetes <sup>*</sup> (%)	2 (4)

**Table 6.1: Patient demographics.** \* n = 47

The culprit artery was the right coronary in 17 cases, the left anterior descending in 26 cases and the circumflex in 4 cases. The indications were primary PCI in 25 cases, rescue PCI in 12 cases and convalescent PCI (defined as PCI within 24h of successful thrombolytic therapy) in 10 cases. The median time from onset of pain to reperfusion (by stenting or thrombolysis) was 4.3 hours.

All patients were preloaded with 300mg of Clopidogrel and aspirin. Aspiration thrombectomy was performed in 22 (46%) cases and glycoprotein 2b3a inhibitor was given in 31 (66%) cases. The mean number of stents implanted was 1.4 per patient. In 32 cases bare metal stents were inserted, drug eluting stents in 15 cases.

**6.3.2 IMR<sub>true</sub>, IMR<sub>app</sub> and TIMI flow grade pre and post stenting (table 6.2)**

There was a reduction in IMR<sub>app</sub> following stenting (41.3[28.3-66.9] to 32.3[52.6]; p = 0.02) but when collateral flow was accounted for (IMR<sub>true</sub>) there was no change (36.5 [24.7 – 62.6] to 30.5 [22.4 – 51.5] ; p = 0.35). When collateral flow was accounted for only prior to stenting but not afterwards following the resolution of the epicardial arterial stenosis the change reduced further (36.5 [24.7 – 62.6] to 32.3[52.6] ; p = 0.82).

However FFR improved significantly following stenting from 0.78 (0.14) to 0.91 (0.07); p = < 0.001, as did TIMI flow grade from 1.3 (1.2) to 2.8 (0.4); p < 0.001.

	Pre stenting	Post stenting	P value
IMR app	41.3 [28.8 – 52.6]	32.3 [22.8-52.6]	<b>0.02</b>
IMR true	36.5 [24.7 – 62.6]	30.5 [22.4 – 51.5]	<b>0.35</b>
IMR true/IMR app	36.5 [24.7 – 62.6]	32.3 [22.8 – 52.6]	<b>0.82</b>
FFR	0.78 (0.14)	0.91 (0.07)	<b>&gt;0.001</b>
TFG	1.3 (1.2)	2.8 (0.4)	<b>&gt;0.001</b>

**Table 6.2: The comparison of pressure wire data and TIMI flow grade before and after stenting. IMR is presented a median [IQR] and FFR and TFG mean (SD)**

### **6.3.3 Influence of adjunctive therapy on change in IMR**

There were no significant differences in IMR pre or post stenting in those who did (p=0.73) or did not receive GP2b3a inhibitors (p=0.11). Similarly there were no differences in IMR pre and post stenting in those who did (p = 0.83) or did not undergo aspiration thrombectomy (p=0.9).

### **6.3.4 Influence of change in IMR on evidence of myocardial damage (Table 6.3)**

The IMR decreased in 24 patients and increased in 23 patients. Forty three patients underwent baseline CMR at 2 day and 37 had follow up scanning at 2 months. The LVEF at 2 days was significantly lower in those in whom IMR increased (p=0.001) but this difference had resolved by 2 months. There was a trend towards higher infarct volumes in

the group in which IMR increased both at baseline and at follow up but this did not meet statistical significance. Peak troponin I was significantly higher in those in whom IMR increased ( $p = 0.03$ ) but there was no difference in ECG ST segment resolution index ( $p = 0.36$ ) or cTFC ( $p = 0.23$ ).

	IMR increase	IMR decrease	P value
LVEF at baseline (%)	49.5 (9.4)	60.9 (11.6)	<b>0.001</b>
LVEF at 3 months (%)	58.9 (13.3)	62.4 (12.3)	<b>0.41</b>
Infarct size at baseline (%)	22.6(17.4)	15 (13.4)	<b>0.15</b>
Infarct size at 3 months (%)	13.7 (13)	9.4(10.2)	<b>0.31</b>
Troponin I (units)	67 (65)	34.6(25)	<b>0.03</b>
STR index (%)	63.6(36.6)	73.4(31.4)	<b>0.23</b>
cTFC	20.1(12.4)	16.4(6.4)	<b>0.23</b>

**Table 6.3: The differences between indicators of myocardial damage grouped according to change in IMR following emergency PCI for STEMI. All values are mean (SD).**

### **6.3.5 The influence of angiographic no reflow in change in IMR**

I defined angiographic no reflow as a reduction in TIMI flow grade at any point during the emergency PCI procedure. This occurred in 11 cases altogether. The mean change in IMR in that group was 5.3 (29.4) and the change in those with no angiographic evidence of no-reflow was minus 2.6 (16.6). There was no significant difference between the two groups ( $p=0.46$ )



## 6.4 Discussion

Myocardial microvascular obstruction was first described as no – reflow phenomenon in 1974<sup>24</sup> . Distal embolisation of atherosclerotic material has been recognised as an important factor in decreased myocardial perfusion in the setting of ST elevation myocardial infarction. This has been shown by the injection of microspheres to represent atherosclerotic debris in the experimental canine setting<sup>27</sup> and was first noted in autopsy of 25 cases of sudden death due to acute coronary thrombosis. *Falk* noted that in 73% of cases there was fragmentation of the proximal thrombus with peripheral embolisation causing micro-embolic occlusion of the small intra-myocardial arterioles associated with microinfarcts.<sup>28</sup> A further autopsy study confirmed this in patients who died within 30 days of thrombolysis or balloon angioplasty for treatment of ST – elevation myocardial infarction.<sup>29</sup> Initial studies using distal protection devices confirmed high number of patients in whom this was present and suggested improvement in surrogate markers of microvascular perfusion.<sup>30</sup>

Hence it was hypothesized, distal protection devices that prevent embolisation during primary PCI may improve distal perfusion and improve patient outcomes<sup>140</sup>. This concept however has not been proven in the numerous randomised controlled trials which remained inconclusive despite capture of atheromatous material and the DEDICATION study further confirmed that the routine use of distal protection by a filterwire system during primary PCI did not seem to improve microvascular perfusion, limit infarct size, or reduce the occurrence of MACCE.<sup>32-34</sup>

Our study is the first to compare invasive assessment of the coronary microvasculature at the beginning and end of an emergency PCI procedure, prior to and following mechanical reperfusion. This study therefore suggests that stenting itself does not have a detrimental effect on the coronary microvasculature despite a significant improvement in TIMI flow grade. Given that the postulated detrimental effect of mechanical revascularisation in this patient population is caused by downstream embolisation<sup>30</sup> this may explain why previous studies looking at distal protection devices have not met their predefined endpoints. Furthermore, given that there is not a significant improvement in microvascular resistance following revascularisation of the epicardial artery despite a significant improvement in TIMI flow grade, we feel our study adds to the body of evidence that revascularisation alone is not sufficient to achieve optimal myocardial tissue level reperfusion following STEMI.<sup>140</sup>

Our findings are broadly in keeping with two recent studies, in stable patients, which have shown that when collateral flow is accounted for prior to PCI IMR does not change following stent implantation.<sup>138, 189</sup> An interesting observation is that IMR was higher in our study reflecting the complex pathophysiological influences on the coronary microvasculature in the setting of STEMI as opposed to the stable setting.

We have previously shown that IMR is a powerful independent predictor of myocardial damage assessed by CMR<sup>180</sup>. We have shown here that although a peri-procedural

increase in IMR is associated with a higher peak troponin I it is not associated with longer-term left ventricular damage as assessed by CMR.

## **6.5 Limitations**

There are some important limitations in our study. Firstly the authors recognise that microvascular damage in this context is a complex pathophysiological process which is most likely a dynamic phenomenon around the peri-infarct period. Our study only looked at two time-points within this process. We are therefore only able to provide a “snapshot” rather than an overview of the status of the microvasculature, and therefore leave questions unanswered. However, given that coronary stenting is the cornerstone of our treatment of STEMI<sup>13</sup> we feel that knowledge that this important intervention does not significantly change the invasive indices of microvascular function is useful information.

This study was powered to look for an overall change in IMR prior to and following stent implantation for emergency PCI. Although the sub group analysis such as angiographic evidence of no reflow indicates some interesting trends this aspect of the paper is limited by the small numbers involved in each sub-group. A larger patient population would be needed to be able to make definitive statements regarding the sub group analysis.

We included 3 patient groups in our study. We found that the IMR was significantly lower in those who had PCI within 24h of successful thrombolytic therapy than in the

rescue or primary PCI groups. This may represent to time lapse between the acute event and the invasive physiological assessment.

## **6.6 Conclusions**

Microvascular resistance does not change significantly following emergency stenting in patients with ST elevation myocardial infarction. This suggests that stent deployment itself does not significantly alter the status of the coronary microvasculature, and furthermore, that mechanical reperfusion of the infarct related epicardial artery does not achieve optimal treatment of the coronary microcirculation.

**Chapter 7: The relationship between  
coronary pressure wire derived  
markers of microvascular obstruction  
and “traditional” indices of  
myocardial damage and  
microvascular obstruction in ST –  
elevation myocardial infarction**

## 7.1 Background

Independent interrogation of the coronary microvasculature is possible by the measurement of IMR. But, correlations between IMR and other more conventional and validated indices associated with microvascular and myocardial dysfunction following myocardial infarction is limited. We therefore investigated relationship between IMR and tradition indices of microvascular perfusion and myocardial injury in patients with re-perfused STEMI treated with emergency PCI

## 7.2 Methods

Patients underwent comprehensive physiological assessment using a coronary pressure/temperature tipped guide-wire following emergency PCI for STEMI. IMR was calculated using  $P_d \times T_{mn}$ , Pw was recorded and CFIp was calculated using  $P_w/P_a$ . Corrected TIMI frame count, TIMI flow grade and ST segment resolution index were calculated by a blinded observer(JL). Peak troponin I was recorded.

## 7.3 Results

### 7.3.1 A comparison of pressure wire data with TIMI flow grade prior to PCI

TIMI flow grade	n	Median IMR [IQR]	Median CFIp [IQR]	Median Pw [IQR]
0	28	37.6 [26.4-56]	0.27 [0.2-0.33]	23 [15.3-30.7]

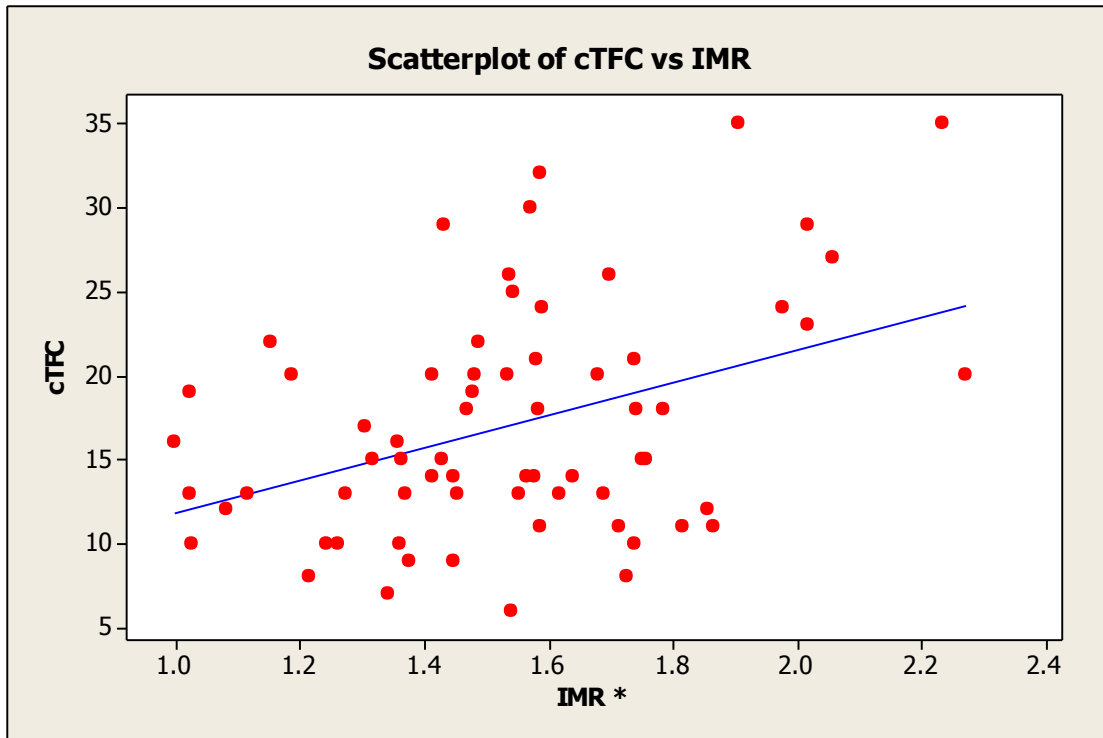
1	20	36.3 [23.8-64.4]	0.26 [0.21-0.36]	21 [17-25.7]
2	11	30.0 [15.3-49]	0.28 [0.16-0.34]*	25 [16.2-27.7]*
3	10	24.9 [17.7-34.8]	0.28 [0.19-0.35]	23 [16-33]

**Table 7.1. Pressure wire indices following PCI grouped by TIMI flow grade prior to PCI. \* (n=10) Comparison between each group using the Mann Whitney test for comparison on non-normal data.**

IMR was significant lower in patients with TIMI 3 flow compared to those with TIMI 0 flow ( $p=0.009$ ) and those with TIMI 1 flow ( $p=0.04$ ). There were no other significant differences between groups. There were no significant differences in CFIP or distal coronary wedge pressure according to TIMI flow grade.

### **7.3.2 A comparison between the invasive physiological indices of MVO and corrected TIMI frame count immediately after emergency PCI**

Increased IMR correlated closely with cTFC,  $r = 0.36$ ,  $p = 0.002$ . Both CFIP and Pw did not correlate with cTFC,  $r = -0.11$ ,  $p = 0.37$  and,  $r = -0.07$ ,  $p = 0.56$  respectively.



**Figure 7.1: Scatterplot with regression of cTFC vs IMR.\* IMR was log transformed prior to analysis.**

### **7.3.3 A comparison of pressure wire data with ECG ST segment resolution index**

ST segment resolution (STR) was calculated as the percent resolution in the single lead with the maximum baseline ST segment elevation as described in the methods section. These data were divided into ST segment resolution of greater than or less than 70% as previously described. Electrocardiographic data was available for 69 patients. The mean (SD) per cent STR was 68.8 (30.1) with 30 (43%) patients having an STR of less than 70% and 39 (57%) having STR greater than 70% following reperfusion.

These results are contained in table 7.2 below.



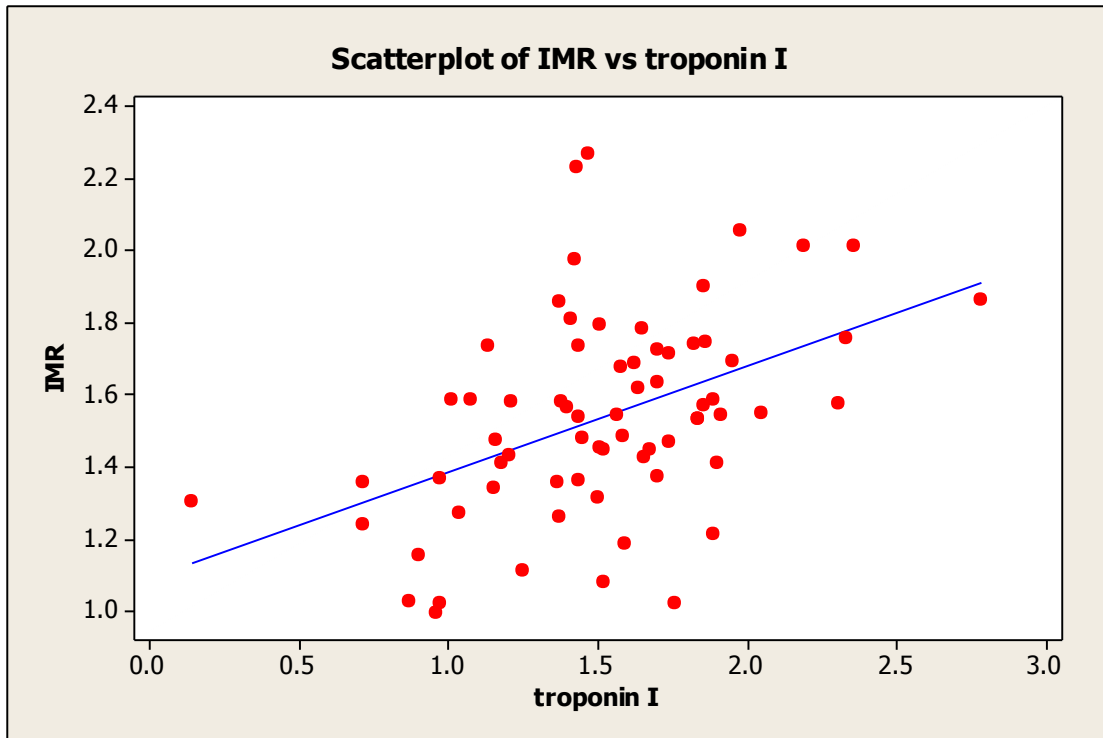
	STR < 70%	STR > 70%	P value
Median IMR [IQR]	<b>38.7</b> [30.1-55.5]	<b>28</b> [20.1-43.4]	0.03
Median CFIP [IQR]	<b>0.26</b> [0.19-0.31]	<b>0.28</b> [0.2-0.34]	0.51
Median Pw [IQR]	<b>22</b> [16.7-27]	<b>24</b> [16-30.3]	0.56

**Table 7.2: Pressure wire data assessed by ST segment resolution index. The Mann Whitney test was used to compare non normal data. A p value of <0.05 was taken as significant.**

IMR was significantly lower in those with an ST segment resolution index of greater than 70%. There were no significant differences in CFIP or Pw.

#### **7.3.4 Comparison between physiological assessment of MVO following PCI and peak troponin I**

In total 69 patients had their peak troponin I measured as described. The range was 1.39 to 606 ng/ml and the median [IQR] was 33 [16.9-67.0]. Given the non-normal distribution of the data all was log transformed prior to comparison. Peak troponin I did not correlate with either distal coronary wedge pressure ( $r = 0.16$ ;  $p = 0.2$ ) or CFIP ( $r = 0.09$ ;  $p = 0.45$ ). However IMR post procedure did correlate with TnI ( $r=0.46$ ;  $p<0.001$ ).



**Figure 7.2: Scatterplot of IMR vs peak troponin I ( $r=0.46$ ;  $p<0.001$ )**

### **7.3.5 The influence on time to presentation and reperfusion on pressure wire data**

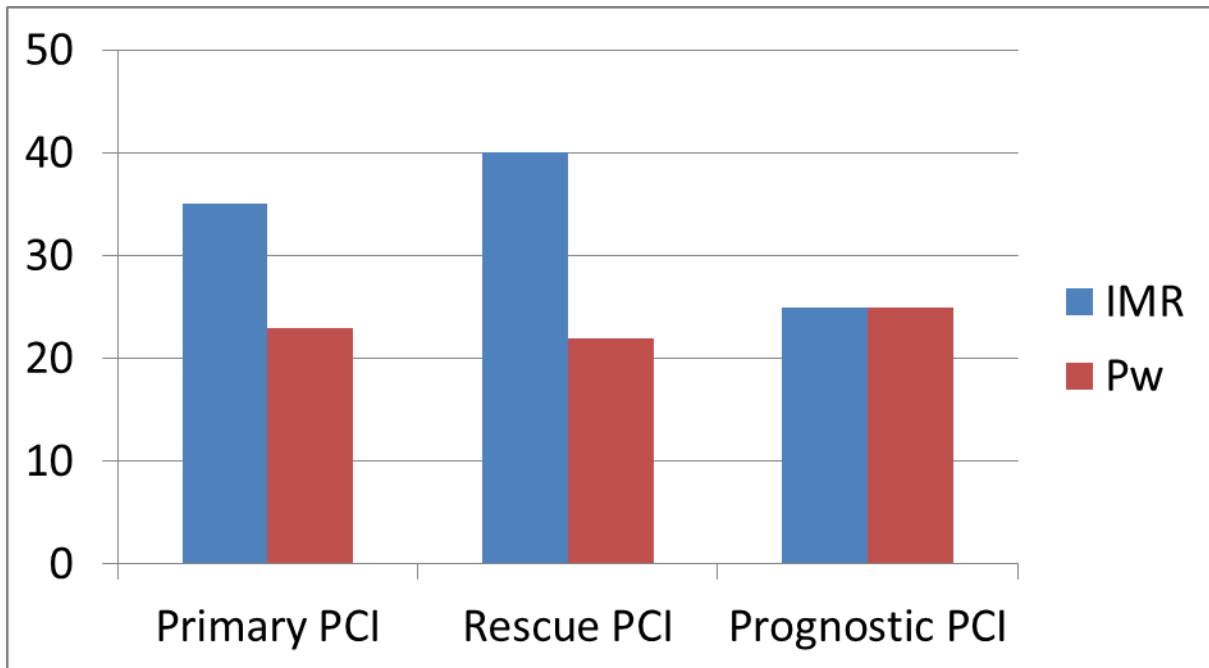
There were no significant correlations between IMR, CFIP and Pw and the time to presentation;  $r=0.14$   $p=0.26$ ,  $r=0.09$   $p=0.49$  and  $r=0.06$   $p=0.64$  respectively. When total time from symptom onset to reperfusion (either by thrombolysis or PCI) was taken into account IMR, but not CFIP or Pw correlated significantly,  $r=0.25$   $p=0.039$ .

### **7.3.6 A comparison of pressure wire data with method of AMI reperfusion**

Median IMR (IQR) was 39.8 (30 -55) in those whom underwent rescue PCI, 35.5 (21-60) in those whom underwent primary PCI and 24.4 (17-35) in those in whom PCI was performed within 24 hours of successful reperfusion therapy (prognostic). There was a significant difference between the rescue and prognostic groups ( $p=0.009$ ) and the primary and prognostic groups ( $p=0.04$ )

Median CFIp [IQR] was 0.27 [0.20 – 0.33] in those whom underwent treatment for STEMI with rescue PCI, 0.27 [0.23 – 0.33] and 0.28 [0.18-0.34] in those in whom PCI was performed within 24 hours of successful reperfusion therapy (prognostic). There was no significant difference between the groups.

Median Pw [IQR] was 23 [14.5-30] in those whom underwent rescue PCI, 22[17.5-30.2] in those whom had primary PCI and 25 [16.0-30] in those in whom PCI was performed within 24 hours of successful reperfusion therapy (prognostic). There was no significant difference between the groups.



**Figure 7.3: Median IMR and Pw in each of the PCI groups**

Nature of PCI	Median IMR (IQR)	Infarct volume (SD) mls
Primary	35.5 (21-60)	25 (24)
Rescue	39.8 (30-55)	29 (24)
Prognostic	24.4 (17-35)	13 (15)

**Table 7.3: median IMR and with mean infarct volumes at 48h by type of PCI**

## 7.4 Discussion

### 7.4.1 The relationship between IMR and other indices for microvascular damage available directly after emergency PCI

Interrogation of the coronary microvasculature is possible by the measurement of IMR.<sup>131, 137</sup> But, correlations between IMR and other more conventional and validated indices associated with microvascular damage in the context of STEMI is limited. In this aspect of my thesis I will discuss the relationship between IMR and the “traditionally” used indices of microvascular perfusion with patients with re-perfused STEMI treated with emergency PCI.

Electrocardiographic ST segment resolution following reperfusion is known to be an indirect marker of microvascular perfusion and is discussed previously in this work. In this thesis the median IMR was significantly higher in those who did not achieve ST resolution of 70%.

There was a close correlation between IMR and CTFC post PCI and a close correlation between IMR and CF<sub>Ip</sub>, and IMR and Pw following intervention.

*Fearon et al* compared IMR, ST segment resolution, myocardial blush grade, cTFC and CFR in their ability to predict wall motion injury assessed echocardiographically in 29 patients. They did not, however, directly compare these indices.<sup>47</sup>

*Sezer et al* compared IMR with Pw, CFIP, CFR, ST segment resolution and MBG in 42 patients 48h following successful primary PCI.<sup>190</sup>

My work in a larger group of patients found a close correlation between IMR, Pw and CFIP similar to *Sezer et al*. I believe, at the time of writing, that this is a largest study directly comparing IMR with these surrogate markers of microvascular damage following emergency PCI. I believe that my work adds to that of *Sezer et al* by implying that the relationship between IMR and the surrogate markers for tissue perfusion indicate that the impairment of microvascular perfusion is most likely due to increased microvascular resistance or at least indicates that increased microvascular resistance following emergency PCI is one of the most important mechanisms in impairment of microvascular perfusion.

I think this aspect of my thesis adds to the body of evidence that IMR could prove to be a valuable and robust modality in evaluating the coronary microcirculation following PCI.

#### **7.4.2 The relationship between IMR, time to reperfusion and method of reperfusion**

Meta-analysis has revealed that primary PCI is superior to thrombolysis in acute myocardial infarction.<sup>13</sup> There has been a direct relationship between time to treatment with thrombolysis for STEMI and mortality.<sup>191, 192</sup> It has been suggested that despite longer time to treatment seen generally with primary PCI, mortality is not as time

dependent as seen with thrombolysis.<sup>193</sup> One suggestion is that thrombolysis is associated with slower and incomplete epicardial recanalisation in combination with downstream micro-embolisation of thrombotic and vasoactive material.<sup>194</sup>

I therefore investigated the link between time to reperfusion and IMR and the differences in IMR depending on the method of reperfusion.

There was a link between IMR and time to reperfusion but not with CFIP or distal coronary wedge pressure. Interestingly there was no link between time of symptom onset to time of presentation and IMR. Although the link between IMR and time to reperfusion is weakly significant ( $p = 0.039$ ), animal models have shown that duration of coronary artery occlusion is directly related to infarct size<sup>195</sup> therefore I feel it does further strengthen the link between IMR and extent of myocardial injury.

Within my patient population the median IMR was higher in those whom underwent rescue PCI in comparison to primary PCI although this was not statistically significant. I think this is understandable, primarily given that by definition these patients have not re-perfused electrocardiographically therefore have their coronary artery occluded for a longer period and therefore would be expected to have larger infarcts. This trend is confirmed by infarct volume analysis on the 48h CMR scanning.

Both IMR and infarct volumes are significantly reduced in the patients whom underwent prognostic PCI within 24h of re-perfused STEMI with thrombolysis. The reduction in

IMR is most likely due to the time delay between electrocardiographic reperfusion and PCI. I accept this as a limitation within the study.

Overall however I think this aspect of the thesis emphasizes the link between IMR and extent of myocardial injury.

#### **7.4.3 The relationship between pressure wire derived indices of microvascular damage and peak troponin I**

In my study I found a close correlation between peak troponin I and IMR. Elevated cardiac troponin in patients with ST elevation and non ST elevation myocardial infarction is associated with adverse outcomes, including a higher incidence of congestive heart failure, shock, and death. Large clinical trials have revealed the important prognostic role of troponin in this patient population.<sup>196-198</sup> The Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) II reported that in patients with STEMI, there was a higher risk of 30-day mortality in groups of patients with a positive admission troponin T compared to those in whom it was negative ( 13.0% and 4.7% respectively).<sup>196</sup> This was confirmed in a GUSTO sub-study which enrolled over 12000 patients. In this study elevated troponin T was associated with a worse early and long term prognosis.<sup>197</sup>



The use of troponin has now become widespread in the diagnosis of myocardial infarction, its role as a biochemical marker of infarct size has also become well validated by using SPECT imaging<sup>199</sup> and more recently in a large study (n = 1237) correlating peak troponin T with scintigraphically determined myocardial infarct size in patients with STEMI undergoing contemporary primary percutaneous intervention<sup>200</sup>.

*Younger et al* found that both 12 hour and 72 hour troponin I concentration correlated with infarct size as assessed by ceCMR ( $r = 0.56$ ,  $p = 0.0003$ ;  $r = 0.62$ ,  $p < 0.0001$  respectively).

The close relationship between IMR and peak troponin I in my study therefore adds to the hypothesis that IMR is a robust marker of myocardial damage when measured directly after PCI.

## **7.5 Conclusions**

IMR calculated following STEMI correlated closely with tradition angiographic, pressure wire and biochemical markers of microvascular and myocardial damage following STEMI. This adds to the growing body of evidence that IMR is a robust marker of myocardial damage following STEMI.

**Chapter 8: Advances in cardiac imaging  
in STEMI survivors: diagnostic utility of  
cardiac magnetic resonance**

## 8.1 Introduction

Clinical guidelines recommend imaging of the heart for risk assessment after ST elevation myocardial infarction (STEMI)<sup>68</sup>, and cardiac imaging is required for the assessment of post MI complications including left ventricular dysfunction.

Cardiac magnetic resonance imaging (CMR) is a powerful diagnostic method and provides prognostically relevant information<sup>201</sup>. In addition to being useful for quantifying heart function, volumes and viability after acute MI<sup>85, 87, 202</sup>, CMR can reveal myocardial injury characteristics, such as microvascular obstruction (MVO) and infarct size<sup>15</sup>. CMR within the first week post-MI is also safe but there is limited evidence on the safety and feasibility of the test in the heterogeneous group of patients who survive STEMI in the very early post infarct period.

Contrast-enhanced CMR (ceCMR) provides diagnostic information which collectively cannot be provided by any other single imaging test. Although echocardiography is the standard of care for imaging post-MI it is limited by acoustic shadows and reveals little about extra-cardiac disease. Both forms of imaging should be performed and interpreted by trained individuals. Historically, CMR has generally not been feasible in STEMI patients because of logistical and cost issues, however it is becoming increasingly available in regional hospitals, including those which provide primary percutaneous coronary intervention (PCI).

In order to better understand the potential role of CMR for early risk assessment in STEMI, we prospectively studied the feasibility and diagnostic utility of CMR in a broad range of invasively managed STEMI patients treated in two different hospital settings. We included patients with angiographically incomplete myocardial reperfusion, heart failure, arrhythmia and those post thrombolysis. Furthermore we hypothesised that the utility of CMR might be enhanced by disclosure of clinically relevant cardiac findings in the early post infarct period as well as incidental non-cardiac findings<sup>203</sup>, provided these observations do not also trigger unnecessary tests or interventions. In addition we studied the clinical significance between early CMR findings and adverse cardiac events within 30 days of discharge.

## **8.2 Methods**

### **8.2.1 Patient population**

Two hundred patients with STEMI who underwent primary, rescue or convalescent PCI were referred for a CMR scan. Exclusion criteria were : lack of informed consent, lack scanner availability, standard contra-indications to MRI including an estimated glomerular filtration rate  $< 30 \text{ ml/min/1.73 m}^2$  or on-going hemodynamic instability, defined as patients receiving support with intra-aortic balloon counter pulsation, temporary pacing wire or inotropic therapy. Patients with ventricular and supraventricular

arrhythmia were considered if the cardiac rhythm had been stable for > 6 hours. In all cases the scan was performed pre-discharge. The research was approved by the West of Scotland Ethics Committee and Clinical Governance office of the National Waiting Times Board. standard contra-indications to MRI including an estimated glomerular filtration rate < 30 ml/min/1.73 m<sup>2</sup>.

STEMI was defined according to a history of symptoms consistent with acute myocardial ischemia and ST-segment elevation on the electrocardiogram (ECG) associated with a typical rise of troponin I (TnI) concentration<sup>68</sup>. Acute heart failure was diagnosed according to Killip class<sup>172</sup>.

Acute MI management followed contemporary guidelines<sup>68</sup>. Aspiration thrombectomy, direct stenting, anti-thrombotic drugs and other therapies were administered according to local protocols. Pulse pressure was recorded at the beginning of the PCI. The Thrombolysis in Myocardial Infarction (TIMI) flow classification was used to grade culprit artery flow at initial angiography and at the end of the procedure<sup>58</sup>.

### **8.2.2 Follow-up**

Patients were followed-up for 30 days from hospital discharge to detect early adverse events and assess for an association between cardiac events and early CMR findings. An adverse cardiac event was defined as death or an unplanned hospitalization for heart failure or an acute coronary syndrome (ACS) in line with contemporary criteria<sup>68</sup>. The diagnosis was established based on a comprehensive review of hospital and general

practitioner records made by attending clinicians who were not members of the research team.

### **8.2.3 CMR scans**

CMR was performed under medical supervision early after admission to the Coronary Care Unit in order to facilitate patient management as previously described.

### **8.2.4 CMR image analysis and reporting**

All MR images were analyzed on a Siemens workstation by a trained cardiologist with at least 2 years MRI experience. Left ventricular (LV) dimensions, volumes and ejection fraction were quantified using computer assisted planimetry. A CMR report was written into the case notes immediately after the scan to facilitate early in-patient management.

### **8.2.5 Incidental findings**

An incidental finding is a previously unknown medical problem which is unrelated to the condition being studied. In our study, we defined a clinically significant cardiac or non-cardiac incidental finding as one which triggered a change in management (e.g. change in treatment) by the attending cardiologist. The field of view included the upper abdomen, including the liver, kidneys and spleen. We adopted a screening approach to the diagnostic evaluation of extra-cardiac disease based on the limitations of the scan being primary for assessment of the myocardium.

Our approach was motivated on a desire to detect clinically-significant pathology (e.g. a lung cancer) should ever it be present in the imaging field of view. The trade-off for this approach is the likelihood of reporting observations that are not clinically significant and the risk that such observations might trigger additional tests. Our approach to the interpretation of non-cardiac findings therefore involved a low threshold for a radiology consult and defined criteria for doing so.

The presence of a lung nodule triggered a radiological consult. Isolated fibrotic change of lung parenchyma or pulmonary plaque was not considered as clinically significant. A liver mass > 2cm was taken as an indication for ultrasonography. Splenomegaly was defined as greater than 11 cm at its largest dimension and any renal mass was referred for a radiology consult due to the potential for renal cell carcinoma to present as an incidental finding at an early stage. Left ventricular thrombus was diagnosed based on endocardial cardiac mass which did not enhance with first pass or late gadolinium enhanced CMR.

#### **8.2.6 Biochemical assessment of infarct size**

Troponin I was measured (AxSYM®; Abbott) as a biochemical measure of infarct size.

A blood sample was routinely obtained 12 hours after hospital admission.

### 8.3 Statistical analysis

Normality was confirmed or excluded using the Shapiro-Francia test. Mean (SD) values and medians (interquartile range) were calculated. All tests were two-tailed. Between-group comparisons of normally distributed continuous data were undertaken using a Student's t test. Between-group comparisons of non-normally distributed data were performed with a Mann Whitney test. A Fisher's exact test was used to assess the difference in proportions. The association between MRI findings and cardiovascular events was assessed with Log Rank test.  $P < 0.05$  was taken as significant. The data were analyzed with SPSS (version 15.0).

### 8.4 Results

The mean age of the study population was  $58 \pm 10$  years with 78% being male. Primary PCI had been performed in 82% with the remainder undergoing rescue or convalescent PCI after thrombolysis. Killip class II – IV was present in 13% and 22% had prior hemodynamic instability (Table 8.1). 13 (6.5%) patients required electrical cardioversion for a ventricular arrhythmia. Of these, 10 (5%) were reperfusion arrhythmias that were treated in the catheter laboratory and 3 (1.5%) of these occurred in the coronary care unit.

All	$\leq 24$ h post-admission	$> 24$ h post-admission	P
200	128 (64%)	72 (36%)	



---

*Admission characteristics*

Age $\pm$ SD, years	58 $\pm$ 10	58 $\pm$ 10	58 $\pm$ 11	0.98
Male gender, n (%)	157 (78)	104 (81)	53 (74)	0.21
Previous MI, n (%)	11 (6)	5 (4)	6 (8)	0.21
Diabetes, n (%)	10 (5)	7 (6)	3 (4)	1.00
BMI $\pm$ SD, kg/m <sup>2</sup>	26 $\pm$ 4	27 $\pm$ 4	26 $\pm$ 4	0.60
Killip class				
I	174 (87)	112 (88)	62 (86)	
II	14 (7)	9 (7)	5 (7)	
III	11 (5.5)	7 (6)	4 (6)	
IV	1 (0.5)	0 (0)	1 (1)	

*Catheter laboratory characteristics*

Pain to balloon time $\pm$ SD, hours	5.4 $\pm$ 5.2	5.1 $\pm$ 5.0	5.8 $\pm$ 5.5	0.65
TIMI grade post-PCI, n (%)				
0	1 (0.5)	0 (0)	1 (1)	0.21
1	1 (0.5)	0 (0)	1 (1)	
2	15 (8)	8 (6)	7 (10)	
3	183 (91)	120 (94)	63 (88)	

*Hemodynamic instability prior to CMR,*

*n (%)*

---

Intra-aortic balloon therapy	1 (0.5)	0 (0)	1 (1.0)	
	10 (5)	5 (2.5)	5 (2.5)	
Non-sustained ventricular tachycardia	7 (3.5)	4 (2)	3 (1.5)	
Ventricular tachycardia	6 (3)	3 (1.5)	3 (1.5)	
Ventricular fibrillation	13 (6)	10 (8)	3 (4)	
BP < 90/60 mmHg				
<i>Laboratory characteristics</i>				
Serum creatinine $\pm$ SD, $\mu$ mol/L	78 $\pm$ 29	76 $\pm$ 30	87 $\pm$ 19	0.42
Troponin I $\pm$ SD, $\mu$ g/L	59 $\pm$ 65	59 $\pm$ 57	57 $\pm$ 77	0.83
<i>Drug therapy at time of MRI</i>				
Glycoprotein IIb/IIIa inhibitor, n (%) <sup>*</sup>	173 (85)	115 (90)	58 (76)	0.06
Thrombolytic before CMR, n (%)	35 (18)	14 (11)	21 (29)	
I.V. diuretic before CMR, n (%)	20 (10)	12 (9)	8 (11)	0.72
<i>Other Imaging prior to CMR<sup>†</sup></i>				
CXR, n (%)	117 (58)	85 (66)	32 (44)	0.002
Orbit X-Ray, n (%)	10 (5)	4 (3)	6 (8)	0.10
Echocardiography, n (%)	45 (22)	19 (15)	26 (36)	0.001

**Table 8.I: Clinical characteristics**

MI: myocardial infarction; BMI: body mass index; LAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery; IABP: intra-aortic balloon pump; VT: ventricular tachycardia; VF: ventricular fibrillation; NSVT: non-sustained ventricular tachycardia; BP: blood pressure; TIMI grade: thrombolysis in myocardial infarction

grade; PCI: percutaneous coronary intervention;; CXR: chest X-ray; LVF: left ventricular failure Killip Class I: no heart failure; II: heart failure; III: severe heart failure; IV: cardiogenic shock. TIMI grade post-PCI: Grade 0: no perfusion; Grade 1: penetration without perfusion; Grade 2: partial perfusion; Grade 3: complete perfusion.

\* In patients who were being treated with intravenous glycoprotein IIb/IIIa inhibitor therapy at the time of MRI, the infusion was stopped for the duration of the scan.

† Imaging performed prior to CMR was prospectively documented in order to record new findings

#### **8.4.1 CMR scans**

The CMR scan was performed < 24 hours after hospital admission in 128 (64%) patients and the characteristics of patients who underwent very early CMR were similar to those imaged at a later time (Table 1). The remaining 72 patients (36%) were imaged between 24 and 72 hours after admission. The median (inter quartile range) time from hospital admission to the CMR scan was 22 (16, 28) hours and the average ( $\pm$ SD) scan duration was  $44 \pm 10$  min. Of the patients who had CMR within 24 hours of admission, 13 (10%) were scanned < 12 hours, 54 (42%) were scanned 13 - < 18 hours and 61 (48%) were scanned 18 - 24 hours after invasive management.

CMR provided complete information on LV mass and function in 195 (98%) patients and no complications or adverse events occurred. Infarct size and MVO were measured in 191 (96%) patients (Table 8.2). The CMR scan was stopped before a complete

assessment of LV function in 5 (2%) patients and in 4 (2%) other patients ceCMR was not tolerated. The reasons for an incomplete CMR examination were claustrophobia (8 (4%) patients) and back pain (1 (0.5%) patient). Two (1%) patients had real time cine CMR because of heart rhythm irregularity. Fifteen patients (8%) had limited ability to breath-hold and information on infarct scar was facilitated in these patients using single shot LGE CMR.

Chest radiography and echocardiography had been performed before CMR in 117 (58%) and 45 (22%) patients, respectively.

#### **8.4.2 Cardiac findings (Table 8.2)**

Impaired LV systolic function ( $LVEF < 55\%$ ) was common (61% of all patients). Fourteen (7%) patients had a severe reduction in LVEF ( $<55\%$ ), 35 (18%) patients had a moderate reduction in LVEF ( $35\% - <45\%$ ) and 73 (60%) patients a mild reduction in LVEF ( $45 - < 55\%$ ). Ninety eight (50%) patients had an increased LV end-systolic volume index.

CMR findings in patients imaged within 24 hr of hospital admission were similar to CMR findings in patients imaged later suggesting that patient selection for a very early CMR scan was not influenced by the severity of MI. Table 8.2. MRI scans and findings in 195 STEMI patients who underwent CMR early after hospital admission.\*

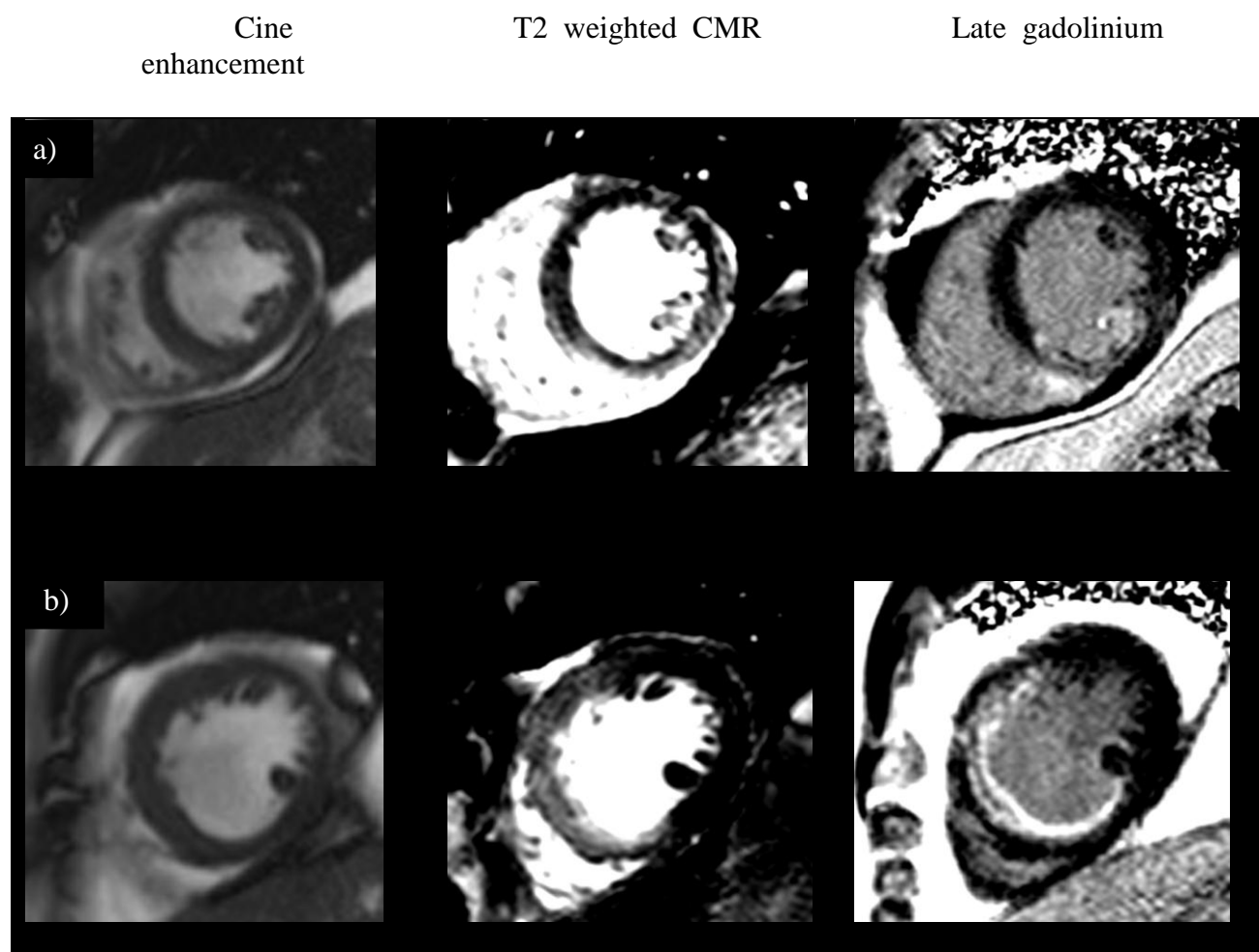
MRI scan	All	< 24 h post-admission	≥ 24 h post-admission	P
Heart rate ± SD, min	73 ± 13	73 ± 13	73 ± 13	0.7
Duration, ± SD, min	43.87 ± 10.22	43.63 ± 9.43	44.32 ± 11.58	0.77
Scan completed, n (%)	191 (95.5)	122 (95.3)	69 (95.8)	1.00
Complications	0 (0)	0 (0)	0 (0)	-
LVEF± SD, %	52 ± 11	51 ± 10	53 ± 12	0.34
LVEDV ± SD, ml: Male	160 ± 33	159 ± 30	167 ± 41	0.44
Female	126 ± 34	131 ± 38	115 ± 22	0.31
Infarct size ± SD, % of LV	22.1 ± 14.8	23.4 ± 14.3	19.6 ± 15.5	0.10
Microvascular obstruction ± SD, % of LV	2.8 ± 3.7	3.1 ± 3.8	2.2 ± 3.3	0.07

### Table 8.2: CMR results

\* Of the 200 patients who had had a CMR scan, 195 had complete information on LV function. Four of these patients did not tolerate CMR after contrast administration. Real time cine and single shot delayed enhancement CMR were done in 2(1%) and 15(8%) patients, respectively.

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; BSA: body surface area; infarct size and microvascular obstruction are recorded as a percentage of left ventricular myocardium

For discrete variables  $\chi^2$  test was used, except \* (Fisher's exact test). For continuous variables, 2-tailed independent samples T-test was used



**Figure 8.1.**

**1: Transmural inferior myocardial infarction with haemorrhagic microvascular obstruction, (a) still image from retrospective cine; (b) T<sub>2</sub>-weighted CMR image; (c) LGE.**

**2: Non-transmural MI in the left ventricular septum with transmural oedema and microvascular obstruction, (a) still image from retrospective cine; (b) T<sub>2</sub>-weighted CMR image; (c) LGE.**

### 8.4.3 Incidental findings

Incidental findings are described in Table 8.3. Six patients (3%) had a lung mass discovered which triggered respiratory investigations including chest computed

tomography. Three of these patients had a final diagnosis of lung cancer (2 patients had non-small cell lung cancer and 1 patient had an adenocarcinoma with ipsilateral metastases). The admission chest X-ray was normal in two of these patients and in the other patient the chest X-ray was independently read abnormal. The three other patients had benign lung disease.

One 43 year old woman who did not smoke and had no prior history of coronary disease presented with an acute inferior STEMI. Coronary angiography revealed an occluded right coronary artery and otherwise angiographically normal coronary arteries. Following primary PCI, she underwent CMR directly without prior echocardiography in order to assess for a possible cardiac source of embolus. CMR revealed a patent foramen ovale and a valsalva manoeuvre supported a diagnosis of paradoxical embolus. There was no history of systemic illness and no other reason to suspect a non-cardiac source of embolus. The PFO was closed percutaneously the day after the CMR scan. One other patient had marked splenomegaly. This man was referred for a haematology consult and a new diagnosis of myeloproliferative disorder was established. Two patients had evidence of left ventricular thrombus revealed by CMR which had not been revealed by echocardiography.

System	Pathology	Patients, n (%)	Prognostic importance	Management change	Comment

Cardiac					
	PFO^	1 (0.5)	Yes^	Yes	Transcatheter closure
	LV thrombus	2 (1)	Yes	Yes	Anti-coagulation
	Bicuspid aortic valve	1 (0.5)	Yes	Yes	Referred to cardiology out-patient clinic
	Pleural effusion associated with pulmonary oedema	15 (8)	Yes	Yes	Intravenous furosemide was subsequently administered in the CCU in those not previously treated with iv diuretic
Lung	Pulmonary mass	3 (1.5)	Yes	Yes	2 confirmed as non-small cell lung cancer and 1 as lung adenocarcinoma with ipsilateral lung metastases
Spleen	Splenomegaly	1 (0.5)	Yes	Yes	Myeloproliferative disorder
Spine	Vertebral crush fractures	1 (0.5)	Yes	Yes	Referred for management of osteoporosis
All		24 (12)			

### Table 8.3: Incidental findings

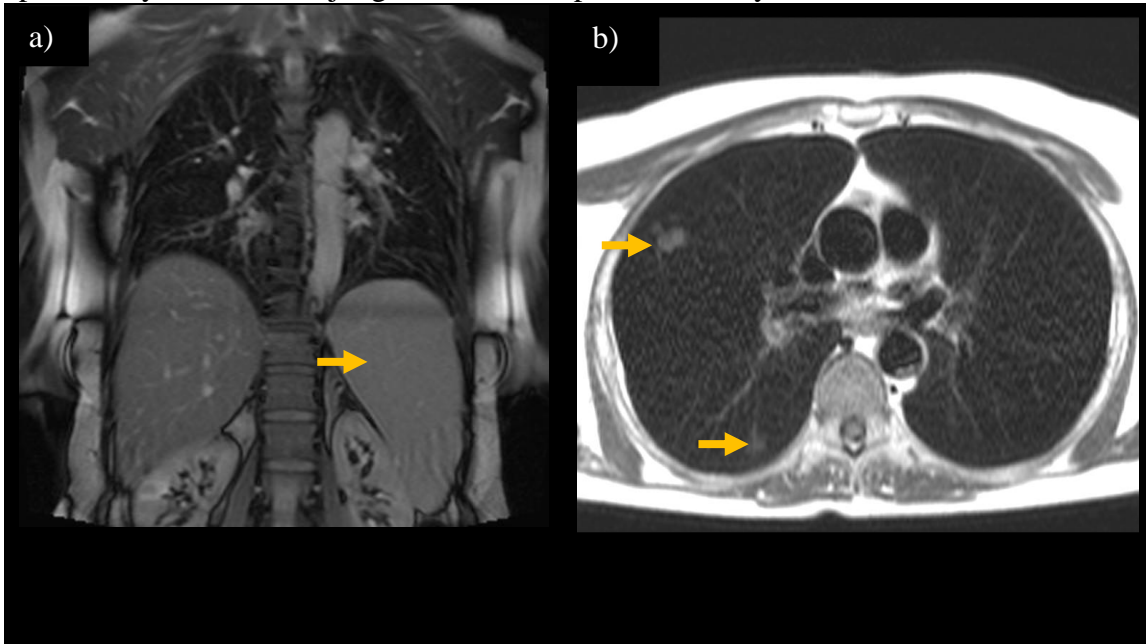
The following other abnormalities were observed which did not result in further tests or treatment: previous MI 14 (7%), cor triatriatum sinistrum 1 (0.5%), intra-myocardial lipomata 1 (0.5%), pulmonary fibrosis and/or plaque 5 (3%), hepatic cyst 3 (2%), splenic cyst 1(0.5%),

The following other abnormalities were observed which resulted in abdominal ultrasound but no further treatment: liver haemangioma 3(2%), renal cyst 1 (0.5%),



^CMR revealed a patent foramen ovale and the aetiology of STEMI in this patient was paradoxical embolus. The PFO underwent percutaneous closure the day after the CMR scan.

^^^ Pulmonary oedema was observed on T2 weighted HASTE CMR. In all of these patients, intravenous diuretic was administered in the coronary care unit afterward since pulmonary oedema was judged to be a complication of myocardial infarction.



**Figure 8.2**

**1: Splenomegaly (arrow) in a patient with an undiagnosed low-grade hemoproliferative condition. The observation was revealed on T1 localiser imaging.**

**2: HASTE MRI reveals a right upper lobe parenchymal lung tumour (arrow) with a second lesion in lower lobe (arrow). A diagnosis of metastatic adeoncarcinoma was subsequently made.**

#### **8.4.4 CMR findings are associated with early rehospitalisation for heart failure or ACS**

Eight (4%) patients had an unplanned hospital readmission within 30 days of discharge because of heart failure (3 (1.5%) patients) or a confirmed ACS (5 (2.5%) patients), of whom 2 (1%) had acute stent thrombosis. All of the ACS patients had repeat angiography and 4 of these patients underwent PCI. Compared to patients who were not readmitted for heart failure or an ACS, the patients who were readmitted had a lower initial LV ejection fraction ( $40.3 \pm 11.5\%$  vs.  $52.1 \pm 10.6\%$ ;  $p=0.005$ ) and higher initial LV end-diastolic volume index ( $50.5 \pm 16.7 \text{ ml/kg/m}^2$  vs.  $37.5 \pm 12.7 \text{ ml/kg/m}^2$ ;  $p=0.034$ ) and infarct size ( $36.5 \pm 12.12\%$  vs.  $21.6 \pm 14.6\%$ ;  $p=0.006$ ).

### **8.5 Discussion**

We have described a series of 200 STEMI survivors who underwent early in-patient CMR. Our study describes one of the largest STEMI cohorts evaluated by CMR to-date. CMR was feasible, safe and informative in 98% of patients. In addition to providing prognostically important information, such as LV ejection fraction, infarct size and microvascular obstruction, CMR revealed clinically relevant incidental findings.

Our first aim was to evaluate the feasibility and safety of CMR in a broad range on STEMI survivors. Two thirds of the STEMI patients had a CMR scan within 24 hours of hospital admission and one fifth had a history of heart failure or hemodynamic instability. *Ad hoc* CMR was achieved by reserving the first CMR scan appointment each day for new admissions and by making use of the scanner when patients with elective appointments did not attend. CMR was performed under medical supervision and no complications occurred.

Our findings extend those of Larose *et al* <sup>204</sup> who successfully scanned 102 patients < 12 h post-STEMI in the Québec Heart Institute. All of their patients had undergone successful primary PCI (grade III TIMI flow at the end of the procedure) whereas our patients were higher risk. For example, in our cohort nearly one fifth of the patients had been initially treated with tenectaplastase, some had sub-optimal catheter lab outcomes and patients with a history of hemodynamic instability (including one patient initially treated with an intra-aortic balloon pump) were included. Our findings indicate that CMR can be safely performed even in high risk patients supporting the potential utility of CMR in clinical practice.

Finally, CMR revealed new observations of varying clinical significance. Some cardiac pathologies were obviously clinically significant (e.g. LV thrombus, patent foramen ovale associated with embolic right coronary occlusion). The LV thrombus had not been observed by prior echocardiography or left ventriculography. In one other patient, CMR revealed a PFO leading to a diagnosis of paradoxical embolus. This woman underwent

transcatheter closure of the PFO during the index admission. Similarly some extra-cardiac pathologies (e.g. metastatic lung disease, splenomegaly Figure 8.2) were prognostically important. Chest radiography did not reveal the lung mass in two of the 3 patients with lung cancer. Splenomegaly was observed in a patient who was subsequently diagnosed with a myeloproliferative disorder. Some observations had less certain clinical significance (e.g. pulmonary oedema) however the attending staff decided to administer diuretic, which we think is a pragmatic empirical decision commonly made in medicine. On the other hand, there were several observations which were not clinically significant, such as simple cysts. Simple cysts are common and even in the current study were all found confirmed by ultrasound as simple and did not alter management. MRI that includes gadolinium can characterize many of these cysts and avoid an unnecessary ultrasound.

Overall, our approach to CMR was to screen for extra-cardiac findings using defined criteria and request a radiology opinion in selected cases as appropriate (e.g. for lung, and kidney masses). In this way, we sought to avoid unnecessary tests and improve diagnostic confidence. We accept that chest radiography and echocardiography were not performed in all patients before CMR and so direct comparisons with other diagnostic methods is not possible. However, a formal comparative imaging study was not our aim. Consistent with findings by Weir *et al* <sup>203</sup>, we conclude that CMR has high diagnostic utility in STEMI survivors.

Usually, when a CMR is requested for an STEMI patient the scan is performed at least a few days after hospital admission in line with clinical guideline recommendations <sup>68</sup>. Historically, CMR has been delayed in patients with recent MI because of safety concerns. However, STEMI patients managed invasively have a lower risk of post-MI complications than STEMI patients treated with thrombolysis alone. Based on our experience, CMR can be safely performed under medical supervision even within 12 h of hospital admission in stabilized patient, in line with observations from other groups <sup>76</sup>

In addition to providing LV ejection fraction and volumes in almost all of the patients, ceCMR was completed in 95% of patients delineating infarct burden and MVO. We did not perform a comparative study of CMR and echocardiography since the comparative strengths of each form of imaging are well described <sup>71</sup>. Echocardiography can be performed at the bedside and is cheaper. Alternatively, CMR has higher diagnostic accuracy for assessment of LV ejection fraction and volumes<sup>71</sup> and only CMR can provide information on prognostically-important infarct characteristics (infarct size, MVO) <sup>15, 87, 176</sup>.

The clinical utility of CMR is influenced by whether the test is feasible and if so, whether the diagnostic information from the scan leads to a change in management or provides new insights into prognosis (Table 8.3). CMR is an expensive diagnostic test and

therefore the health economic considerations of CMR post-MI are important. Increasingly, the emergency care of STEMI patients is centralised to 'heart attack' hospitals which provide primary PCI and coronary angiography for patients transferred after thrombolysis. These hospitals are usually resourced with advanced medical equipment such as MRI, meaning that the centralization of invasive cardiac services in hospitals potentially increases access of STEMI patients to CMR. Even in this setting, in practical terms, although CMR may have the highest diagnostic accuracy for imaging post-MI<sup>71</sup> it is unlikely to be feasible for all STEMI patients therefore its use should be selected to high risk subgroups in whom CMR is most likely to provide prognostically important information that could result in improved health outcomes. What we have shown is that CMR findings were associated with early readmission to hospital for a heart failure or recurrent ACS. We think this is because the diagnostic accuracy of CMR is high and the scans reveal the nature and severity of heart injury unlike echocardiography or chest radiography. Thus, our preliminary findings suggest that CMR may have a role for risk stratification. Should future studies demonstrate that CMR can identify patients at risk of early readmission to hospital then interventions could be tested to prevent these events. Going forward, we hypothesise that CMR will be most cost-effective in the following groups of STEMI survivors or scenarios 1) patients in whom echocardiography is limited (e.g. poor acoustic window), 2) availability of a future evidence-based therapy targeted at pathology which can be selectively revealed by MRI (e.g. MVO). Therefore, the cost-utility of CMR would likely increase if targeted to these patient groups.

## 8.6 Limitations

About one third of all STEMI patients who were treated in our hospitals underwent CMR. When CMR was not performed it was usually for logistical reasons e.g. out-of-office hours. Whenever an eligible patient agreed to have a scan, the MRI department was usually able to perform the scan *ad hoc*.

CMR is not feasible in patients with some types of devices and foreign bodies meaning that around 5% of patients may be ineligible. Recent developments are helping to overcome some of these limitations. Firstly, technical developments with CMR mean that breath-holding is no longer mandatory and CMR can be performed in free-breathing patients including those with irregular heart rhythms. CMR compatible device leads are also now being used.

Since rehospitalisations were uncommon we did not perform multivariable analyses for predictors of 30-day outcomes.

## 8.7 Conclusions

CMR is feasible and safe in the hours following emergency PCI in a broad range of patients following STEMI. It provides useful prognostic information in the early stages following revascularisation to potentially identify “high risk” patients and furthermore has potential to uncover clinically relevant extra-cardiac abnormalities.

## **Chapter 9 - Conclusions and clinical implications**

### **9.1 Postulated therapeutic interventions to minimize microvascular damage in STEMI**

Although the pathophysiological understanding of MVO has improved, mechanical and therapeutic interventions to prevent or minimize its impact have yet to be translated from the experimental level into hard clinical end-points.

Distal protection devices effectively have been shown to effectively retrieve embolic debris during primary PCI but have not been shown to improve microvascular flow, reduce infarct size or improve event free survival.<sup>33</sup>

Although aspiration thrombectomy improves reperfusion on comparison with conventional PCI a significant number of patients continue to experience incomplete myocardial perfusion<sup>205</sup> and indeed in my own study there was no difference in the IMR between each group with this operator dependent variable.

Intra-aortic balloon pump counter pulsation reduced MVO in the experimental model but clinical studies using this intervention in the setting of STEMI have shown no improvement in LV ejection fraction or increased survival at follow up.<sup>206, 207</sup>



Administration of intra-coronary verapamil after PCI decreased evidence of no-reflow<sup>208</sup> and glycoprotein IIb/IIIa inhibition has been shown to significantly improve microvascular flow in dog models and has increased the rate of ST segment resolution and CTFC in clinical trials.<sup>209-211</sup>

Selective intracoronary administration of the microcirculatory vasodilator adenosine improved microvascular perfusion leading to improved regional ventricular function in the infarcted canine model. In the clinical setting, however, although infarct size was reduced, a three hour intravenous infusion of adenosine in re-perfused STEMI patients failed to show an improvement in outcome.<sup>212</sup>

IMR recorded 48h after successful primary PCI has been used as a marker for increased myocardial microvascular perfusion following the administration of intracoronary streptokinase at the time of the procedure.<sup>139</sup> The group which had the lower IMR following administration of the intracoronary thrombolytic were shown to have lower infarct volumes and higher ejection fractions at long term follow up.<sup>213</sup>

More recently *Ito et al* randomized patients whom underwent successful PCI to receive a bolus of intracoronary nicorandil, a vasodilator which acts both as a nitrate and on the K-ATP channel, or a bolus of saline. There was a significant reduction in IMR following this in the nicorandil group, although interestingly this change was not seen in those whom had a low IMR at baseline.<sup>214</sup>

## **9.2 Clinical implications for use of IMR in STEMI**

In summary, I found that IMR correlated with traditional markers for infarct size and myocardial damage. I found that IMR was significantly higher in those whom had evidence of MVO on ceCMR imaging. Increased was also a strong independent predictor of increased infarct volumes and low ejection fraction at baseline and follow up. The other postulated invasive markers of microvascular disease, CFIP and distal coronary wedge pressure did not correlate with myocardial damage by ceCMR. IMR can therefore provide an indicator of microvascular injury at the time of emergency PCI. This allows this at risk patient group immediately after the cornerstone of AMI treatment and could allow potential intervention to occur directly thereafter.

It is known a significant proportion of patients who have TIMI 3 flow post PCI have evidence of microvascular damage. Significant microvascular obstruction post PCI is not, however, universal. This may in part explain why studies aimed at modifying microvascular damage post PCI that have recruited “all comers” have been successful on a theoretical basis but not in larger clinical studies. IMR has already been used as a marker of microvascular damage post PCI before and after therapeutic interventions. I think the future of IMR will be to identify the “at risk” population at the time of PCI. This will allow targeting of future therapies at the earliest opportunity. I think by targeting those who are known to have microvascular damage future studies will be more

likely to be beneficial. It is worth noting that in their recent study looking at Nicorandil *Ito et al* did not see any significant difference in the group who had a low baseline IMR, indicating that those with low levels of microvascular injury have the least to gain from intervention.

The IMR is a simple wire based technique that can provide a quantitative assessment of microvascular function at the time of emergency PCI. I have shown that an elevated IMR is linked to microvascular and myocardial damage as revealed by ceCMR in the early post infarction period and at longer term follow up. Accordingly, I suggest measurement of IMR represents a new approach to risk assessment at the very earliest stage of acute MI management, and potentially, therefore enables triage of higher risk patients to more intensive therapy.

## Reference List

- (1) Luepker RV, Berger AK. Is Acute Myocardial Infarction Disappearing?  
*Circulation* 2010 March 8;CIR.
- (2) Buckley BS, Simpson CR, McLernon DJ, Murphy AW, Hannaford PC. Five  
year prognosis in patients with angina identified in primary care: incident cohort  
study. *BMJ* 2009 August 6;339(aug06\_2):b3058.
- (3) BHF. British heart foundation coronary heart disease statistics 2008. 2010.
- (4) Justin A.Ezekowitz<sup>1</sup> and Padma Kaul<sup>1</sup>. The epidemiology and management of  
elderly patients with myocardial infarction or heart failure. *Heart Failure  
Reviews* 2010 March 10.
- (5) WRITING GROUP, Lloyd-Jones D, Adams R et al. Heart Disease and Stroke  
Statistics--2009 Update: A Report From the American Heart Association  
Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009  
January 27;119(3):e21-181.
- (6) Steg PG, Dabbous OH, Feldman LJ et al. Determinants and Prognostic Impact  
of Heart Failure Complicating Acute Coronary Syndromes: Observations From  
the Global Registry of Acute Coronary Events (GRACE). *Circulation* 2004  
February 3;109(4):494-9.

- (7) Desai MM, Stauffer BD, Feringa HHH, Schreiner GC. Statistical Models and Patient Predictors of Readmission for Acute Myocardial Infarction: A Systematic Review. *Circ Cardiovasc Qual Outcomes* 2009 September 1;2(5):500-7.
- (8) Santoro GM, Carrabba N, Migliorini A, Parodi G, Valenti R. Acute heart failure in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. *European Journal of Heart Failure* 2008 August;10(8):780-5.
- (9) Lewis EF, Velazquez EJ, Solomon SD et al. Predictors of the first heart failure hospitalization in patients who are stable survivors of myocardial infarction complicated by pulmonary congestion and/or left ventricular dysfunction: a VALIANT study. *European Heart Journal* 2008 March;29(6):748-56.
- (10) Torabi A, Cleland JGF, Khan NK et al. The timing of development and subsequent clinical course of heart failure after a myocardial infarction. *European Heart Journal* 2008 April;29(7):859-70.
- (11) Torabi A, Rigby AS, Cleland JGF. Declining In-Hospital Mortality and Increasing Heart Failure Incidence in Elderly Patients With First Myocardial Infarction. *Journal of the American College of Cardiology* 2009 December 29;55(1):79-81.
- (12) Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining In-Hospital Mortality and Increasing Heart Failure Incidence in

Elderly Patients With First Myocardial Infarction. *Journal of the American College of Cardiology* 2009 January 6;53(1):13-20.

- (13) Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet* 2003 January 4;361(9351):13-20.
- (14) Gershlick AH, Stephens-Lloyd A, Hughes S et al. Rescue Angioplasty after Failed Thrombolytic Therapy for Acute Myocardial Infarction. *N Engl J Med* 2005 December 29;353(26):2758-68.
- (15) Hombach V, Grebe O, Merkle N et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. *Eur Heart J* 2005 March 2;26(6):549-57.
- (16) Bolognese L, Carrabba N, Parodi G et al. Impact of Microvascular Dysfunction on Left Ventricular Remodeling and Long-Term Clinical Outcome After Primary Coronary Angioplasty for Acute Myocardial Infarction. *Circulation* 2004 March 9;109(9):1121-6.
- (17) Gibson CM, Cannon CP, Murphy SA et al. Relationship of the TIMI Myocardial Perfusion Grades, Flow Grades, Frame Count, and Percutaneous Coronary Intervention to Long-Term Outcomes After Thrombolytic Administration in Acute Myocardial Infarction. *Circulation* 2002 April 23;105(16):1909-13.

- (18) Brosh D, Assali AR, Mager A et al. Effect of No-Reflow During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction on Six-Month Mortality. *The American Journal of Cardiology* 2007 February 15;99(4):442-5.
- (19) Henriques JPS, Zijlstra F, 't Hof AWJ et al. Angiographic Assessment of Reperfusion in Acute Myocardial Infarction by Myocardial Blush Grade. *Circulation* 2003 April 29;107(16):2115-9.
- (20) McLaughlin MG, Stone GW, Aymong E et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: The controlled abciximab and device investigation to lower late angioplasty complications (CADILLAC) trial. *Journal of the American College of Cardiology* 2004 September 15;44(6):1215-23.
- (21) Galiuto L, Garramone B, Scara A et al. The Extent of Microvascular Damage During Myocardial Contrast Echocardiography Is Superior to Other Known Indexes of Post-Infarct Reperfusion in Predicting Left Ventricular Remodeling: Results of the Multicenter AMICI Study. *Journal of the American College of Cardiology* 2008 February 5;51(5):552-9.
- (22) Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial No-Reflow in Humans. *Journal of the American College of Cardiology* 2009 July 21;54(4):281-92.

- (23) de Lemos JA, Warner JJ. New tools for assessing microvascular obstruction in patients with ST elevation myocardial infarction. *Heart* 2004 February 1;90(2):119-20.
- (24) Robert A.Kloner et al. Effect of a Transient Period of Ischemia on Myocardial Cells: II. Fine Structure During the First Few Minutes of Reflow. 9, editor. *Am J Pathol* 74(3), 399-422. 1-3-1974.
- (25) Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med* 1992 January 23;326(4):242-50.
- (26) Lerman A, Holmes DR, Herrmann J, Gersh BJ. Microcirculatory dysfunction in ST-elevation myocardial infarction: cause, consequence, or both? *Eur Heart J* 2007 April 1;28(7):788-97.
- (27) Hori M, Inoue M, Kitakaze M et al. Role of adenosine in hyperemic response of coronary blood flow in microembolization. *Am J Physiol Heart Circ Physiol* 1986 March 1;250(3):H509-H518.
- (28) Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation* 1985 April 1;71(4):699-708.



- (29) Saber RS, Edwards WD, Bailey KR, McGovern TW, Schwartz RS, Holmes DR, Jr. Coronary embolization after balloon angioplasty or thrombolytic therapy: an autopsy study of 32 cases. *J Am Coll Cardiol* 1993 November 1;22(5):1283-8.
- (30) Limbruno U, Micheli A, De Carlo M et al. Mechanical Prevention of Distal Embolization During Primary Angioplasty: Safety, Feasibility, and Impact on Myocardial Reperfusion. *Circulation* 2003 July 15;108(2):171-6.
- (31) Henriques JPS, Zijlstra F, Ottervanger JP et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J* 2002 July 2;23(14):1112-7.
- (32) Kelbaek H, Terkelsen CJ, Helqvist S et al. Randomized Comparison of Distal Protection Versus Conventional Treatment in Primary Percutaneous Coronary Intervention: The Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction (DEDICATION) Trial. *J Am Coll Cardiol* 2008 March 4;51(9):899-905.
- (33) Stone GW, Webb J, Cox DA et al. Distal Microcirculatory Protection During Percutaneous Coronary Intervention in Acute ST-Segment Elevation Myocardial Infarction: A Randomized Controlled Trial. *JAMA* 2005 March 2;293(9):1063-72.
- (34) Gick M, Jander N, Bestehorn HP et al. Randomized Evaluation of the Effects of Filter-Based Distal Protection on Myocardial Perfusion and Infarct Size After

Primary Percutaneous Catheter Intervention in Myocardial Infarction With and Without ST-Segment Elevation. *Circulation* 2005 September 6;112(10):1462-9.

- (35) T.Reffelmann<sup>1</sup> and R.A.Kloner. The no-reflow phenomenon: A basic mechanism of myocardial ischemia and reperfusion. *Basic Research in Cardiology* 2010;Volume 101, Number 5 / September, 2006.
- (36) Yellon DM, Hausenloy DJ. Myocardial Reperfusion Injury. *N Engl J Med* 2007 September 13;357(11):1121-35.
- (37) Ambrosio G, Weisman HF, Mannisi JA, Becker LC. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. *Circulation* 1989 December 1;80(6):1846-61.
- (38) Ambrosio G, Tritto I. Reperfusion injury: Experimental evidence and clinical implications, . *American Heart Journal* 1999 August;138(2, Supplement 1):S69-S75.
- (39) Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. [Miscellaneous Article]. *Coronary Artery Disease* 2004 August;15(5):259-64.
- (40) Prasad A, Stone GW, Stuckey TD et al. Impact of diabetes mellitus on myocardial perfusion after primary angioplasty in patients with acute myocardial infarction. *J Am Coll Cardiol* 2005 February 15;45(4):508-14.

- (41) Marso SP, Miller T, Rutherford BD et al. Comparison of Myocardial Reperfusion in Patients Undergoing Percutaneous Coronary Intervention in ST-Segment Elevation Acute Myocardial Infarction With Versus Without Diabetes Mellitus (from the EMERALD Trial). *The American Journal of Cardiology* 2007 July 15;100(2):206-10.
- (42) de Lemos JA, Antman EM, Giugliano RP et al. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. *The American Journal of Cardiology* 2000 February 1;85(3):299-304.
- (43) McLaughlin MG, Stone GW, Aymong E et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: The controlled abciximab and device investigation to lower late angioplasty complications (CADILLAC) trial. *Journal of the American College of Cardiology* 2004 September 15;44(6):1215-23.
- (44) van't Hof AW, Liem A, de Boer MJ, Zijlstra F. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. *The Lancet* 1997 August 30;350(9078):615-9.
- (45) Sezer M, Nisanci Y, Umman B et al. New support for clarifying the relation between ST segment resolution and microvascular function: degree of ST segment resolution correlates with the pressure derived collateral flow index. *Heart* 2004 February 1;90(2):146-50.

- (46) Porto I, Burzotta F, Brancati M et al. Relation of Myocardial Blush Grade to Microvascular Perfusion and Myocardial Infarct Size After Primary or Rescue Percutaneous Coronary Intervention. *The American Journal of Cardiology* 2007 June 15;99(12):1671-3.
- (47) Fearon WF, Shah M, Ng M et al. Predictive Value of the Index of Microcirculatory Resistance in Patients With ST-Segment Elevation Myocardial Infarction. *Journal of the American College of Cardiology* 2008 February 5;51(5):560-5.
- (48) Carrabba N, Parodi G, Valenti R et al. Significance of Additional ST Segment Elevation in Patients with No Reflow After Angioplasty for Acute Myocardial Infarction. *Journal of the American Society of Echocardiography* 2007 March;20(3):262-9.
- (49) Galiuto L, Garramone B, Scara A et al. The Extent of Microvascular Damage During Myocardial Contrast Echocardiography Is Superior to Other Known Indexes of Post-Infarct Reperfusion in Predicting Left Ventricular Remodeling: Results of the Multicenter AMICI Study. *Journal of the American College of Cardiology* 2008 February 5;51(5):552-9.
- (50) Angeja BG, Gunda M, Murphy SA et al. TIMI Myocardial Perfusion Grade and ST Segment Resolution: Association With Infarct Size as Assessed by Single Photon Emission Computed Tomography Imaging. *Circulation* 2002 January 22;105(3):282-5.

- (51) Terkelsen CJ, Andersen HR. Value of ST-resolution analysis in the era of primary percutaneous coronary intervention. *Heart* 2008 January 1;94(1):13-5.
- (52) Hof AWJ, Liem A, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F. Angiographic Assessment of Myocardial Reperfusion in Patients Treated With Primary Angioplasty for Acute Myocardial Infarction : Myocardial Blush Grade. *Circulation* 1998 June 16;97(23):2302-6.
- (53) Henriques JPS, Zijlstra F, 't Hof AWJ et al. Angiographic Assessment of Reperfusion in Acute Myocardial Infarction by Myocardial Blush Grade. *Circulation* 2003 April 29;107(16):2115-9.
- (54) Gibson CM, Cannon CP, Murphy SA et al. Relationship of the TIMI Myocardial Perfusion Grades, Flow Grades, Frame Count, and Percutaneous Coronary Intervention to Long-Term Outcomes After Thrombolytic Administration in Acute Myocardial Infarction. *Circulation* 2002 April 23;105(16):1909-13.
- (55) De Luca G, Suryapranata H, de Boer MJ et al. Combination of electrocardiographic and angiographic markers of reperfusion in the prediction of infarct size in patients with ST-segment elevation myocardial infarction undergoing successful primary angioplasty. *International Journal of Cardiology* 2007 April 25;117(2):232-7.

- (56) Seyfeli E, Abaci A, Kula M et al. Myocardial Blush Grade: To Evaluate Myocardial Viability in Patients With Acute Myocardial Infarction. *Angiology* 2007 November 1;58(5):556-60.
- (57) Porto I, Burzotta F, Brancati M et al. Relation of Myocardial Blush Grade to Microvascular Perfusion and Myocardial Infarct Size After Primary or Rescue Percutaneous Coronary Intervention. *The American Journal of Cardiology* 2007 June 15;99(12):1671-3.
- (58) Gibson CM, Cannon CP, Daley WL et al. TIMI Frame Count : A Quantitative Method of Assessing Coronary Artery Flow. *Circulation* 1996 March 1;93(5):879-88.
- (59) French JK, Hyde TA, Straznicky IT et al. Relationship between corrected TIMI frame counts at three weeks and late survival after myocardial infarction. *Journal of the American College of Cardiology* 2000 May;35(6):1516-24.
- (60) Hamada S, Nishiue T, Nakamura S et al. TIMI frame count immediately after primary coronary angioplasty as a predictor of functional recovery in patients with TIMI 3 reperfused acute myocardial infarction. *Journal of the American College of Cardiology* 2001 September;38(3):666-71.
- (61) Ohara Y, Hiasa Y, Takahashi T et al. Relation between the TIMI frame count and the degree of microvascular injury after primary coronary angioplasty in patients with acute anterior myocardial infarction. *Heart* 2005 January 1;91(1):64-7.

- (62) Hayat SA, Senior R. Myocardial contrast echocardiography in ST elevation myocardial infarction: ready for prime time? *Eur Heart J* 2008 February 1;29(3):299-314.
- (63) Lepper W, Belcik T, Wei K, Lindner JR, Sklenar J, Kaul S. Myocardial Contrast Echocardiography. *Circulation* 2004 June 29;109(25):3132-5.
- (64) Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of Myocardial Blood Flow With Ultrasound-Induced Destruction of Microbubbles Administered as a Constant Venous Infusion. *Circulation* 1998 February 10;97(5):473-83.
- (65) Ito H, Tomooka T, Sakai N et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation* 1992 May 1;85(5):1699-705.
- (66) Greaves K, Dixon SR, Fejka M et al. Myocardial contrast echocardiography is superior to other known modalities for assessing myocardial reperfusion after acute myocardial infarction. *Heart* 2003 February 1;89(2):139-44.
- (67) Bassand JP, Hamm CW, Ardissino D et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *European Heart Journal* 2007 July;28(13):1598-660.

- (68) Antman EM, Hand M, Armstrong PW et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. *Journal of the American College of Cardiology* 2008 January 15;51(2):210-47.
- (69) Weir RAP, McMurray JJV, Velazquez EJ. Epidemiology of Heart Failure and Left Ventricular Systolic Dysfunction after Acute Myocardial Infarction: Prevalence, Clinical Characteristics, and Prognostic Importance. *The American Journal of Cardiology* 2006 May 22;97(10, Supplement 1):13-25.
- (70) Grothues F, Smith GC, Moon JCC et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *The American Journal of Cardiology* 2002 July 1;90(1):29-34.
- (71) Bellenger NG et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J* 2010;2000 Aug;21(16):1387-96.
- (72) Amico AF et al. Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction. *Am Heart J* 1989;Dec;118(6):1259-65.



- (73) Iskandrian AE et al. Validation of left ventricular volume measurements by gated SPECT 99mTc-labeled sestamibi imaging. *J Nucl Cardiol* 2010;1998 Nov-Dec;5(6):574-8.
- (74) Sharir T, Germano G, Kavanagh PB et al. Incremental Prognostic Value of Post-Stress Left Ventricular Ejection Fraction and Volume by Gated Myocardial Perfusion Single Photon Emission Computed Tomography. *Circulation* 1999 September 7;100(10):1035-42.
- (75) Heuschmid M et al. Assessment of left ventricular myocardial function using 16-slice multidetector-row computed tomography: comparison with magnetic resonance imaging and echocardiography. *Eur Radiol* 2010;2006 Mar;16(3):551-9.
- (76) Larose E et al. Contrast-enhanced cardiovascular magnetic resonance in the hyperacute phase of ST-elevation myocardial infarction. *Int J Cardiovasc Imaging* 2010;2009 Jun;25(5):519-27.
- (77) Longmore DB et al. Dimensional accuracy of magnetic resonance in studies of the heart. *Lancet* 2010;1985 Jun 15;1(8442):1360-2.
- (78) Rehr RB et al. Left ventricular volumes measured by MR imaging. *Radiology* 2010;1985 Sep;156(3):717-9.

- (79) Sechtem U, Pflugfelder PW, White RD et al. Cine MR imaging: potential for the evaluation of cardiovascular function. *Am J Roentgenol* 1987 February 1;148(2):239-46.
- (80) Sechtem U et al. Measurement of right and left ventricular volumes in healthy individuals with cine MR imaging. *Radiology* 2010;1987 Jun;163(3):697-702.
- (81) Kondo C, Caputo GR, Semelka R, Foster E, Shimakawa A, Higgins CB. Right and left ventricular stroke volume measurements with velocity- encoded cine MR imaging: in vitro and in vivo validation. *Am J Roentgenol* 1991 July 1;157(1):9-16.
- (82) Myerson SG, Bellenger NG, Pennell DJ. Assessment of Left Ventricular Mass by Cardiovascular Magnetic Resonance. *Hypertension* 2002 March 1;39(3):750-5.
- (83) Katz J et al. Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging. *J Am Coll Cardiol* 1993;May;21(6):1475-81.
- (84) Shapiro EP, Rogers WJ, Beyar R et al. Determination of left ventricular mass by magnetic resonance imaging in hearts deformed by acute infarction. *Circulation* 1989 March 1;79(3):706-11.

- (85) Semelka RC et al. Interstudy reproducibility of dimensional and functional measurements between cine magnetic resonance studies in the morphologically abnormal left ventricle. *Am Heart J* 1990;Jun;119(6):1367-73.
- (86) Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *American Heart Journal* 2004 February;147(2):218-23.
- (87) Kim RJ, Chen EL, Lima JAC, Judd RM. Myocardial Gd-DTPA Kinetics Determine MRI Contrast Enhancement and Reflect the Extent and Severity of Myocardial Injury After Acute Reperfused Infarction. *Circulation* 1996 December 15;94(12):3318-26.
- (88) Kim RJ, Fieno DS, Parrish TB et al. Relationship of MRI Delayed Contrast Enhancement to Irreversible Injury, Infarct Age, and Contractile Function. *Circulation* 1999 November 9;100(19):1992-2002.
- (89) Fieno DS, Kim RJ, Chen EL, Lomasney JW, Klocke FJ, Judd RM. Contrast-enhanced magnetic resonance imaging of myocardium at risk : Distinction between reversible and irreversible injury throughout infarct healing. *Journal of the American College of Cardiology* 2000 November 15;36(6):1985-91.
- (90) Wagner A, Mahrholdt H, Holly TA et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for

detection of subendocardial myocardial infarcts: an imaging study. *The Lancet* 2003 February 1;361(9355):374-9.

- (91) Rehwald WG, Fieno DS, Chen EL, Kim RJ, Judd RM. Myocardial Magnetic Resonance Imaging Contrast Agent Concentrations After Reversible and Irreversible Ischemic Injury. *Circulation* 2002 January 15;105(2):224-9.
- (92) Selvanayagam JB, Porto I, Channon K et al. Troponin Elevation After Percutaneous Coronary Intervention Directly Represents the Extent of Irreversible Myocardial Injury: Insights From Cardiovascular Magnetic Resonance Imaging. *Circulation* 2005 March 1;111(8):1027-32.
- (93) Wu E, Judd RM, Vargas JD, Klocke FJ, Bonow RO, Kim RJ. Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *The Lancet* 2001 January 6;357(9249):21-8.
- (94) Choi KM, Kim RJ, Gubernikoff G, Vargas JD, Parker M, Judd RM. Transmural Extent of Acute Myocardial Infarction Predicts Long-Term Improvement in Contractile Function. *Circulation* 2001 September 4;104(10):1101-7.
- (95) Martin TN, Groenning BA, Murray HM et al. ST-Segment Deviation Analysis of the Admission 12-Lead Electrocardiogram as an Aid to Early Diagnosis of Acute Myocardial Infarction With a Cardiac Magnetic Resonance Imaging Gold Standard. *Journal of the American College of Cardiology* 2007 September 11;50(11):1021-8.

- (96) Klein C, Nekolla SG, Bengel FM et al. Assessment of Myocardial Viability With Contrast-Enhanced Magnetic Resonance Imaging: Comparison With Positron Emission Tomography. *Circulation* 2002 January 15;105(2):162-7.
- (97) Knhl HP, Beek AM, van der Weerd AP et al. Myocardial viability in chronic ischemic heart disease: Comparison of contrast-enhanced magnetic resonance imaging with 18F-fluorodeoxyglucose positron emission tomography. *Journal of the American College of Cardiology* 2003 April 16;41(8):1341-8.
- (98) Judd RM, Lugo-Olivieri CH, Arai M et al. Physiological Basis of Myocardial Contrast Enhancement in Fast Magnetic Resonance Images of 2-Day-Old Reperfused Canine Infarcts. *Circulation* 1995 October 1;92(7):1902-10.
- (99) Lima JAC, Judd RM, Bazille A, Schulman SP, Atalar E, Zerhouni EA. Regional Heterogeneity of Human Myocardial Infarcts Demonstrated by Contrast-Enhanced MRI : Potential Mechanisms. *Circulation* 1995 September 1;92(5):1117-25.
- (100) Stein P, Cord M, Ole JG et al. Microvascular obstruction is a major determinant of infarct healing and subsequent left ventricular remodelling following primary percutaneous coronary intervention. *Eur Heart J* 2009 August 1;30(16):1978-85.
- (101) Tarantini G, Cacciavillani L, Corbetti F et al. Duration of Ischemia Is a Major Determinant of Transmurality and Severe Microvascular Obstruction After Primary Angioplasty: A Study Performed With Contrast-Enhanced Magnetic

Resonance. *Journal of the American College of Cardiology* 2005 October 4;46(7):1229-35.

- (102) Yan AT, Gibson CM, Larose E et al. Characterization of Microvascular Dysfunction After Acute Myocardial Infarction by Cardiovascular Magnetic Resonance First-Pass Perfusion and Late Gadolinium Enhancement Imaging. *Journal of Cardiovascular Magnetic Resonance* 2006;8(6):831-7.
- (103) Albert T, Kim R, Judd R. Assessment of no-reflow regions using cardiac MRI. *Basic Research in Cardiology* 2006 September 1;101(5):383-90.
- (104) Mather AN et al. Appearance of microvascular obstruction on high resolution first-pass perfusion, early and late gadolinium enhancement CMR in patients with acute myocardial infarction. *Journal of Cardiovascular Magnetic Resonance* 2009 August 21;11(1):33.
- (105) Lund GK, Stork A, Saeed M et al. Acute Myocardial Infarction: Evaluation with First-Pass Enhancement and Delayed Enhancement MR Imaging Compared with 201Tl SPECT Imaging<sup>1</sup>. *Radiology* 2004 July;232(1):49-57.
- (106) Alexandre A.Cochet et al. Major prognostic impact of persistent microvascular obstruction as assessed by contrast-enhanced cardiac magnetic resonance in reperfused acute myocardial infarction. *European Radiology* 2010;Volume 19, Number 9 / September, 2009.

- (107) Luo AK WC. Imaging microvascular obstruction and its clinical significance following acute myocardial infarction. *Heart Failure Reviews* 2006 November 12;Volume 11, Number 4 / December, 2006.
- (108) Lund GK, Stork A, Saeed M et al. Acute Myocardial Infarction: Evaluation with First-Pass Enhancement and Delayed Enhancement MR Imaging Compared with 201Tl SPECT Imaging<sup>1</sup>. *Radiology* 2004 July;232(1):49-57.
- (109) Wu KC, Kim RJ, Bluemke DA et al. Quantification and time course of microvascular obstruction by contrast-enhanced echocardiography and magnetic resonance imaging following acute myocardial infarction and reperfusion. *Journal of the American College of Cardiology* 1998 November 15;32(6):1756-64.
- (110) Tarantini G, Razzolini R, Cacciavillani L et al. Influence of Transmurality, Infarct Size, and Severe Microvascular Obstruction on Left Ventricular Remodeling and Function After Primary Coronary Angioplasty. *The American Journal of Cardiology* 2006 October 15;98(8):1033-40.
- (111) Wu KC, Zerhouni EA, Judd RM et al. Prognostic Significance of Microvascular Obstruction by Magnetic Resonance Imaging in Patients With Acute Myocardial Infarction. *Circulation* 1998 March 3;97(8):765-72.
- (112) Weir RAP, Martin TN, Murphy CA et al. Comparison of serial measurements of infarct size and left ventricular ejection fraction by contrast-enhanced cardiac magnetic resonance imaging and electrocardiographic QRS scoring in

- reperfused anterior ST-elevation myocardial infarction. *Journal of Electrocardiology* 2005 May;43(3):230-6.
- (113) Rochitte CE, Lima JAC, Bluemke DA et al. Magnitude and Time Course of Microvascular Obstruction and Tissue Injury After Acute Myocardial Infarction. *Circulation* 1998 September 8;98(10):1006-14.
- (114) Wu KC, Kim RJ, Bluemke DA et al. Quantification and time course of microvascular obstruction by contrast-enhanced echocardiography and magnetic resonance imaging following acute myocardial infarction and reperfusion. *Journal of the American College of Cardiology* 1998 November 15;32(6):1756-64.
- (115) Pijls NH, De Bruyne BD. ***Coronary pressure***. 2nd ed. 2000.
- (116) Chilian WM, Gutterman DD. Prologue: new insights into the regulation of the coronary microcirculation. *Am J Physiol Heart Circ Physiol* 2000 December 1;279(6):H2585-H2586.
- (117) Chilian WM. Coronary Microcirculation in Health and Disease: Summary of an NHLBI Workshop. *Circulation* 1997 January 21;95(2):522-8.
- (118) Marcus ML, Chilian WM, Kanatsuka H, Dellsperger KC, Eastham CL, Lamping KG. Understanding the coronary circulation through studies at the microvascular level. *Circulation* 1990 July 1;82(1):1-7.



- (119) Westerhof N, Boer C, Lamberts RR, sipkema P. Cross-talk between cardiac muscle and coronary vasculature. *Physiological Review* 2008;86:1263-308.
- (120) Knaapen P, Camici P, Marques K et al. Coronary microvascular resistance: methods for its quantification in humans. *Basic Research in Cardiology* 2009 September 1;104(5):485-98.
- (121) Pijls NH, Uijen GJ, Hoevelaken A et al. Mean transit time for the assessment of myocardial perfusion by videodensitometry. *Circulation* 1990 April 1;81(4):1331-40.
- (122) Pijls NH, Aengevaeren WR, Uijen GJ et al. Concept of maximal flow ratio for immediate evaluation of percutaneous transluminal coronary angioplasty result by videodensitometry. *Circulation* 1991 March 1;83(3):854-65.
- (123) Gould KL, Lipscombe K, hamilt n GW. Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperaemia as measures of coronary flow reserve. *American Journal of Cardiology* 1974;33:87-94.
- (124) De Bruyne B, Pijls NHJ, Smith L, Wievegg M, Heyndrickx GR. Coronary Thermodilution to Assess Flow Reserve: Experimental Validation. *Circulation* 2001 October 23;104(17):2003-6.

- (125) Pijls NHJ, De Bruyne B, Smith L et al. Coronary Thermodilution to Assess Flow Reserve: Validation in Humans. *Circulation* 2002 May 28;105(21):2482-6.
- (126) De Bruyne B, Pijls NHJ, Smith L, Wievegg M, Heyndrickx GR. Coronary Thermodilution to Assess Flow Reserve: Experimental Validation. *Circulation* 2001 October 23;104(17):2003-6.
- (127) Tonino PAL, De Bruyne B, Pijls NHJ et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *N Engl J Med* 2009 January 15;360(3):213-24.
- (128) Kern MJ. Coronary Physiology Revisited : Practical Insights From the Cardiac Catheterization Laboratory. *Circulation* 2000 March 21;101(11):1344-51.
- (129) De Bruyne B, Bartunek J, Sys SU, Pijls NHJ, Heyndrickx GR, Wijns W. Simultaneous Coronary Pressure and Flow Velocity Measurements in Humans: Feasibility, Reproducibility, and Hemodynamic Dependence of Coronary Flow Velocity Reserve, Hyperemic Flow Versus Pressure Slope Index, and Fractional Flow Reserve. *Circulation* 1996 October 15;94(8):1842-9.
- (130) Ng MKC, Yeung AC, Fearon WF. Invasive Assessment of the Coronary Microcirculation: Superior Reproducibility and Less Hemodynamic Dependence of Index of Microcirculatory Resistance Compared With Coronary Flow Reserve. *Circulation* 2006 May 2;113(17):2054-61.

- (131) Fearon WF, Balsam LB, Farouque HMO et al. Novel Index for Invasively Assessing the Coronary Microcirculation. *Circulation* 2003 July 1;107(25):3129-32.
- (132) Aarnoudse W, van den Berg P, Van De Vosse F et al. Myocardial resistance assessed by guidewire-based pressure-temperature measurement: in vitro validation. *Cathet Cardiovasc Intervent* 2004;62:56-63.
- (133) Marzilli M, Sambuceti G, Fedele S, L'Abbate A. Coronary microcirculatory vasoconstriction during ischemia in patients with unstable angina. *Journal of the American College of Cardiology* 2000 February;35(2):327-34.
- (134) Sambuceti G, Marzilli M, Fedele S, Marini C, L'Abbate A. Paradoxical Increase in Microvascular Resistance During Tachycardia Downstream From a Severe Stenosis in Patients With Coronary Artery Disease : Reversal by Angioplasty. *Circulation* 2001 May 15;103(19):2352-60.
- (135) Chamuleau SAJ, Siebes M, Meuwissen M, Koch KT, Spaan JAE, Piek JJ. Association between coronary lesion severity and distal microvascular resistance in patients with coronary artery disease. *Am J Physiol Heart Circ Physiol* 2003 November 1;285(5):H2194-H2200.
- (136) Fearon WF, Aarnoudse W, Pijls NHJ et al. Microvascular Resistance Is Not Influenced by Epicardial Coronary Artery Stenosis Severity: Experimental Validation. *Circulation* 2004 May 18;109(19):2269-72.

- (137) Aarnoudse W, Fearon WF, Manoharan G et al. Epicardial Stenosis Severity Does Not Affect Minimal Microcirculatory Resistance. *Circulation* 2004 October 12;110(15):2137-42.
- (138) Yong ASC, Ho M, Shah MG, Ng MKC, Fearon WF. Coronary Microcirculatory Resistance Is Independent of Epicardial Stenosis. *Circulation: Cardiovascular Interventions* 2012 February 1;5(1):103-8.
- (139) Sezer M, Oflaz H, Goren T et al. Intracoronary Streptokinase after Primary Percutaneous Coronary Intervention. *N Engl J Med* 2007 May 3;356(18):1823-34.
- (140) Piek JJ. Beyond Epicardial Reperfusion. *N Engl J Med* 2007 May 3;356(18):1880-2.
- (141) Balachandran KP, Berry C, Norrie J et al. Relation between coronary pressure derived collateral flow, myocardial perfusion grade, and outcome in left ventricular function after rescue percutaneous coronary intervention. *Heart* 2004 December 1;90(12):1450-4.
- (142) Pijls NHJ, Willem Bech GJ, El Gamal MIH et al. Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. *Journal of the American College of Cardiology* 1995 June;25(7):1522-8.

- (143) Yamamoto K, Ito H, Iwakura K et al. Pressure-derived collateral flow index as a parameter of microvascular dysfunction in acute myocardial infarction. *Journal of the American College of Cardiology* 2001 November 1;38(5):1383-9.
- (144) Sezer M, Nisanci Y, Umman B et al. New support for clarifying the relation between ST segment resolution and microvascular function: degree of ST segment resolution correlates with the pressure derived collateral flow index. *Heart* 2004 February;90(2):146-50.
- (145) Sezer M, Nisanci Y, Umman B et al. Pressure-derived collateral flow index: a strong predictor of late left ventricular remodeling after thrombolysis for acute myocardial infarction. [Miscellaneous Article]. *Coronary Artery Disease* 2006 March;17(2):139-44.
- (146) Whan Lee C, Park SW, Cho GY et al. Pressure-derived fractional collateral blood flow: a primary determinant of left ventricular recovery after reperfused acute myocardial infarction. *Journal of the American College of Cardiology* 2000 March 15;35(4):949-55.
- (147) Pijls NHJ, Klauss V, Siebert U et al. Coronary Pressure Measurement After Stenting Predicts Adverse Events at Follow-Up. *Circulation* 2002 June 25;105(25):2950-4.
- (148) Olsson RA, Davis CJ, Khouri EM, Patterson RE. Evidence for an adenosine receptor on the surface of dog coronary myocytes. *Circulation Research* 1976 July 1;39(1):93-8.

- (149) Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990 November 1;82(5):1595-606.
- (150) Jeremias A, Whitbourn RJ, Filardo SD et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *American heart journal* 140[4], 651-657. 1-10-2000.
- (151) Murtagh B, Higano S, Lennon R, Mathew V, Holmes DR, Lerman A. Role of incremental doses of intracoronary adenosine for fractional flow reserve assessment. *American heart journal* 146[1], 99-105. 1-7-2003.
- (152) Aqel RA, Zoghbi GJ, Trimm JR, Baldwin SA, Iskandrian AE. Effect of caffeine administered intravenously on intracoronary-administered adenosine-induced coronary hemodynamics in patients with coronary artery disease. *The American Journal of Cardiology* 2004 February 1;93(3):343-6.
- (153) Nahser PJ Jr et al. The effect of aminophylline on pharmacological stress with intravenous adenosine. *Am J Card Imaging* 1996;(1996 Jul;10(3):149-53).
- (154) Yamada H et al. Intracoronary adenosine 5'-triphosphate as an alternative to papaverine for measuring coronary flow reserve. *Am Heart J* 2012;1994 Nov 1;74(9):940-1.

- (155) De Bruyne B, Pijls NHJ, Barbato E et al. Intracoronary and Intravenous Adenosine 5'-Triphosphate, Adenosine, Papaverine, and Contrast Medium to Assess Fractional Flow Reserve in Humans. *Circulation* 2003 April 15;107(14):1877-83.
- (156) Yeh BK et al. Sodium nitroprusside as a coronary vasodilator in man. I. Effect of intracoronary sodium nitroprusside on coronary arteries, angina pectoris, and coronary blood flow. *Am Heart J* 1977 April 3;1977 May;93(5):610-6.
- (157) Amit G, Cafri C, Yaroslavtsev S et al. Intracoronary nitroprusside for the prevention of the no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction. A randomized, double-blind, placebo-controlled clinical trial. *American heart journal* 152[5], 887. 1-11-2006.
- (158) Parham WA, Bouhasin A, Ciaramita JP, Khoukaz S, Herrmann SC, Kern MJ. Coronary Hyperemic Dose Responses of Intracoronary Sodium Nitroprusside. *Circulation* 2004 March 16;109(10):1236-43.
- (159) Jagathesan R, Barnes E, Rosen SD, Foale R, Camici PG. Dobutamine-induced hyperaemia inversely correlates with coronary artery stenosis severity and highlights dissociation between myocardial blood flow and oxygen consumption. *Heart* 2006 September 1;92(9):1230-7.

- (160) Sun KT, Czernin J, Krivokapich J et al. Effects of Dobutamine Stimulation on Myocardial Blood Flow, Glucose Metabolism, and Wall Motion in Normal and Dysfunctional Myocardium. *Circulation* 1996 December 15;94(12):3146-54.
- (161) Meimoun P, Sayah S, Tcheuffa JC et al. Transthoracic Coronary Flow Velocity Reserve Assessment: Comparison Between Adenosine and Dobutamine. *Journal of the American Society of Echocardiography* : official publication of the American Society of Echocardiography 19[10], 1220-1228. 1-10-2006.
- (162) Wilson RF, White CW. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. *Circulation* 1986 March 1;73(3):444-51.
- (163) VROLIX M, PIESENS J, GEEST HD. Torsades de pointes after intracoronary papaverine. *European Heart Journal* 1991 February 1;12(2):273-6.
- (164) Christensen CW, Rosen LB, Gal RA, Haseeb M, Lassar TA, Port SC. Coronary vasodilator reserve. Comparison of the effects of papaverine and adenosine on coronary flow, ventricular function, and myocardial metabolism. *Circulation* 1991 January 1;83(1):294-303.
- (165) Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of Impaired Endothelium-Dependent Coronary Vasodilatation in Patients with Angina Pectoris and Normal Coronary Angiograms. *N Engl J Med* 1993 June 10;328(23):1659-64.



- (166) Tatineni S, Kern MJ, Deligonul U, Aguirre F. The effects of ionic and nonionic radiographic contrast media on coronary hyperemia in patients during coronary angiography. *Am Heart J* 1992 March;123(3):621-7.
- (167) Hogson J, Williams DO. Superiority of intracoronary papaverine to radiographic contrast for measuring coronary flow reserve in patients with ischemic heart disease. *Am Heart J* 1987;1987 Oct;114(4 Pt 1):704-10.
- (168) Cerqueira MD. The future of pharmacologic stress: selective a<sub>2a</sub> adenosine receptor agonists. *The American Journal of Cardiology* 2004 July 22;94(2, Supplement 1):33-40.
- (169) Udelson JE, Heller GV, Wackers FJT et al. Randomized, Controlled Dose-Ranging Study of the Selective Adenosine A<sub>2A</sub> Receptor Agonist Binodenoson for Pharmacological Stress as an Adjunct to Myocardial Perfusion Imaging. *Circulation* 2004 February 3;109(4):457-64.
- (170) Hendel RC, Bateman TM, Cerqueira MD et al. Initial Clinical Experience With Regadenoson, a Novel Selective A<sub>2A</sub> Agonist for Pharmacologic Stress Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging. *J Am Coll Cardiol* 2005 December 6;46(11):2069-75.
- (171) McGeoch RJ, Oldroyd KG. Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology. *Cathet Cardiovasc Intervent* 2008;71(2):198-204.

- (172) Killip T 3rd KJT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *American Journal of Cardiology* 20(4), 457-467. 2007.
- (173) De Waha S, Desch S, Eitel I, Gutberlet M, Schuler G, Thiele H. IMPACT OF EARLY VERSUS LATE MICROVASCULAR OBSTRUCTION ASSESSED BY MAGNETIC RESONANCE IMAGING ON LONG-TERM OUTCOME AFTER ST-ELEVATION MYOCARDIAL INFARCTION. *Journal of the American College of Cardiology* 2010 March 9;55(10, Supplement 1):A65.
- (174) Albert K.Luo and Katherine C.Wu. Imaging microvascular obstruction and its clinical significance following acute myocardial infarction. *Heart Failure Reviews* 2010;Volume 11, Number 4 / December, 2006.
- (175) Kim RJ, Wu E, Rafael A et al. The Use of Contrast-Enhanced Magnetic Resonance Imaging to Identify Reversible Myocardial Dysfunction. *N Engl J Med* 2000 November 16;343(20):1445-53.
- (176) Choi KM, Kim RJ, Gubernikoff G, Vargas JD, Parker M, Judd RM. Transmural Extent of Acute Myocardial Infarction Predicts Long-Term Improvement in Contractile Function. *Circulation* 2001 September 4;104(10):1101-7.
- (177) Pitt B, White H, Nicolau J et al. Eplerenone Reduces Mortality 30 Days After Randomization Following Acute Myocardial Infarction in Patients With Left

Ventricular Systolic Dysfunction and Heart Failure. *Journal of the American College of Cardiology* 2005 August 2;46(3):425-31.

- (178) Sezer M, Aslanger EK, Cimen AO et al. Concurrent Microvascular and Infarct Remodeling After Successful Reperfusion of ST-Elevation Acute Myocardial Infarction. *Circ Cardiovasc Interv* 2010 June 1;3(3):208-15.
- (179) Lim HS, Yoon MH, Tahk SJ et al. Usefulness of the index of microcirculatory resistance for invasively assessing myocardial viability immediately after primary angioplasty for anterior myocardial infarction. *European Heart Journal* 2009 December 1;30(23):2854-60.
- (180) McGeoch R, Watkins S, Berry C et al. The Index of Microcirculatory Resistance Measured Acutely Predicts the Extent and Severity of Myocardial Infarction in Patients With ST-Segment Elevation Myocardial Infarction. *JACC: Cardiovascular Interventions* 2010 July;3(7):715-22.
- (181) Wu E, Ortiz JT, Tejedor P et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart* 2008 June 1;94(6):730-6.
- (182) Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J* 2001 May 1;22(9):729-39.

- (183) Friedrich MG, Kramer CM, Sodickson DK, Flamm SD, Buser P, Neubauer S. Meeting Highlights of the 10th Annual Scientific Sessions of the Society for Cardiovascular Magnetic Resonance and 6th Annual Meeting of the Working Group for Cardiovascular Magnetic Resonance of the European Society of Cardiology: Rome, Italy, February 2-4, 2007. *Journal of the American College of Cardiology* 2007 September 4;50(10):983-7.
- (184) Hombach V, Grebe O, Merkle N et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. *Eur Heart J* 2005 March 2;26(6):549-57.
- (185) Camici PG, Crea F. Coronary Microvascular Dysfunction. *N Engl J Med* 2007 February 22;356(8):830-40.
- (186) Hirsch A, Nijveldt R, Haack JDE et al. Relation Between the Assessment of Microvascular Injury by Cardiovascular Magnetic Resonance and Coronary Doppler Flow Velocity Measurements in Patients With Acute Anterior Wall Myocardial Infarction. *Journal of the American College of Cardiology* 2008 June 10;51(23):2230-8.
- (187) Kitabata H, Imanishi T, Kubo T et al. Coronary Microvascular Resistance Index Immediately After Primary Percutaneous Coronary Intervention as a Predictor of the Transmural Extent of Infarction in Patients With ST-Segment Elevation

- Anterior Acute Myocardial Infarction. *JACC: Cardiovascular Imaging* 2009 March;2(3):263-72.
- (188) Rochitte CE. Microvascular Obstruction: The Final Frontier for a Complete Myocardial Reperfusion. *Journal of the American College of Cardiology* 2008 June 10;51(23):2239-40.
- (189) Layland J, MacIsaac AI, Burns AT et al. When Collateral Supply is Accounted For Epicardial Stenosis Does Not Increase Microvascular Resistance. *Circulation: Cardiovascular Interventions* 2012 February 1;5(1):97-102.
- (190) SEZER MURA, UMMAN BERR, OKULAR IREM, NISANCI YILM, UMMAN SABA. Relationship between Microvascular Resistance and Perfusion in Patients with Reperfused Acute Myocardial Infarction. *Journal of Interventional Cardiology* 2007 October 27;20(5):340-50.
- (191) GISSI. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 2010;Feb 22;1(8478):397-402.
- (192) An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. *New England Journal of Medicine* 1993 September 2;329(10):673-82.
- (193) G.De Luca, Suryaprantanta H, Zijlstra F. Myocardial Infarction Study Group. Symptom-onset-to-balloon time and mortality in patients with acute myocardial

- infarction treated by primary angioplasty. *Journal of the American College of Cardiology* 1998;2.
- (194) Bekkers SCAM, Yazdani SK, Virmani R, Waltenberger J. Microvascular Obstruction: Underlying Pathophysiology and Clinical Diagnosis. *Journal of the American College of Cardiology* 2010 April 20;55(16):1649-60.
- (195) Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon on ischaemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;56:786-94.
- (196) Ohman EM, Armstrong PW, Christenson RH et al. Cardiac Troponin T Levels for Risk Stratification in Acute Myocardial Ischemia. *New England Journal of Medicine* 1996 October 31;335(18):1333-42.
- (197) Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. Prognostic Significance of Admission Troponin T Concentrations in Patients With Myocardial Infarction. *Circulation* 1996 September 15;94(6):1291-7.
- (198) Antman EM, Tanasijevic MJ, Thompson B et al. Cardiac-Specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes. *New England Journal of Medicine* 1996 October 31;335(18):1342-9.
- (199) Steen H, Giannitsis E, Futterer S, Merten C, Juenger C, Katus HA. Cardiac Troponin T at 96 Hours After Acute Myocardial Infarction Correlates With

- Infarct Size and Cardiac Function. *Journal of the American College of Cardiology* 2006 December 5;48(11):2192-4.
- (200) Byrne RA, Ndrepepa G, Braun S et al. Peak Cardiac Troponin-T Level, Scintigraphic Myocardial Infarct Size and One-Year Prognosis in Patients Undergoing Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction. *The American Journal of Cardiology* 2010 November 1;106(9):1212-7.
- (201) Hundley WG, Bluemke DA, Finn JP et al. ACCF/ACR/AHA/NASCI/SCMR 2010 Expert Consensus Document on Cardiovascular Magnetic Resonance: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2010 June 8;55(23):2614-62.
- (202) Semelka RC, Tomei E, Wagner S et al. Normal left ventricular dimensions and function: interstudy reproducibility of measurements with cine MR imaging. *Radiology* 1990 March 1;174(3):763-8.
- (203) Weir RAP, Martin TN, Petrie CJ et al. Cardiac and Extracardiac Abnormalities Detected by Cardiac Magnetic Resonance in a Post-Myocardial Infarction Cohort. *Cardiology* 2009;113(1):1-8.
- (204) Larose E, Rod+@s-Cabau J, Pibarot P et al. Predicting Late Myocardial Recovery and Outcomes in the Early Hours of ST-Segment Elevation Myocardial Infarction: Traditional Measures Compared With Microvascular Obstruction, Salvaged Myocardium, and Necrosis Characteristics by

Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010 June 1;55(22):2459-69.

- (205) Svilaas T, Vlaar PJ, van der Horst IC et al. Thrombus Aspiration during Primary Percutaneous Coronary Intervention. *New England Journal of Medicine* 2008 February 7;358(6):557-67.
- (206) Amado LC, Kraitichman DL, Gerber BL et al. Reduction of "no-reflow" phenomenon by intra-aortic balloon counterpulsation in a randomized magnetic resonance imaging experimental study. *Journal of the American College of Cardiology* 2004 April 7;43(7):1291-8.
- (207) Sjaauw KD, Engström AE, Vis MM et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? *European Heart Journal* 2009 February 1;30(4):459-68.
- (208) Taniyama Y, Ito H, Iwakura K et al. Beneficial Effect of Intracoronary Verapamil on Microvascular and Myocardial Salvage in Patients With Acute Myocardial Infarction. *Journal of the American College of Cardiology* 1997 November 1;30(5):1193-9.
- (209) Antman EM, Giugliano RP, Gibson CM et al. Abciximab Facilitates the Rate and Extent of Thrombolysis : Results of the Thrombolysis In Myocardial Infarction (TIMI) 14 Trial. *Circulation* 1999 June 1;99(21):2720-32.



- (210) de Lemos JA, Antman EM, Gibson CM et al. Abciximab Improves Both Epicardial Flow and Myocardial Reperfusion in ST-Elevation Myocardial Infarction : Observations from the TIMI 14 Trial. *Circulation* 2000 January 25;101(3):239-43.
- (211) Kunichika H, Ben Yehuda O, Lafitte S, Kunichika N, Peters B, DeMaria AN. Effects of glycoprotein iib/iiia inhibition on microvascular flow after coronary reperfusion: A quantitative myocardial contrast echocardiography study. *Journal of the American College of Cardiology* 2004 January 21;43(2):276-83.
- (212) Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A Randomized, Double-Blinded, Placebo-Controlled Multicenter Trial of Adenosine as an Adjunct to Reperfusion in the Treatment of Acute Myocardial Infarction (AMISTAD-II). *Journal of the American College of Cardiology* 2005 June 7;45(11):1775-80.
- (213) Sezer M, İimen A, Aslanger E et al. Effect of Intracoronary Streptokinase Administered Immediately After Primary Percutaneous Coronary Intervention on Long-Term Left Ventricular Infarct Size, Volumes, and Function. *Journal of the American College of Cardiology* 2009 September 15;54(12):1065-71.
- (214) Ito N, Nanto S, Doi Y et al. High Index of Microcirculatory Resistance Level After Successful Primary Percutaneous Coronary Intervention Can Be Improved by Intracoronary Administration of Nicorandil. *Circulation Journal* 2010;74(5):909-15.

## **Appendix A**

Version 1.1 Oct 2006

### **Patient Information Sheet (1)**

You are being asked to take part in a clinical research study. It is important that you understand why you are being asked to take part and what it is involved for you.

Participation in this trial is voluntary and it is entirely up to you whether you want to take part or not.

#### **Title of Project**

Correlation of invasive measurements for assessment of microvascular dysfunction with cardiac magnetic resonance imaging to predict those most at risk following acute myocardial infarction.

#### **What does this title mean and what is the purpose of the study?**

Heart attack (myocardial infarction) affects not only the large heart arteries but also the small heart arteries. We can see the large heart arteries at angiography. There is not currently a reliable way to measure damage to the heart's small blood vessels. There are new measurements which can be taken at the time of angioplasty which we now know

represent damage to the hearts small blood vessels. We plan to take these measurements during angioplasty. We will then perform a special heart scan, an MRI scan, which would allow us to look at the blood supply to the heart, to look at the amount of damage to the heart as a whole and at the amount of damage to the small blood vessels. Our aim is to identify patients with significant damage to the hearts small blood vessels at the time of angioplasty therefore allowing us to identify future patients with treatment to minimise damage at the earliest opportunity.

### **What will happen to me if I take part?**

If you require an angioplasty (using balloons and stents to open the larger heart arteries) we will make measurements that represent damage to the hearts small blood vessels. This will add 10 minutes on to your procedure and does not pose any additional risk to you.

Angioplasty involves placing tiny wires into the heart arteries that then allows us to inflate balloons and deploy stents (like tiny scaffolds) over the blockage restoring blood flow. We would use a wire with a special tip allowing us to make the measurements representing damage to the heart small blood vessels.

In order to make these measurements accurately we will have to give you a drip of a drug called *adenosine*. This drug allows more blood to pass into the heart. Its main side effect is that it can cause tightness in the chest and can make you feel breathless. Although uncomfortable this senSAtion is harmless and does not indicate heart damage. It will pass

seconds after the drip is stopped. Rarely adenosine can cause the heart to slow down but this again is only temporary and your heart rate will be monitored throughout the procedure.

Adenosine can cause to become more breathless if you have asthma or COPD (smoking related lung disease). You will not be able to participate in the trial if you have either of these conditions.

You will also receive a heart MRI scan during this hospital admission and in 3 months time. We will give you further information about this and the trial as a whole after your procedure when you are settled. At this point you can decide whether you wish to continue in the study.

Thank you for taking the time to read this patient information sheet.

## Appendix B

Version 1.2 Oct 2006

### CONSENT FORM (1)

#### Title of project:

Correlation of invasive measurements for assessment of microcirculatory dysfunction with cardiac magnetic resonance imaging to predict those most at risk following acute myocardial infarction.

**Name of researcher:** Dr Ross McGeoch

**Please initial box**

1. I confirm that I have read and understand patient information sheet (1) for the above study. I have had the opportunity to ask questions and I understand the information provided to me. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

\_\_\_\_\_  
Name of patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person taking consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

(if different from researcher)

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

I have witnessed the informed consent process and attest that the information contained in the patient information sheet was accordingly explained to the patient. I believe the explanation was understood and that consent to participate was freely given.

\_\_\_\_\_  
Name of impartial witness

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

## Appendix C

Version 1.3 Jan 2007

### **Patient Information Sheet (2)**

You are being asked to take part in a clinical research study. Before you decide it is important for you to understand why the research is being done and what it will involve for you. Please take time to read the following carefully and discuss it with others if you wish. Please ask us if there is anything you are unclear about or if you would like more information. Take time to decide whether or not you wish to take part.

#### **Title of Project**

Correlation of invasive measurements for assessment of microvascular dysfunction with cardiac magnetic resonance imaging to predict those most at risk following acute myocardial infarction.

#### **What does the title mean and what is the purpose of the study?**

Treatment of heart attack (myocardial infarction) has traditionally concentrated on opening the large heart arteries, whether by “clot busting” medication or balloons and stents (angioplasty). We now know that damage to the heart’s tiny blood vessels also occurs during heart attack and this can contribute to longer-term heart damage. We plan

to take measurements, which represent damage to the heart's small blood vessels during treatment for heart attack with angioplasty. We will then perform a special heart scan, an MRI scan, which would allow us to look at the blood supply to the heart, to look at the amount of damage to the heart as a whole and at the amount of damage to the small blood vessels. We would also like to obtain a blood and urine sample at the time of each MRI scan in order to study some circulating cells and chemicals that may be involved in heart muscle and blood vessel repair. Our aim is to identify patients with significant damage to the hearts small blood vessels at the time of angioplasty therefore allowing us to identify future patients with treatment to minimise damage at the earliest opportunity.

### **Why have I been chosen?**

You have had a heart attack and you require an emergency angiography procedure to look at the arteries that supply the heart.

### **Do I have to take part?**

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at anytime, or a decision not to take part, will not affect the standard of care you receive.

### **What will happen to me if I take part?**

If you require an angioplasty (using balloons and stents to open the larger heart arteries) we will make measurements that represent damage to the hearts small blood vessels. This involves injecting dye into the heart arteries under x-ray guidance allowing us to identify if any blockages are present. Angioplasty involves placing a tiny wire into the relevant heart artery allowing us to inflate balloons and deploy stents (like small scaffolds) over the blocked area. We will use a pressure and temperature sensitive guidewire during the procedure rather than a normal wire. The measurements will take an additional 10 minutes during the procedure and do not pose any additional risk to you. While these measurements are being taken a drug called adenosine is used to increase the blood flow through the heart arteries.

You will have two heart MRI scans. One will occur within 48 hours of your heart attack during this current hospital admission and the other will be at around two months after your heart attack at a time that is convenient for you.

The MRI scans last approximately one hour each. The scanner is basically tunnel shaped, like large “polo” mint, which is open at both ends. You are slid into the centre of the “polo” on an electric bed and the scans are taken. Some people find it a little enclosing but you can come out at any time.



Before you go into the scanner, you will be invited to provide a urine sample. Following this, two small plastic cannulas (similar to that used when putting in a drip) will be inserted into the veins in your arms by a doctor. We would like to draw about 40 millilitres (about 3 tablespoonfuls) of blood from one of the plastic cannulas, and also ask you to provide a urine sample. We will examine some routine parameters, such as blood platelets, but also some new markers, known as endothelial progenitor cells, that may be involved in heart blood vessel repair. We will also measure some of the circulating growth factors (small chemicals in the blood) which stimulate the release of these cells. We will count the number of these cells in each blood sample, and also prepare DNA and RNA from these cells to examine whether the genetic make-up has any connection with heart muscle and blood vessel repair (as assessed by MRI). Small blood and urine samples will be stored in a freezer to be analysed at a later stage, particularly when new markers of heart disease will have been developed by us or by other scientists.

Following this, the cannula will permit us to inject gadolinium dye during your MRI scan and also to administer a drug called adenosine.

Gadolinium is a clear fluid like water. It is used in MRI scanning because it accumulates in abnormal tissue and “lights up” that area so the scanner can detect it. It is useful in telling us which parts of the heart are abnormal, if any. After a short while the gadolinium fades away and is removed from your body (within a few hours).

When you are in the scanner you will need to wear a pair of headphones. These are necessary because of the loud knocking noise that occurs when the pictures are being taken. The headphones allow you to listen to music of your choice (you may bring your own CD) and allow us to communicate with you throughout the scan. Whilst in the scanner, you will be given an emergency buzzer and can very quickly be taken out should you feel uncomfortable. During the scan you will be asked to hold your breath at times to improve the quality of the pictures.

**Women only:** The effect of MRI scans on babies is unknown- for this reason, anyone who is pregnant or becomes pregnant during the study will be excluded. If you think you may be pregnant please inform the study doctor.

### **What are the risks?**

There is no additional risk by taking these extra measurements during your angioplasty.

The MRI scanner is very safe if you have no metal implants in your body.

The dye used during the cardiac MRI scans is called gadolinium. It is generally harmless and will be washed out of your system by your kidneys. Side effects include mild headache and nausea. Rarely (less than 1 % of the time) low blood pressure and light-headedness occurs. Very rarely (less than one in a thousand), patients are allergic to the contrast agent.

Senior doctors will be present during your angioplasty procedure and a senior doctor will be present during your cardiac MRI scans.

The amount of blood and urine drawn does not place you at any risk.

### **What are the potential benefits of taking part?**

You may not benefit directly from taking part in the study but the information that we get may help to improve treatment of patients in the future. You will be getting special scans of your heart that are not usually provided as part of routine care. This will provide additional information about your health, which could influence your future treatment. While the blood and urine results may be useful for clinical research purposes, we do not anticipate these results to be useful for the treatment of your condition.

### **What if something goes wrong?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms will be available to you.

### **Will my GP be informed?**

If you agree we will inform your GP that you have agreed to take part in this study.

**Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. Your personal information will be kept on file and stored in a secure place at the BHF Glasgow Cardiovascular Research Centre and in the Department of Cardiology. All examinations (including urine and blood results and gene data) will be labelled with a code and not with any personal details so that all analyses will be carried out anonymously. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital or the Clinical Investigation Unit will have your name and address removed so that you cannot be recognised from it.

**What will happen to the results of the research study?**

When the results become available they will be submitted to medical journals where they will be considered for publication. The final results will also be submitted to national and international medical conferences where they will be considered for publication. At the

BHF Glasgow Cardiovascular Research Centre we will have events to inform the public about our ongoing research and about results from this and other studies.

You will not be identified in any report or publication.

If you would like a copy of the results, please ask your study doctor.

**Who is organising and funding the research?**

This study is organised by doctors from the Department of Cardiology, Western Infirmary and scientists from the BHF Glasgow Cardiovascular Research Centre at Glasgow University. The study is funded by charities and researchers will not receive any payment for conducting this study.

**Who has reviewed the study?**

The West Ethics committee of the North Glasgow University Hospitals NHS Trust has reviewed this study.

**Who can I contact for further information?**

Study doctor:	Dr Ross J McGeoch	
	Department of Cardiology	
	Western Infirmary	0141-211-8527

Supervisor: Dr K G Oldroyd

## Appendix D

Version 1.1 Aug 2006

### CONSENT FORM (2)

**Title of project:**

Correlation of invasive measurements for assessment of microcirculatory dysfunction with cardiac magnetic resonance imaging to predict those most at risk following acute myocardial infarction.

**Name of researcher:** Dr Ross McGeoch

**Please initial box**

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

☐☐☐☐

\_\_\_\_\_  
Name of patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

## Appendix V

### Prognostic Value of the Index of Microcirculatory Resistance after Primary Percutaneous Coronary Intervention

**Authors:** Andy S.C. Yong, Joshua Loh, Ross McGeoch, Maulik Shah, Michael Ho, David Daniels, Adrian Low, Keith Oldroyd, William F. Fearon

**Background:** The Index of Microcirculatory Resistance (IMR) is an invasive, wire-based method for assessing microvascular function which can predict persistent left ventricular dysfunction after primary percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction. The aim of this prospective multicenter study is to evaluate the ability of IMR to predict events in patients undergoing primary PCI.

**Methods:** IMR was measured immediately after primary PCI in 253 patients from 3 institutions using a pressure-temperature sensor wire. The primary end point was rate of death or rehospitalization for heart failure.

**Results:** The mean IMR was  $40.2 \pm 32.4$ . Patients with  $\text{IMR} \geq 40.2$  had higher 1 year primary end point rates compared to patients with  $\text{IMR} < 40.2$  (17.1% vs. 6.6%,  $P = 0.027$ ). During a median follow-up period of 2.8 years, 34 patients (13.4%) suffered the primary end point and 11 patients (4.3%) died. Using Cox proportional hazards analysis,  $\text{IMR} \geq 40.2$  was associated with an increased risk of death or rehospitalization for heart failure (hazard ratio [HR] 2.08,  $P = 0.033$ ) and death (HR 3.90,  $P = 0.03$ ). Survival curves are shown below. In multivariate analysis, independent predictors of the primary end



point include  $\text{IMR} \geq 40.2$  (HR 2.50,  $P = 0.011$ ), age (HR 1.04,  $P = 0.02$ ) and diabetes (HR 4.24,  $P < 0.001$ ).

**Conclusions:** An elevated IMR at the time of primary PCI predicts poor long term outcomes. Measurement of IMR may identify high risk patients who will benefit from novel therapy.

