Quantitative Cardiac Magnetic Resonance Imaging Biomarkers for the Characterisation of Ischaemic Cardiomyopathy

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Supervisors
Professor Charlotte H Manisty
Professor James C Moon
Declaration of originality

I, Andreas Seraphim, confirm that the work presented in my thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.”

Dr Andreas Seraphim

London, 1st of September 2022

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Abstract

Our understanding of the processes that determine outcomes in patients with ischaemic cardiomyopathy is based on conventional physiological concepts such as ischaemia and viability. Qualitative methods for characterising these processes tend to be binary and often fail to capture the complexity of the underlying biology. Importantly, these are perhaps inadequate to evaluate treatment effects, including the impact of coronary revascularisation.

The aim of this thesis was to deploy novel quantitative cardiac magnetic resonance (CMR) techniques to evaluate and distinguish between the pathophysiological processes that determine outcomes in patients with ischaemic cardiomyopathy, through integration of anatomical, functional, perfusion and tissue characterisation information. The work is centred around the use of coronary artery bypass graft (CABG) surgery as the method for revascularisation, and focuses on the impact of myocardial blood flow alterations on cardiac physiology and clinical outcomes.

In this work, I first evaluate the impact of surgical revascularisation on myocardial structure and function in patients with impaired left ventricular (LV) systolic function, using paired assessments before and after CABG. I found that at 6 months following revascularisation, despite improvement in functional capacity, more than a third of total myocardial segments examined are no longer considered revascularised. As a result, the overall augmentation in global myocardial blood flow (MBF) following CABG surgery is significantly blunted.
There are however technical concerns regarding the quantitative estimation of myocardial blood flow in patients with coronary artery grafts, particularly in relation to the impact of long coronary grafts on contrast kinetics. I therefore evaluated the impact of arterial contrast delay on myocardial blood flow estimation in patients with left internal mammary artery (LIMA) grafts. I showed that absolute MBF estimation is minimally affected by delayed contrast arrival in patients with LIMA grafts, and that irrespective of graft patency, residual native disease severity is a key determinant of myocardial blood flow.

Following these findings, I then assessed the prognostic impact of myocardial blood flow in a large cohort of patients with prior CABG. The only imaging study to date examining the prognostic role of quantitative perfusion indices in this population, it demonstrated that both stress MBF and myocardial perfusion reserve (MPR) independently predict adverse cardiovascular outcomes and all cause-mortality.

Finally, using the existing quantitative perfusion technique and its associated framework, I co-developed and implemented a non-invasive, in-line method of measuring pulmonary transit time (PTT) and pulmonary blood volume (PBV) during routine CMR scanning. I then found that both imaging parameters can be used as independent quantitative prognostic biomarkers in patients with known or suspected coronary artery disease.

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I am grateful to the cardiothoracic team at Barts Heart Centre who have supported and facilitated part of this work. I would also like to acknowledge the contributions of the administrative staff, radiographers and the entire cardiac imaging group at Barts Heart Centre. Importantly, I would like to thank the fellows and colleagues, whose team work has been the source of our joint achievements. Thanks to the many patients that took part in the studies that constitute this thesis.

Lastly, I am most grateful to my family. What I have and perhaps will ever achieve in my life is thanks to them.
Impact statement

Diagnosis and treatment of coronary artery disease has been one of the most extensively researched topics in clinical medicine. Despite this, patients with ischaemic cardiomyopathy continue to pose diagnostic and management challenges and our ability to intervene on the natural history of the disease remains limited. Technological advances have enhanced the effectiveness and safety of revascularisation, but whether this translates to improved outcomes remains unclear. Our treatment strategies are universal and not personalised and often fail to capture the complexity of the underlying pathophysiology, largely ignoring the substantial biological variability between individuals. There is a need to challenge traditional principles on which some our understanding of the pathophysiology of disease is based and to identify new methods of measuring the effects of treatment.

Cardiovascular magnetic resonance (CMR) imaging is a reference imaging modality for simultaneous assessment of cardiac structure, function, myocardial perfusion and tissue characterisation. Clinical CMR reporting however is primarily based on qualitative descriptors and basic geometric quantifiers. In this thesis, novel quantitative CMR techniques were deployed to characterise the impact of surgical revascularisation in patients with ischaemic cardiomyopathy. The work initially focused on the physiological impact of revascularisation on the myocardium, especially its impact on myocardial blood flow (MBF). In a proof-of-concept analysis we show that coronary artery bypass surgery often results in only partial myocardial revascularisation and that the aetiology of this is multifactorial. Subsequent technical work assessed the impact of arterial delay
on MBF estimation in patients with coronary artery grafts, providing further validation of the technique in this specific disease model. Although the work carried out was in the context of a particular perfusion sequence, the impact of arterial contrast delay on MBF estimation is likely to be applicable to a range of different perfusion techniques that are based on first pass perfusion imaging. Following this, the prognostic role of MBF was confirmed in patients with prior CABG - the first study across all imaging modalities to demonstrate this. The impact of this work is two-fold: a) it demonstrates for the first time that MBF is a strong determinant of outcomes in patients after CABG surgery, providing indirect evidence of a possible beneficial impact of complete revascularisation in this patient population; b) it adds to a growing body of evidence regarding the feasibility and prognostic value of MBF indices across a range of disease models, providing additional support for the adoption of quantitative perfusion assessment in clinical workflows Figure 8-1.

Finally, a novel, entirely automated method of pulmonary transit time estimation was developed and tested in a large cohort of patients, demonstrating an independent prognostic effect beyond established clinical and imaging biomarkers. Its utility in different heart failure models remains to be explored, potentially serving as a novel imaging biomarker of cardiopulmonary physiology. The method deployed to develop this tool was based on an existing framework of a quantitative perfusion sequence already in use in multiple CMR units worldwide. This enables measurement of PTT within clinical workflows using existing infrastructure, thereby allowing almost instantaneous dissemination of this imaging biomarker, offering the opportunity for multi-center validation and evaluation in other disease models.
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Visual abstract A - (Chapter 4)

In this proof-of-concept analysis, patients with impaired LV function undergoing CABG surgery had a significant improvement in functional status at 197 days, as assessed with a 6-minute walk test and patient-reported symptoms. CABG surgery resulted in only partial revascularisation of the myocardium based on an anatomical definition of revascularisation at follow up CT coronary angiography. When myocardial segments were successfully revascularised using coronary grafts conduits, there was significant improvement of segmental stress myocardial blood flow (MBF) and perfusion reserve (MPR) (EQ-VAS: European Quality of Life – Visual analogue score; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction).
Among 38 patients with angiographically confirmed patent LIMA grafts and no evidence of myocardial infarction, 71% (27/38) of patients had inducible perfusion defects within the LIMA-LAD myocardial territories. Presence of native LAD chronic total occlusion (CTO) was the main determinant of MBF in this territory, having a greater impact in basal compared to apical segments. Arterial contrast delay through LIMA grafts had minimal impact on absolute MBF (Adapted from Seraphim et al, JCMR 2021).
Visual abstract C – (Chapter 6)

Quantitative myocardial perfusion predicts outcomes in patients with prior surgical revascularization. Event-free survival curve for death and major adverse cardiovascular events (non-fatal myocardial infarction and unplanned revascularization) according to stress myocardial blood flow. This effect is independent to the presence of previous infarction and the presence of regional ischaemia during stress on visual assessment (Reproduced with permission from Seraphim et al. J Am Coll Cardiol. 2022 Mar 29;79(12):1141-1151)
Visual abstract D – (Chapter 7)

Dynamic first pass perfusion imaging of a basal short axis slice showing the RV and LV cavities (t; seconds). Blood pool detection performed automatically allowing estimation of gadolinium time-concentration curves in the RV and LV cavities. The dashed lines indicate the location of the centroid in each cavity and the difference (i.e. the pulmonary transit time) between each centroid is indicated by the arrow. Kaplan Meier curves (with log-rank tests) showing event-free survival for major adverse cardiovascular events (Adapted from Seraphim et al. JACC Cardiovasc Imaging. 2021 Nov;14(11):2107-2119.)
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Abbreviations

6MWT: 6-Minute-Walk Test
ACE-I: Angiotensin-Converting-Enzyme Inhibitor
AF: Atrial Fibrillation
AHA: American Heart Association
AIF: Arterial Input Function
ARB: Angiotensin-Receptor Blocker
BMI: Body Mass Index
BSA: Body Surface Area
BTEX: Blood Tissue Exchange
CABG: Coronary Artery Bypass Graft
CHD: Coronary Arterial Disease
CMR: Cardiovascular Magnetic Resonance
CNN: Convolutional Neural Network
CTCA: Computed Tomography Coronary Angiography
CTO: Chronic Total Occlusion
ECM: Extracellular Matrix
ECV: Extracellular Volume Fraction
eGFR: Estimated Glomerular Filtration Rate
EDVi: End-Diastolic Volume Index
ESVi: End-Systolic Volume Index
EuroScore II: European System for Cardiac Operative Risk Evaluation II
FWHM: Full-Width Half Maximum
HCT: Haematocrit
ICD: Implantable Cardioverter Defibrillator
LAD: Left Anterior Descending
LIMA: Left Internal Mammary Artery
LGE: Late Gadolinium Enhancement
LVEF: Left Ventricular Ejection Fraction
MACE: Major Adverse Cardiovascular Events
MBF: Myocardial Blood Flow
MOLLI: Modified Look-Locker Inversion
MPR: Myocardial Perfusion Reserve
PAWP: Pulmonary Artery Wedge Pressure
PBV: Pulmonary Blood Volume
PCI: Percutaneous Coronary Intervention
PET: Positron Emission Tomography
PTT: Pulmonary Transit Time
PTTn: Pulmonary Transit Time normalised for heart rate
TA: Arterial Time Delay
Chapter 1 Introduction

1.1 Definition and epidemiology of ischaemic cardiomyopathy

Coronary artery disease is a dynamic process associated with a spectrum of pathological manifestations that range from acute to chronic coronary syndromes (1). According to the World Health Organisation, coronary heart disease (CHD) was the commonest cause of death worldwide in 2019, responsible for 16% of the world’s total deaths (2). In the UK, despite dramatic reductions in mortality over the past decades, CHD remains one of the leading causes of death, responsible for approximately 1 death every 8 minutes (3).

Large or recurrent ischaemic insults to the myocardium ultimately result in the development of left ventricular dysfunction and the syndrome of heart failure. Coronary artery disease is the commonest cause of heart failure (HF) (4,5), and despite geographic variations among population studies (6), 50-70% of all heart failure cases can be attributed to coronary artery disease (7,8). Partly driven by improvement in survival following acute coronary syndromes (9), the prevalence of heart failure as a consequence of coronary artery disease has steadily increased in recent decades (10), resulting in a shift from traditional causes such as hypertension and valvular heart disease (11). Together, these conditions are responsible for an enormous societal and financial burden across all healthcare systems (12). In the UK, heart failure related hospitalisations account for 2% of all hospital stays, and represent the most common cause for admission in people over 65 years, with its associated cost approaching 2% of the entire NHS budget (13). At the same time, despite a reduction in the age-adjusted incidence of HF in developed countries, the overall prevalence is increasing, with more than 8
million people expected to be living with heart failure in the United States by 2030 (14). Importantly, a number of studies of patients with heart failure suggest that those with underlying coronary artery disease have worse long-term outcomes compared to other aetiologies (11,15).

Despite the scale of the problem, our ability to intervene on the natural history of heart failure caused by coronary disease, often described as ischaemic cardiomyopathy, is limited. Although heart failure in the context of coronary artery disease has been the focus of extensive research spanning several decades, its description as a distinct disease entity is inconsistent. In the clinical setting, the term ischaemic cardiomyopathy is invariably used to describe the presence of left ventricular (LV) dysfunction that is primarily driven by ischaemic myocardial damage caused by coronary artery disease, a clinical situation that is both exceptionally common and universally accepted as being associated with substantial morbidity and mortality (16). Although this simple description has merits, both in terms of informing treatment strategies and patient risk stratification, it fails to capture the biological complexity of the spectrum of pathophysiological processes it defines. Indeed, the term ischaemic cardiomyopathy describes a spectrum of pathophysiological states, that range from myocardial stunning, to hibernation and to variable degrees of myocardial scarring (17). Despite attempts of providing a more detailed definition based on the severity of underlying coronary disease (18) particularly in the context of clinical research, the term ischaemic cardiomyopathy has either not been incorporated in formal classification systems of cardiomyopathies (19,20), or has been differently defined (21). The term however continues to be used both
clinically and in recent European Society of Cardiology (ESC) clinical practice
guidelines (22) and consensus statements (23). Irrespective of the definition
used, myocardial damage driven by coronary artery disease is a common clinical
scenario, that despite advances in the diagnostic and therapeutic options for both
coronary artery disease and heart failure, these disease processes continue to
pose major challenges, with significant rates of mortality reported even in
contemporary studies using optimal medical therapy (24).

1.2 The role of myocardial revascularisation

A number of randomized controlled trials spanning a period of more than 50 years
(25) have assessed the role of myocardial revascularisation either with coronary
artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI)
in the context of stable coronary artery disease (26–33). Despite this, the rational
for revascularisation appears to have evolved over time and in some aspects
remains unclear. The potential clinical benefit derived from myocardial
revascularisation appears to be largely dependent on individual patient
parameters, such as the anatomical distribution of coronary disease, existing
myocardial injury and left ventricular (LV) function, co-morbidities and the method
of revascularisation offered (34).

1.2.1 Myocardial revascularisation in patients with normal LV function

Most evidence on the role of myocardial revascularisation in stable coronary
artery disease is derived from patients with normal, or “preserved” LV function.
A plethora of studies have compared PCI, CABG and medical therapy in terms
of their impact on clinical outcomes. Extracting a clear message from these trials
however has not been straightforward and at times conflicting. Beyond this, over the past decades there has been a rapid evolution and optimisation of both medical therapy and revascularisation techniques, which complicates the extrapolation of original study findings into contemporary clinical practice. Despite this, it is widely accepted that the aim of myocardial revascularisation irrespective of the method deployed is the improvement of symptoms (mainly angina) (35–38) and in some cases to improve prognosis (Figure 1-1) (39).

Figure 1-1 Indications for myocardial revascularisation in stable coronary artery disease.


Revascularisation with PCI, independent of the type of stent used, has so far failed to demonstrate a clear mortality benefit within the context of a single randomized controlled trial, even among those with substantial ischaemia (33,40,41). The lack of an obvious survival benefit with PCI has therefore shifted the focus towards the role of this technique for symptom relief. However, even the widely accepted idea that revascularisation with PCI improves symptoms beyond medical therapy was further questioned by the results of the ORBITA study (42), the only trial in this field using a placebo intervention with double-blinded design. Interestingly, these findings are in contrast to the prognostic impact of PCI observed in the context of acute coronary syndrome (41), given the both disease models share similar underlying pathophysiology.
Coronary artery bypass graft (CABG) surgery predates the advent of PCI, and in some aspects remains the cornerstone of myocardial revascularisation. Evidence for a prognostic role of CABG surgery beyond that achieved with medical therapy is slightly more clear, and is mainly derived from meta-analysis of randomized controlled trials (43). These studies demonstrated an overall prognostic benefit of surgery, particularly in the context of left mainstem (44) and multivessel disease (45), and in patients with diabetes (46). Nevertheless, the vast majority of data originates from studies performed several decades ago (Table 1-1), resulting in substantial differences in patient characteristics and definitions of optimal medical therapy compared to contemporary medical practice. Both the outcomes of CABG surgery and the standards of medical therapy have significantly improved over the past 40 years. For example, in the Veterans Administration Cooperative Study where surgery was performed between 1972 to 1974, the 30-day operative mortality post CABG was 5.8% (27), whereas according to data from the UK National Adult Cardiac Surgery Audit, the in-hospital mortality for non-emergency CABG between the year 2017-2018 was 0.99% (47). Similarly, pharmacological therapies in the form of statins and aspirin (48,49) that have demonstrated a clear impact on clinical outcomes in these patients were not widely adopted at the time of these original landmark trials. Despite this, a more recent network meta-analysis suggested that CABG is associated with a survival benefit and reduced risk of myocardial infarction compared to medical therapy (32), and when data was restricted to more contemporary studies (ie studies initiated in 1999 or later), the findings were not significantly altered.
Both PCI and CABG are well established methods of revascularisation. An extensive body of work has focused on evaluating differences in clinical outcomes between the two methods in the various groups of patients with difference disease distribution (50,51) and comorbidities (52). Importantly however, it is possible that the mechanisms by which PCI and CABG can potentially alter clinical outcomes, symptoms and cardiac function may substantially differ (53). In the latest 2021 American College of Cardiology guidelines, revascularisation for prognosis is recommended in the setting of left mainstem or multivessel coronary disease with higher level of evidence attached to the use of CABG compared to PCI (54). In clinical practice, the decision on the method of revascularisation is often made in the context of a “Heart team” and depends on a number of clinical, anatomical and technical characteristics (1), as well as patient preferences.

1.2.2  Myocardial revascularisation in patients with impaired LV function

Pharmacological therapy is the cornerstone of treatment of patients with left ventricular dysfunction (LVD) irrespective of the underlying aetiology (including epicardial coronary artery disease) (55). However, beyond the introduction of only a few novel agents such as the angiotensin receptor–neprilysin inhibitors (56) and the emerging evidence surrounding inhibitors of sodium–glucose cotransporter 2 (SGLT2) (57,58) pharmacological therapies specific to the management of LV dysfunction remained largely unchanged over the past 30 years. Unlike other medical fields such as oncology, the development of pharmacological disease-modifying agents acting directly on the underlying
myocardial pathology has been slow, with currently no licensed agents available to directly modify key pathological processes such as myocardial fibrosis.

Evidence on the role of revascularisation in patients with ischaemic cardiomyopathy is limited and often conflicting, reflecting both the biological complexity and heterogeneity among individuals, as well as the challenges in designing appropriate studies to evaluate this. The original evidence supporting the use of revascularisation in patients with impaired LV function in the form of CABG surgery - theoretically the gold standard method for ‘complete’ revascularisation - mainly comes from subgroup analysis of studies performed more than 4 decades ago (59–61). Patients with impaired LV systolic function were largely excluded or under-represented from the original randomized controlled studies comparing the effectiveness of surgical revascularisation versus medical therapy (26,28).

Despite differences in study design and patient populations recruited, these original studies (Table 1-1), pointed towards the possibility of a surgical benefit among patients deemed to be at high risk, including those with LV impairment. These landmark trials were further supported by a number of observational studies (62–64), and together informed societal guidelines and clinical practice for decades.
<table>
<thead>
<tr>
<th>Study name</th>
<th>Years of recruitment</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>LVEF cut off</th>
<th>Follow-up time (years)</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterans Administration Cooperative Study</td>
<td>1972-76</td>
<td>1984</td>
<td>686</td>
<td>LVEF &gt;25-30%</td>
<td>11.2</td>
<td>No survival benefit from CABG at 11 years</td>
</tr>
<tr>
<td>European Coronary Surgery Study</td>
<td>1973-76</td>
<td>1988</td>
<td>767</td>
<td>LVEF &gt;50%</td>
<td>12</td>
<td>Survival benefit from CABG at 12 years</td>
</tr>
<tr>
<td>Coronary Artery Surgery Study (CASS)</td>
<td>1975-79</td>
<td>1983</td>
<td>780</td>
<td>LVEF &gt;35%</td>
<td>5</td>
<td>Surgery can be safely deferred if medical therapy controls symptoms</td>
</tr>
</tbody>
</table>

Patients with impaired LV function were excluded or under-represented in these studies, with only 4% of participants having symptomatic heart failure (60).
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year of publication</th>
<th>Summary Recommendation for CABG in patients with LV impairment</th>
<th>Class/ Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESC/HFA Heart</td>
<td>2021</td>
<td>May be considered to improve outcome in patients with Heart failure and reduced LVEF (≤40%)</td>
<td>IIb/C</td>
</tr>
<tr>
<td>ESC Revascularisation</td>
<td>2018</td>
<td>Revascularisation recommended in patients with severe LV systolic dysfunction</td>
<td>1/B</td>
</tr>
<tr>
<td>ACC/AHA/SCAI revascularisation</td>
<td>2021</td>
<td>In patients with LVEF &lt;35% CABG is recommended to improve survival</td>
<td>1/B</td>
</tr>
<tr>
<td>ACC/AHA/SCAI revascularisation</td>
<td>2021</td>
<td>In patients with LVEF 35-50% CABG is reasonable to improve survival</td>
<td>IIa/B</td>
</tr>
</tbody>
</table>

ESC- European Society of Cardiology; HFA – Heart failure Association; ACCF – American College of Cardiology Foundation; ACC – American College of Cardiology; SCAI - Society for Cardiovascular Angiography and Interventions
More recently, the Surgical Treatment for Ischaemic Heart Failure (STICH) trial, the largest randomized trial that specifically evaluated the role of revascularisation in patients with ischaemic cardiomyopathy attempted to address the gap in the available evidence (65). The study randomized 1212 patients with LVEF <35% to either surgical revascularisation or medical therapy and showed that at 56 months, there was no significant difference between medical therapy and CABG with respect to all-cause mortality (65). The STICH extension study subsequently evaluated the 10-year effects of CABG in the same cohort and demonstrated a survival benefit associated with surgical revascularisation, in terms of both cardiovascular and all-cause mortality (29). To date, the STICH trial remains the only completed randomized controlled study that specifically addressed the impact of surgery in patients with impaired ventricles. Similar lack of data exists in the context of percutaneous coronary intervention (PCI). The recently published REVIVED-BCIS has shown no benefit of revascularisation by PCI over medical therapy in terms of the incidence of death and hospitalisation for heart failure among patients with ischaemic left ventricular dysfunction (24), casting more doubts as to the role of revascularisation in this patient group.

Clinical decisions regarding the optimal method of revascularisation in patients with multi-vessel coronary artery disease and LV dysfunction remain a challenge. In the original randomized trials comparing PCI to CABG, patients with significant LV impairment were again under-represented. In the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, less than 5% of patients had evidence of heart failure (66), whereas in the
Freedom (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (52), patients with reduced LVEF only comprised a small subgroup of 32 patients. As a result, the evidence informing clinical guidelines is therefore extrapolated from these key trials, or is derived from observational data. For example, in one of the largest retrospective studies including 12113 patients with reduced left ventricular ejection fraction, Sun et al recently reported that patients who received PCI had higher rates of mortality and major adverse events compared to those undergoing CABG (67). Similar data have been reported from recent meta-analyses of predominantly observational studies, demonstrating a significantly improved survival with CABG surgery over PCI (68,69).

It is therefore not surprising that the current societal guidelines are not uniform in their recommendations regarding revascularisation for patients with co-existing coronary artery disease and LV systolic dysfunction, with different levels of evidence attached to their recommendations. In the 2018 ESC/EACTS guidelines on myocardial revascularisation (1), revascularisation is recommended in patients with impaired LV function (LVEF <35%) (Class 1, Level of evidence A) with CABG recommended “as the first revascularization strategy choice in patients with multivessel disease and acceptable surgical risk” (Class I, Level of evidence B). In the recent ESC 2021 Heart failure guidelines, revascularisation may be considered (Class IIb, C) to improve outcomes in patients with HFrEF (Heart failure and reduced ejection fraction) if coronary anatomy suitable (eg proximal stenosis >90% of large vessel, left main or proximal LAD (70). In the more recent ACC/AHA guidelines on coronary revascularisation (2021) CABG is
recommended for patients with LVEF <35% to improve survival (Class I, Level of evidence B), whereas it is a “reasonable” option for patients with LVEF 35%-50% (IIa/B) (54).

Despite research spanning several decades, the management of ischaemic cardiomyopathy therefore remains a challenge. Patients with low LVEF have been shown to have a higher risk of peri-operative mortality and morbidity both in old and contemporary studies (71–73). These patients have a higher risk of low cardiac output syndrome requiring prolonged inotropic or post-operative mechanical support (73,74) and a higher incidence of post-operative complications such as acute renal failure (75), atrial fibrillation and stroke (73). Indeed, pre-operative LVEF remains a one of the key clinical predictors determining both mortality and major adverse cardiovascular events in the recently developed Syntax II 2020 score (76).

Improved understanding of the pathophysiology of this disease, as well as accurate evaluation of the treatments offered, including the impact of revascularisation itself, is therefore needed. Improved patient characterisation and phenotyping can potentially assist in patient selection and risk stratification, both key paths to improving clinical outcomes. Novel quantitative methods of cardiac evaluation using CMR may therefore have a role in integrating anatomical, functional, perfusion and tissue characterisation information, ultimately moving towards the delivery of more personalised patient care.
1.3 Pathophysiological concepts in patients with heart failure and coronary artery disease

Our understanding of ischaemic cardiomyopathy is focused on distinct pathological processes affecting two different cardiac compartments: the coronary circulation and the myocardium. Although inter-linked, the treatment strategies deployed to manage these processes are different, and are ultimately based on traditional pathophysiological concepts such as ischaemia and viability. These concepts simplify not only the biological variability between individuals, but also the convoluted processes taking place at molecular, cellular, macro- and micro-circulation levels by defining them in a binary fashion (e.g. by describing viability as present or absent), and have remained largely unchallenged over the past century. Our understanding of these processes, and our willingness to adapt our practice has to some degree remained resistant to new information potentially made available by new technologies, particularly within the field of cardiac imaging. Importantly, these concepts continue to guide the efforts for novel therapy development and clinical decision-making in modern clinical practice (1).

Technological advances in the field of cardiac imaging both in terms of imaging quality and automation, enable the non-invasive evaluation of viability and ischaemia quantitatively and at scale, providing new insights into pathophysiological processes (77–79) as well as providing new methods of patient risk stratification (80,81). A number of these tools were not available at the time when key landmark clinical studies evaluating treatment strategies in patients with ischaemic cardiomyopathy were performed, which renders their potential clinical impact unclear (82). A review of the fundamental principles of the biological processes these novel tools are meant to evaluate is therefore
warranted, so that both the capabilities and limitations of new technology can be appreciated.

1.3.1 Coronary circulation and myocardial blood flow

Under basal resting conditions, myocytes are able to maintain a high level of oxygen extraction (83), a property which is unique to cardiac tissue. As a result, any increase in myocardial oxygen demand has to be met through an increase in coronary blood flow which is itself dependent on a dynamic interaction between large epicardial conductance vessels (>400μm) and a network of small vessels, ranging from <100μm to 400μm which offer the greatest resistance to flow (84) (Figure 1-2).
Figure 1-2 The coronary circulation

Left: Post-mortem cast of the coronary circulation demonstrating the abundance of the coronary microcirculatory network which is not visible at angiography.
Right: Representation of the functional subdivision of the coronary arterial system in conductive vessels, pre-arterioles and arterioles demonstrating their differential effects on pressure and their relative responsiveness. Adapted from the ESC Textbook of Cardiovascular Medicine (61).

The balance between the driving pressure from the epicardial coronary arteries, itself primarily governed by diastolic pressure, and the vascular resistance mediated almost entirely by small coronary resistance arteries (pre-arteriolar and arteriolar vessels) are the key haemodynamic parameters that determine myocardial blood flow (MBF) (85) (Figure 1-2). These are maintained in a state of autoregulation during conditions of rest (86). Induction of maximal vasodilatation with the use of pharmacological stress agents such as adenosine (87) and dipyridamole (88) reduces this microvascular resistance, essentially disrupting myocardial blood flow autoregulation by eliminating active vasomotor tone and unmasking haemodynamically significant epicardial coronary stenoses.
Vascular tone is therefore a key principle that governs coronary resistance and coronary flow and indeed forms the basis of both invasive and non-invasive tests for evaluation of indices of coronary and myocardial blood flow. However, it is worth appreciating that additional intrinsic properties of the coronary circulation have significant impact on myocardial blood flow. Although the coronary circulation is often presented as a static vascular network, the entire coronary tree including the large epicardial coronaries as well as the microcirculation display a degree of functional and structural plasticity (89). This involves adaptations of the microcirculation such as the process of capillary rarefaction (90) as well as changes within the entire coronary circulation, such as arteriogenesis; the development of coronary collaterals (91). Importantly, the extent of this remodelling becomes particularly relevant in the context of ischaemic cardiomyopathy, as it not only affects the natural history of the disease (92,93), but impacts on the diagnostic performance of both invasive and non-invasive tests for evaluation of ischaemia.

Patients with ischaemic cardiomyopathy represent the severe form of the disease spectrum and often suffer not only from multi-vessel epicardial coronary disease but also have abnormalities of the myocardium. Even within the normal myocardium there is significant heterogeneity in myocardial blood flow distribution (94) resulting from both vascular and metabolic variations between myocardial territories (95). In the context of ischaemic cardiomyopathy, metabolic variations between stunned, hibernating (96) or infarcted myocardium can result in significant variations in MBF making evaluation of epicardial coronary disease challenging. Similarly, the role of microvascular coronary disease in these
patients is unclear. Microvascular dysfunction is initiated by the same cardiovascular risk factors that are responsible for epicardial coronary disease (97), and is therefore bound to be present in these patients.

Therefore, there are specific biological considerations which further complicate ischaemia testing in this patient population (Figure 1-3). Quantitative methods of blood flow evaluation can perhaps offer incremental value in the evaluation of ischaemia especially in this context, but interpretation of MBF can only be done once these additional anatomical and myocardial pathophysiological processes are taken into account.

Figure 1-3 Myocardial blood flow in ischaemic cardiomyopathy
Conceptual model of pathophysiological processes that determine myocardial blood flow in patients with ischaemic cardiomyopathy (RAAS: renin-angiotensin-aldosterone system).
1.3.2 Non-invasive quantification of myocardial blood flow

The “ischaemic cascade”, first described by Nesto and Kowalchuk (98) (Figure 1.2), formed the basis of non-invasive ischaemia testing and although it provides a simple conceptual description of “ischaemia” stages at different levels of severity, it does not necessarily apply to a contemporary methods of ischaemia evaluation (99). In fact, a number of tests used for the detection of haemodynamically significant coronary artery disease depend on the visualisation of relative myocardial perfusion defects during exercise or during pharmacologically induced hyperaemia. These methods, increasingly allow the estimation of quantitative indices of myocardial blood flow (MBF), which do not necessarily aim to visualise any aspect of the ischaemic cascade, but potentially encode information not only on the status of epicardial coronary disease, but of general coronary vascular health.

Figure 1-4 The ischaemic cascade
Quantification of indices of myocardial blood flow has historically been performed using nuclear imaging, but technical developments in terms of temporal and spatial resolution have enabled this to be performed essentially across all imaging modalities (100–102). The fundamental principle of myocardial perfusion imaging is the acquisition of a dynamic series of images during the passage of intravenous contrast through the heart. Subsequent tracer kinetic modelling allows the estimation of absolute myocardial blood flow (MBF) (99). Absolute myocardial blood flow (MBF) normalised to distal myocardial mass, expressed in ml/g/min, and myocardial or coronary flow reserve (MPR), the ratio of maximal stress flow to rest flow for a given arterial distribution (103) are the main non-invasive parameters used. However, understanding the physiological origins of these indices, and their association with fractional flow reserve (FFR) are fundamental for their clinical application (104).

Fractional flow reserve (FFR) is a pressure-based estimate that is considered the gold-standard invasive method for defining stenosis-specific ischaemia (31,105,106). A number of randomized control studies (31,105,106) and data from meta-analysis (107) have demonstrated a link between patient outcomes and the severity of coronary artery disease evaluated with FFR, securing its position in routine clinical practice and guidelines. FFR is defined as the ratio of maximal myocardial blood flow in the presence of a stenosis, over maximal blood flow if that artery were to be unobstructed (108). Given that FFR is a measure of pressure, its use is based on the principle that a direct relation between coronary pressure and flow exists under conditions of maximal vasodilatation.
Appreciating the physiological relationship between stress MBF, MPR and FFR is important for acknowledging the limitations of these parameters, when it comes to the detection of ischaemia. Indeed, although a relation between FFR, MPR and stress MBF exists, these are fundamentally very different physiological measures. What is known is that a non-linear relationship between MPR or CFR (coronary flow reserve) and FFR exists, particularly in the presence of stenosis, and that any discordance between FFR (pressure-estimate) and MPR (flow-estimate) is likely a reflection of coronary pathophysiology (109) (Figure 1-5). In essence, the relationship between FFR and MPR is thought to be dependent on the relative contributions of focal, diffuse and microvascular disease (107). Unlike FFR, the use of MPR confers an additional advantage; a physiological description of myocardial blood flow that is reflective of both microvascular and macrovascular (epicardial) vessel status. It is therefore not surprising that recent data of quantitative myocardial perfusion using CMR and PET have shown that both stress MBF (110) and MPR (111) not only serve as markers of haemodynamically significant epicardial coronary artery disease but also closely correlate with invasive markers of microvascular dysfunction.
Figure 1-5 Coronary pressure - flow relationship

A: In the absence of stenosis there is a linear relationship between pressure: flow at maximal vasodilatation; In the presence of stenosis the relationship is non-linear because stenosis resistance becomes flow dependent. Adapted from Kern et al. Circulation; 2006. B: Conceptual Plot demonstrating the relationship of CFR and Fractional Flow Reserve based on the relative contribution of focal and diffuse epicardial and microvascular disease. Reproduced from Johnson et al; JACC CVI; 2012 (112) with permission from Elsevier

When it comes to the specific detection of epicardial vessel disease, absolute cut offs for MBF and MPR are however difficult to establish, as absolute MBF measured non-invasively is largely method-dependent (99). Despite this, non-invasive quantitative indices of myocardial blood flow have gained increased attention over the past few years, particularly since their automation and in-line derivation during routine scanning allowed them to be evaluated at scale (80,113,114). Indeed, although absolute cut offs for defining significant epicardial coronary artery disease may vary, the improved spatial resolution of imaging tools deriving quantitative MBF opens up the opportunity to evaluate myocardial perfusion at an unprecedented detail and scale, providing insights into the pathogenesis and natural history of ischaemic cardiomyopathy.

1.3.3 Non-invasive detection of myocardial ischaemia – a brief review of the evidence

Myocardial ischaemia is caused by an imbalance in myocardial delivery and consumption of oxygen, which triggers a cascade of events that if not reversed in a timely manner will result in myocyte necrosis (115). This notion has been the driving force for the expansion and widespread use of immediate or early
revascularisation in acute coronary syndromes primarily through primary percutaneous intervention (PCI), resulting in a dramatic improvement in patient outcomes over the past decades (116). However, the clinical benefit from identification of ischaemia in the setting of chronic coronary syndromes, particularly in patients with ischaemic cardiomyopathy is less clear. Despite this, it continues to be routinely evaluated primarily for risk stratification and for guiding revascularisation decisions (1).

Ischaemia is a well-defined pathophysiological process, and its detection should encode some form of prognostic information – this is conceptually sensible and biologically plausible. In fact this is supported by a large body of observational data across all imaging modalities, including nuclear (117–120), echocardiography (121–124), computed tomography (CT)(125) and cardiac magnetic resonance imaging (CMR) (80,113,126–128). A limited number of studies focused on the role of ischaemia evaluation in the context of ischaemic cardiomyopathy, however these have produced conflicting results (129–133) Table 1-3.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Modality</th>
<th>Number of patients</th>
<th>LVEF cut off</th>
<th>Follow up (years)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ge et al</td>
<td>2020</td>
<td>CMR</td>
<td>582</td>
<td>&lt;50%</td>
<td>5 years</td>
<td>Presence of ischaemia on stress CMR associated with cardiovascular death or non-fatal MI</td>
</tr>
<tr>
<td>Majmudar et al</td>
<td>2015</td>
<td>PET</td>
<td>510</td>
<td>&lt;45%</td>
<td>0.7</td>
<td>Low CFR associated with cardiac death, heart failure hospitalisation, late revascularisation, aborted sudden cardiac death</td>
</tr>
<tr>
<td>Panza et al</td>
<td>2013</td>
<td>SPECT</td>
<td>399</td>
<td>≤35%</td>
<td>4.7</td>
<td>Ischaemia detection did not predict prognosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Echo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husser et al</td>
<td>2014</td>
<td>CMR</td>
<td>391</td>
<td>&lt;45%</td>
<td>2</td>
<td>Ischaemia was the strongest predictor of outcomes</td>
</tr>
<tr>
<td>Pasquet et al</td>
<td>1999</td>
<td>SPECT</td>
<td>137</td>
<td>*35%</td>
<td>2.8</td>
<td>Ischaemia predicts outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Echo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CMR – cardiac magnetic resonance imaging; PET – positron emission tomography; SPECT – single photon emission computed tomography; LVEF – left ventricular ejection fraction; CFR – coronary flow reserve; MI – myocardial infarction

*Mean value provided only
Few studies evaluated the role of ischaemia in the context of a randomised controlled trial setting, and the evidence that its detection alters patient outcomes is conflicting. Data from the nuclear sub-study of the COURAGE trial, suggested that reduction of residual stress-induced ischaemia from >10% to <5% was associated with a trend for reduction in the risk of death and myocardial infarction (30), implying that identification and subsequent reduction of ischaemia is beneficial. In contrast, the ischaemic burden of patients participating in the BARI 2D trial, which was primarily designed to compare the role of revascularisation versus optimal medical therapy among patients with diabetes, did not impact on prognosis, especially in patients with a large infarct burden (134). Although the change in ischaemia burden was not available, the results casted doubts on the role of ischaemia testing particularly in patients with evidence of a significant degree of myocardial damage. Targeted revascularisation based on fractional flow reserve (FFR), the gold standard method for physiological evaluation of ischaemia-inducing coronary stenosis (135), was deployed in the FAME-2 study (136). Although the study demonstrated superiority of FFR-guided revascularisation over medical therapy alone, the difference in events was driven by the need for urgent revascularisation, with no difference in mortality between the groups. Similarly, a sub-study of the STICH trial (131) the presence of ischaemia did not predict outcomes, nor it identify patients that would benefit from revascularisation. More recently, the ISCHEMIA study (33) suggested that among patients with stable coronary artery disease, detection of moderate to severe ischaemia using non-invasive testing and the presumed rectification following revascularisation did not translate into a survival benefit compared to
medical therapy. It is worth noting however that in the ISCHEMIA study, patients with reduced left ventricular ejection fraction (LVEF <35%) were excluded.

Despite the available evidence, detection of ischaemia in the context of chronic coronary artery continues to be performed using a range of non-invasive imaging tests, and represents a large proportion of cardiac investigations and resulting in significant healthcare costs (137). Both the National Institute of Clinical Excellence (NICE) (138) and European Society of Cardiology guidelines (139) advocate the use of a non-invasive functional testing for evaluation of patients with known coronary artery disease, including those with previous revascularisation.

Greater uncertainty exists as to the role of ischaemia testing in patients with prior surgical revascularisation, particularly given the additional technical challenges associated with ischaemia testing in patients with prior coronary artery bypass graft (CABG) surgery. A number of studies across the entire spectrum of imaging modalities suggested that detection of ischaemia post CABG carries prognostic power, suggesting that evaluation of ischaemia in this group of patients may be clinically important for both risk stratification and for potentially guiding decisions regarding further revascularisation. Historical data using exercise testing suggested that the presence of residual ischaemia post CABG is associated with increased risk of mortality, even among asymptomatic patients (140). A number of non-invasive imaging studies subsequently evaluated the prognostic effect of ischaemia testing, with the majority demonstrating prognostic power Table 1-4
Despite including a large number of patients, collective interpretation of these studies is made difficult by significant study design heterogeneity (141), including differences in stress agents, use of optimal medical therapy, abnormal test definitions and primary end points. Furthermore, very few studies have used advanced imaging techniques (142), including newly developed methods of quantitative myocardial perfusion evaluation which have already demonstrated incremental prognostic utility in patients without prior CABG (80,114,143,144)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year*</th>
<th>Study design</th>
<th>Imaging modality</th>
<th>Stressor</th>
<th>Number of patients</th>
<th>Male (%)</th>
<th>Follow up (months)</th>
<th>Study result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortigiani et al (142)</td>
<td>2019</td>
<td>Observational, multicentre</td>
<td>Stress echo</td>
<td>Dipyridamole</td>
<td>349</td>
<td>77</td>
<td>22</td>
<td>Ischaemia associated with prognosis. CFVR of LAD ≤2 associated with HR 2.28</td>
</tr>
<tr>
<td>Harb et al (145)</td>
<td>2012</td>
<td>Observational, single centre</td>
<td>Stress echo</td>
<td>Exercise</td>
<td>962</td>
<td>88</td>
<td>69</td>
<td>Ischaemia predicted mortality (HR 2.10)</td>
</tr>
<tr>
<td>Cortigiani et al (146)</td>
<td>2010</td>
<td>Observational, single centre</td>
<td>Stress Echo</td>
<td>Dobutamine Exercise Dipyridamole</td>
<td>500</td>
<td>80</td>
<td>25</td>
<td>Peak wall motion score index predicted mortality and MI (HR 3.07)</td>
</tr>
<tr>
<td>Arruda et al (147)</td>
<td>2001</td>
<td>Observational, single centre</td>
<td>Stress Echo</td>
<td>Exercise</td>
<td>718</td>
<td>82</td>
<td>35</td>
<td>18% reduction in hazard for every 10% incremental increase in exercise LVEF</td>
</tr>
<tr>
<td>Ortiz et al (148)</td>
<td>2018</td>
<td>Observational, single centre</td>
<td>SPECT Exercise Adenosine</td>
<td>84</td>
<td>100</td>
<td>119</td>
<td></td>
<td>Defect size 1year following CABG, predicted death and CHF</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Design</td>
<td>Imaging Modality</td>
<td>Isotope</td>
<td>n</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>------------------------</td>
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<td>-----</td>
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<td>-------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Acampa et al (149)</td>
<td>2008</td>
<td>Observational, single centre</td>
<td>SPECT</td>
<td>Dipyridamole, Exercise</td>
<td>362</td>
<td>90%</td>
<td>26%</td>
<td>SPECT performed 5 years after CABG predicted death and MI (HR 3.7).</td>
</tr>
<tr>
<td>Sarda et al (150)</td>
<td>2001</td>
<td>Observational, single centre</td>
<td>SPECT</td>
<td>Dipyridamole, Exercise</td>
<td>115</td>
<td>90%</td>
<td>35%</td>
<td>Extent of stress defect predicted cardiac death and MI</td>
</tr>
<tr>
<td>Shapira et al (151)*</td>
<td>2001</td>
<td>Observational, single centre</td>
<td>SPECT</td>
<td>- , Exercise</td>
<td>170</td>
<td>-</td>
<td>48%</td>
<td>SPECT performed soon after CABG has prognostic value</td>
</tr>
<tr>
<td>Palmas et al (152)</td>
<td>1995</td>
<td>Observational, single centre</td>
<td>SPECT</td>
<td>Exercise</td>
<td>294</td>
<td>86%</td>
<td>31%</td>
<td>Incremental prognostic information provided by SPECT</td>
</tr>
<tr>
<td>Miller et al (152)</td>
<td>1998</td>
<td>Observational, single centre</td>
<td>SPECT</td>
<td>Exercise</td>
<td>411</td>
<td>80%</td>
<td>70%</td>
<td>Exercise T1-201 imaging performed within 2 years of CABG predicts outcomes</td>
</tr>
<tr>
<td>Lauer et al (153,154)</td>
<td>1998</td>
<td>Observational, single centre</td>
<td>SPECT</td>
<td>Exercise</td>
<td>873</td>
<td>91%</td>
<td>36%</td>
<td>Exercise capacity and perfusion defects predict death (HR 2.78) in asymptomatic patients</td>
</tr>
<tr>
<td>Zellweger et al (155)</td>
<td>2001</td>
<td>Observational, single centre</td>
<td>SPECT</td>
<td>Adenosine, Exercise</td>
<td>1765</td>
<td>80%</td>
<td>23%</td>
<td>MPS is strongly predictive of subsequent adverse events</td>
</tr>
<tr>
<td>Pen et al (156)</td>
<td>2014</td>
<td>Observational, multi centre</td>
<td>SITE-PET</td>
<td>Site-specific</td>
<td>953</td>
<td>70.8%</td>
<td>29%</td>
<td>SSS predicted mortality (HR1.6) and cardiac death (HR1.8)</td>
</tr>
</tbody>
</table>
Kinnel et al 2020 Observational, CMR Dipyridamole 852 89 50.4 Qualitative detection of ischaemia predicted CV death (HR 2.15)*

| SPECT: Single-Photon Emission Computed Tomography; CMR: Cardiac Magnetic Resonance; PET: Positron Emission Tomography; HR: hazard ratio; SSS: summed stress score; MI: myocardial infarction; CHF: Congestive heart failure; *abstract available only |
Beyond the methodological variations between the design and execution of clinical studies, it is possible that the uncertainty regarding the prognostic role of ischaemia identification, particularly in the context of ischaemic cardiomyopathy, at least partly stems by our limited capability to accurately evaluate the complex biological conditions that exist in these patients. Indeed, identification of “genuine ischaemia”, or of a surrogate, non-invasive process reflective of a mismatch in myocardial blood supply and demand, in a safe and clinically feasible way is technically very challenging.

1.3.4 Myocardial stunning, hibernation and viability

Myocardial stunning and hibernation

Myocardial stunning and hibernation are concepts that describe pathophysiological consequences of reduced coronary blood flow (158). These two processes relate to different types of ischaemic insult, with stunning referring to a transient, reversible myocardial contractile and metabolic dysfunction caused by acute ischaemia (159). A prerequisite is that adequate reperfusion is established in a timely manner, and that the myocardium does not undergo significant metabolic deterioration that can lead to irreversible damage. Although the observation that myocardial contractility may not recover immediately following reperfusion was suggested more than 4 decades ago, initially from animal models of coronary occlusion (159), the pathophysiological processes involved remain elusive. This continues to be a topic of research, with the generation of oxygen-free radicals (160) and changes in calcium handling (161) considered to play a key role.
Hibernation generally refers to the presence of chronically ischaemic myocardium, where reduced coronary blood flow results in reduced cardiac function (162). The term was originally described in the context of surgical revascularisation with CABG, where dysfunctional myocardium recovered after revascularisation (163). Similar to myocardial stunning, the biology of hibernation remains unclear. Unlike stunning however, it has been argued that hibernation is a form of adaptive mechanism to MBF reduction, therefore enabling the maintenance of a balanced state of myocardial oxygen supply and demand (164,165). Based on this concept, hibernation was originally thought to be characterised by reduced contractile function in the presence of reduced rest MBF, however subsequent work casted doubts on the contribution of rest perfusion in its pathophysiology (166). In fact, how distinct hibernation and stunning are, remains unclear.

Repetitive ischaemic insults in the context of coronary artery disease may result in a form of cumulative stunning and are thought to result in chronic depression of contractile function (167). Indeed, repetitive stunning, results in distinct structural changes within the cardiomyocytes, with loss of contractile apparatus and increased glycogen plaques (168), changes in gene expression and alterations in myocardial metabolism. Data from the PET literature suggests that although stunning and hibernation may have distinct metabolic phenotypes in terms of glucose regulation, reflecting their differences at a cellular level (169–171), these are otherwise difficult to differentiate through imaging evaluation of contractile function or MBF. Indeed, Pagano and colleagues observed that recovery of systolic function of chronically impaired myocardial segments was paralleled by improvement of coronary flow reserve (172) (rather than by increase
in resting MBF), further supporting the notion that chronic, repetitive ischaemic insults (and stunning) may have similar imaging characteristics to what is often described as hibernating myocardium (Figure 1-6). Whether hibernating and stunned myocardium co-exist as a continuum remains unclear, and perhaps the benefit of differentiating them - at least from a clinical standpoint - is questionable.

Figure 1-6 Histopathology of myocardial viability.
From Almeida et al Eur Heart J Cardiovasc Imaging, Volume 22, Issue 8, August 2021

Clinically, the importance of detecting hibernation or stunning, mainly relates to the ability of these myocardial segments to recover their contractile function, ultimately informing decisions on pursuing revascularisation. Indeed, detection of stunned or hibernating myocardium is important predominantly in its differentiation from irreversible myocardial injury, therefore determining what is widely described as myocardial “viability”.

Myocardial viability
The concept of myocardial viability was originally introduced in the early 1970s (173), but its detection and clinical utility has been one of the most extensively investigated (and debated) topics within cardiology. From a pathophysiological perspective, viability refers to the presence of living myocytes demonstrating metabolic and microscopic contractile function (174). From a clinical standpoint, it refers to the ability of chronically dysfunctional myocardial segments to partially
or fully recover contractile function following revascularisation (175). As such, hibernation and stunning can be viewed as subtypes of viable myocardium.

In the context of coronary artery disease, prolonged and significant reduction of myocardial blood flow, often in the context of epicardial vessel occlusion, results in myocyte necrosis. This irreversible injury of ischemic myocardium is thought to develop as a transmural wavefront, involving the subendocardial myocardium first, but ultimately becoming transmural (176), Figure 1-7.
Figure 1-7 Heart with ischaemic cardiomyopathy

There is transmural infarction involving the posterior LV wall (A), that extends from apex to base (B). Reproduced with permission from Wolters Kluwer (Roberts, W C et al. Medicine93(5):211-235, July 2014).

This phenomenon is thought to be partly related to differential autoregulation response of endocardial and epicardial coronary vessels to ischaemia, with endocardial vessels thought to have an exhausted vasodilatory capacity even during conditions of rest. The resulting myocardial death, predominantly mediated by a combination of myocyte necrosis (and to a lesser degree myocyte apoptosis), triggers a cascade of inflammatory processes and metalloproteinases that ultimately aim to minimise additional tissue damage and maintain structural integrity of the myocardium (177). The process involves replacement of necrotic myocardial tissue with fibrotic scar (replacement fibrosis)(178), largely characterised by deposition of type1 collagen fibres and dynamic changes in the composition of the extracellular matrix (ECM) (179,180). The development of fibrosis and ECM expansion is one of the hallmarks of pathological cardiac
remodelling (181), and is thought to be a key determinant of functional recovery following revascularisation, as well as patient outcomes (182).

Most evidence on the clinical utility of viability assessment comes from studies performed more than 2 decades ago, which did not benefit from utilising contemporary methods of viability evaluation. A recent statement of the American Heart Association on myocardial viability (183) recognised that different modalities evaluate diverse surrogates of structural or tissue substrates of myocardial viability (183), potentially requiring variable interpretation (Table 1-5).

Table 1-5 Myocardial viability according to different imaging modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>Tracer</th>
<th>Physiological process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electro-anatomical mapping, surface ECG</td>
<td>n/a</td>
<td>Electrical activity</td>
</tr>
<tr>
<td>SPECT</td>
<td>201 – thallium</td>
<td>Myocyte membrane function</td>
</tr>
<tr>
<td>SPECT</td>
<td>99mTc-sestamibi</td>
<td>Mitochondrial function</td>
</tr>
<tr>
<td>SPECT</td>
<td>99mTc-tetrofosmin</td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>18F-fluorodeoxyglucose</td>
<td>Metabolic activity</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td>Gadolinium</td>
<td>Fibrosis, myocyte loss</td>
</tr>
<tr>
<td>Echo/Cardiac MRI</td>
<td>n/a</td>
<td>Contractile reserve</td>
</tr>
</tbody>
</table>

Despite lack of clear evidence as to the impact of viability testing and clinical outcomes, the 2018 ESC guidelines support the practice that “assessment of myocardial viability may be done in order to select patients that are more likely to benefit from myocardial revascularization” (IIb class of recommendation) (184).
In clinical practice, a simplified approach is also encountered, by which revascularisation of what is deemed non-viable myocardium is thought to result in a low likelihood for clinical benefit. The evidence on which this practice is based is however limited and often conflicting, particularly when different study designs are deployed.

Data from meta-analyses based on retrospective studies demonstrated that in the context of revascularisation, detection of viability predicted both global and regional myocardial functional recovery (185) as well as survival (186). Allman and colleagues extracted data from 24 viability studies including a total of 3088 patients with impaired LV function, that underwent viability assessment using Thallium perfusion, F-18 fluorodeoxyglucose metabolic imaging or dobutamine stress echocardiography. They demonstrated a significant association between viability detected with these methods and survival post revascularisation. Similarly, Gerber et al used delayed-enhancement CMR to evaluate viability in patients with ischaemic cardiomyopathy undergoing revascularisation, demonstrating that the presence of dysfunctional viable myocardium by CMR was an independent predictor of mortality (187).

However, different results were obtained in the setting of randomized controlled trials. In the PARR-2 (PET and Recovery following Revascularization) study, clinical management assisted by the use of fluorodeoxyglucose PET (FDG-PET) for viability detection did not impact on patient outcomes following revascularisation, when compared to routine care (188). Similarly, the viability sub-study of the STICH trial showed no significant interaction between the
presence of viability and the beneficial effect of CABG, both at 5 (189) and 10 years (190). There are a number of reasons for the discrepancies observed between the observational and randomized controlled data, which extend beyond the inherent respective limitations of observational and randomised control study designs (191). Indeed, differences in viability definition and methods of viability detection make collective interpretation of this data challenging. None of the aforementioned randomized controlled studies deployed delayed-enhancement CMR (DE-CMR), the current gold standard non-invasive method of tissue characterisation; whether this would have had an impact on patient outcomes is however unclear. Interestingly, all comments to the editor published in response to the original publication (82) highlighted the lack of tissue characterisation with CMR as a key study limitation (192,193).
1.3.5 Imaging biomarkers of cardiac performance

In the context of ischaemic cardiomyopathy, the final step in the pathophysiological cascade is the development of myocardial dysfunction. This is itself a multi-facet concept ranging from impairment of systolic and diastolic function to pathological remodelling resulting in valve disease and rise in pulmonary arterial pressure. Changes in ventricular geometry, volume, mass and function, collectively described as cardiac remodelling, are often accompanied by alterations in haemodynamic conditions, including the pulmonary circulation. However, our ability to collectively evaluate cardio-pulmonary haemodynamics using non-invasive techniques - and more importantly pre-clinical haemodynamic congestion - is limited (194).

A number of imaging biomarkers have been developed to evaluate cardiac function and structure with various degrees of adoption in routine clinical practice. An intrinsic limitation of these methods is that each imaging biomarker often evaluates specific aspects of cardiac physiology in isolation (Figure 1-8), and no single non-invasive test offers a combined measure of the cardio-pulmonary haemodynamic status (195). For example, volumetric analysis with CMR offers information on cardiac chamber size, including mass and function but does not incorporate the impact of diastolic dysfunction or co-existing valve disease on the haemodynamic performance of the heart. Similarly, myocardial strain analysis can provide detailed insight into myocardial mechanics and contractility, without incorporating the impact of co-existing valve pathology or of changes within the pulmonary circulation. Identification of a non-invasive imaging parameter that can quantify the pathophysiological impact of co-existing pathologies on the cardio-
pulmonary axis, providing a measure of haemodynamic congestion is therefore an unmet clinical need.

Figure 1-8 Imaging evaluation of cardiopulmonary physiology and function

1.3.6 Development of the Indicator dilution principle

The idea that central and pulmonary circulation metrics would encode clinically useful information for grading and monitoring cardiac function and haemodynamic performance was introduced more than 2 centuries ago. The concept first appeared in 1827, when Herring, a Veterinary professor from Stuttgart, suggested that by introducing an indicator in the systemic circulation that can be easily identified downstream, blood velocity could be measured. Sixty-five years later, G. N. Stewart reported a technique of measuring the circulation times of blood through the lungs and the kidneys, by injecting a known amount of sodium chloride solution and detecting changes in electrical conductivity at the outflow of an organ. What Stewart acknowledged however,
was that the area under the indicator dilution curve was somehow linked to the cardiac output. Perhaps the most dominant figure in the development of this method, was William F. Hamilton, who in 1928 published a paper titled: ‘Simultaneous Determination of the Pulmonary and Systemic Circulation Times in Man and a Figure Related to the Cardiac Output’ (196). Following this work, the concept of the “indicator dilution principle” was established as a method of measuring blood flow and cardiac output and has since been a focus of research across various disciplines. The principle is described by the Stewart-Hamilton equation shown below:

\[
Flow = \frac{q}{\int_0^\infty c(t)dt}
\]

where q is the total amount of indicator injected, and c(t) is the concentration of the indicator at a downstream sampling site.

A key limitation of this principle was the appearance of recirculation; the passage of the indicator a second time through the sampling point. In his original paper, Hamilton observed that a “secondary rise occurred in all curves [...] due to some of the injected substance passing through the left heart twice” (196). Hamilton and several other scientists over the following 80 years then worked on this principle, each trying to develop robust methods of eliminating re-circulation (197). Different methods were proposed (198), as the indicator dilution principle and indeed the Stewart-Hamilton equation were only valid if only the first pass of the indicator was taken into account. Irrespective of the mathematical model used (lagged normal density (199), log normal (200), gamma variate (201)) for obtaining the primary concentration-time curve, these methods invariably aimed
to extrapolate the down-limb of the primary (first) curve and are based on the assumption that the decay in the indicator concentration would have been exponential if there was no re-circulation (202)(Figure 1-9).

**Figure 1-9 Eliminating re-circulation using a log-normal curve.**
*The first curve represents the first passage of the indicator (in this case lithium). Extrapolation of the down-limb (the second half of this primary curve) through various mathematical approaches (in this case using a log-normal curve) allows estimation of the true primary indicator dilution curve. From Linton et al Cardiovascular Research Cardiovasc Res. 1995 Dec;30(6):930-8.*

Over the following decades several studies compared the indicator dilution and the direct Fick methods of measuring cardiac output confirming the validity of the former (203,204). According to the Fick principle, cardiac output is derived by the estimation of oxygen consumption (VO$_2$) and the difference in oxygen content between arterial and mixed venous blood (205). The indicator dilution principle subsequently formed the basis of contemporary methods of cardiac output estimation, including the use of lithium dilution-based commercial products deployed in intensive care unit settings (200). The physiological accuracy of the indicator dilution curve and the haemodynamic information encoded within it, prompted several physiologists to evaluate its use in quantifying cardiac pathology in vivo, including the quantification of intra-cardiac shunts (206), and the evaluation of valve regurgitation (207).
Figure 1-10 Timeline of the development of the indicator dilution principle
Following the validation of the indicator dilution principle, it was apparent that the shape and magnitude of the indicator dilution curves encoded information related not only to cardiac output, but also to cardio-pulmonary physiology and haemodynamics. As a result, a number of groups attempted to deploy this method using non-invasive imaging with a variety of tracers, in order to extract physiological parameters as measures of pulmonary congestion. The two main parameters that have been evaluated for this purpose were pulmonary transit time (PTT) and pulmonary blood volume (PBV).

1.3.7 Pulmonary transit time and pulmonary blood volume

Pulmonary transit time (PTT) is defined as the time it takes for a bolus of contrast to travel from the right to the left side of the heart has been evaluated using both invasive catheterisation and non-invasive imaging tests (208–212). Pulmonary blood volume is the product of PTT and cardiac output. Estimation of PTT is based on the indicator dilution principle, and relies on the subtraction of two curves derived from anatomical sites on either side of the pulmonary circulation. An important step in this process, is the method by which these two indicator dilution curves are subtracted which is either based on estimating the time difference between the peaks of the 2 curves or their centres of gravity (Figure 1-11). Ugander et al (213) used a pulsatile flow phantom CMR experiment and demonstrated that the use of the centroid method was more accurate and precise compared to the peak to peak method.

Figure 1-11 Methodological considerations in estimation of PTT

*Top: Different anatomical landmarks across imaging modalities have been used in the estimation of pulmonary transit time (PTT) in contemporary studies using*
non-invasive imaging techniques. Bottom: Estimation of PTT by measuring the time interval between the two peaks (Colin et al EHJ CVI 2020) or the centroids of the two curves (Ugander et al Radiology 2010).

Irrespective of method used, both PTT and PBV have been shown to correlate with both structural and functional parameters of cardiac (209) and pulmonary function (214). A number of groups deployed contrast echocardiography to estimate PTT, demonstrating good correlation with markers of systolic and diastolic function (211,215,216). More recently, Colin et al (214) used computed tomography to derive PTT in patients with heart failure with reduced ejection fraction. In their cohort, PTT correlated with echocardiographic parameters of diastolic and systolic function, NT-pro BNP and invasive haemodynamic metrics obtained during right heart catheterisation (eg. mean pulmonary arterial pressure). Similar findings were reported by Cao et al (209), who used CMR to evaluate pulmonary transit time in heart failure patients with both preserved and reduced ejection fraction.

The association of PTT and PBV with metrics of cardiac performance has also been evaluated in other disease models. Ricci et al (217) found that PBV (indexed for BSA) was an independent predictor of diastolic dysfunction and increased left atrial pressure in patients with hypertrophic cardiomyopathy (HCM). In a similar study, Swift et al (218) demonstrated the PTT closely corelated with cardiac index and pulmonary vascular resistance in patients with pulmonary arterial hypertension.
Despite a large body of work performed by different research groups, a fundamental limitation in PTT and PBV estimation across all imaging modalities remains the difficulty in data acquisition. All previous attempts for estimating PTT involved the use of additional image acquisition (thereby prolonging scanning time) and invariably necessitated manual segmentation of imaging series and analysis. As a result, introduction of PTT into a clinical workflow and at scale evaluation remains problematic. Furthermore, the methodological variations among groups and the variability introduced by manual segmentation and analysis means that direct comparison between studies in terms of their absolute PTT and PBV values remains a challenge.
1.4 Cardiovascular Magnetic Resonance Imaging: clinical applications

Cardiac MRI has emerged as an important imaging modality for assessment of patients with ischaemic cardiomyopathy, given its inherent value for measurement of volume, function, myocardial perfusion and tissue characterisation. It is considered the gold standard test for evaluation of cardiac chamber volume, mass and function (219), demonstrating superior precision compared to transthoracic echocardiography (220,221), allowing for smaller detectable differences on interval scanning (Table 1-6).

Often providing superior endocardial definition than alternative imaging modalities, it enables estimation of cardiac volumes with fewer geometric assumptions, a benefit particularly relevant in the context of cardiac remodelling. CMR can be used to complement decisions regarding implantable defibrillator (ICD) and cardiac resynchronisation therapy (222), which remain based on binary cut off points but have major reclassification implications and impact on clinical decision making.

Its use in the context of heart failure is supported in recent ESC guidelines, both for the assessment of patients with poor echocardiography windows and for determining the underlying aetiology in patients with a new diagnosis of heart failure.
Table 1-6 Minimal detectable changes using CMR

<table>
<thead>
<tr>
<th>Modality</th>
<th>Immediate rescan interval</th>
<th>One year re-scan interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMR (Grothues et al (223))</td>
<td>2D Echo (Grothues et al (223))</td>
</tr>
<tr>
<td>Study date</td>
<td>2002</td>
<td>2002</td>
</tr>
<tr>
<td>Sample size</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Population</td>
<td>Heart failure</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>LVH</td>
<td>LVH</td>
</tr>
<tr>
<td>EF (%)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Mass (g)**</td>
<td>15</td>
<td>49</td>
</tr>
<tr>
<td>EDV (mls)</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>ESV (mls)</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>SV (mls)</td>
<td>10</td>
<td>26</td>
</tr>
</tbody>
</table>

*MDCs are calculated for immediate rescan interval from data published by Grothues et al from the formula published by Moody et al. It is important to note that the method to calculate MDCs can result in different absolute values. Here, the method used by Thavendiranathan et al typically results in slightly lower MDCs compared to Moody et al. **The difference between the MDC for LV Mass with an immediate rescan interval than a one-year scan interval may be attributable to improvements in scan acquisition and epicardial border delineation. (EF – ejection fraction, EDV – end diastolic volume, ESV – end systolic volume, SV – stroke volume

Minimal detectable changes (MDC)* - a precision measurement - of left ventricular parameters using cardiovascular magnetic resonance (CMR) compared to 2D and 3D echocardiography. Adapted from Seraphim et al; Magn Reson Imaging. 2020 Mar;51(3):693-711.
Improvements in methods of tissue characterisation, including the introduction and increasing adoption of parametric mapping techniques (the mapping of the regional estimates of particular parameters) such as T1, T2 and extracellular volume fraction (ECV) estimation, allow quantitative evaluation of myocardial processes such as oedema and diffuse fibrosis. Importantly, although these largely remain supplementary to the use of gadolinium imaging, they provide new tools for patient risk stratification (226), as well as the identification of concomitant or alternative pathological processes (227). Despite initial concerns regarding the safety of cardiac implantable electronic devices, these are no longer an absolute contraindication for CMR scanning, as long as certain conditions are met (228,229). As such, patients with ischaemic cardiomyopathy can benefit from the diagnostic capabilities of CMR, particularly when planning for invasive electrophysiological procedures (230,231). Furthermore, technical advances and implementation of machine learning approaches have transformed the capabilities of CMR, allowing the application of automated, often in-line methods of quantitative evaluation at scale, potentially offering major improvements in both workflow efficiency and diagnostic accuracy.
1.4.1 Cardiovascular Magnetic Resonance for viability assessment

Late gadolinium enhancement

The use of late gadolinium enhancement (LGE) imaging for tissue characterisation is now an indispensable tool of cardiovascular magnetic resonance imaging. This is particularly relevant in the context of ischaemic cardiomyopathy, where the technique has been extensively validated (232), and is often used to detect treatment-effect size in randomized controlled trials (233,234).

There is currently a large body of evidence demonstrating a link between the amount of LGE and outcomes, including data from meta-analysis (235). A number of studies have shown that the presence - and extent - of LGE is an independent predictor of mortality, and is incremental to conventional parameters such as LVEF and LV volumes (236,237), even if this involves a small amount of myocardium (238). LGE-CMR therefore serves as the gold standard method for infarct identification and sizing, and has undergone extensive histopathological validation at both macroscopic and microscopic levels (239,240) (Figure 1-12). Reflecting this, the 2018 ESC consensus statement on the fourth universal definition of myocardial infarction (241) promotes an enhanced role of cardiac magnetic resonance imaging for the diagnosis of myocardial infarction.
Late gadolinium enhancement accurately identifies areas of myocardial infarction. Sample shown is from an animal model of infarction (left), with CMR performed at 7 Tesla (right). Green boxes demonstrate magnification at 5.5X. Scale bar=500μm. Adapted from Schelbert et al, Circ CVI 2010 (240).

The ability of gadolinium to visualise infarction, peri-infarct border zones and its ability to accumulate in a fashion that parallels the extent of fibrosis lies in its pharmacokinetic properties. Gadolinium has a molecular weight of ~800 Da, is an extracellular contrast agent, that can distribute passively between the intravascular and interstitial extracellular space (242). In the context of myocardial infarction, an altered volume of distribution and delayed washout kinetics, generate a signal contrast between normal and infarcted tissue (the exact mechanisms differ between chronic and acute infarctions, but are based...
on the same principles (243)). However, visualisation of scar, or more specifically a region of increased gadolinium concentration detected as increased T1 signal does not necessarily translate into viability.

Early data from animal models suggested that the degree of transmurality of hyper-enhancement related to both the extent of blood flow disruption as well as the future recovery of contractile function (244–246), thereby demonstrating the potential for LGE to serve as a marker of viability. Since the seminal paper by Raymond Kim in 2000, gadolinium enhancement CMR has become the standard method of viability assessment in clinical practice. In this study, the level of hyper-enhancement across the myocardial thickness was postulated to represent the transmural extent of non-viable myocardium. The authors demonstrated that following revascularisation, less than 2% of myocardial segments with >75% transmurality in LGE and the majority of segments with hyper-enhancement of 51 to 75% of tissue, did not improve their contractility post revascularisation. Their results were also confirmed by Selvanayagam et al (247), which used a cohort of patients exclusively undergoing CABG surgery, thereby providing strong evidence of the use of LGE as a reference standard method of viability assessment.

Over the past 20 years, our understanding of how to interpret LGE has not significantly changed. Despite the development of new methods such as dark blood LGE imaging (Figure 1-13), presumably capable of providing higher diagnostic accuracy under certain conditions including the presence of subtle subendocardial scar (248,249), a 50% cut off for LGE transmurality is often
quoted clinically as a binary cut off of viability. This highlights a key limitation of LGE methods when it comes to myocardial segments with intermediate transmurality (25-75%), with these areas quoted as having intermediate probability of functional recovery.

Figure 1-13 Bright and Dark blood LGE

Comparison of Flow-Independent Dark-blood Delayed Enhancement (FIDDLE) technique and conventional delayed enhancement method in an animal model (canine) of infarction. The subendocardial infarct is more clearly depicted by the dark blood technique. Reproduced with permission from Kim et al JACC CVI 2018

Semi- or fully-quantitative methods of LGE evaluation also exist, potentially allowing more objective and reproducible methods for scar evaluation (250). A number of methods have been proposed, including the full-width half maximum (FWHM) method (regions are defined as those with signal that is greater than 50% of maximal signal intensity of an enhanced area) and thresholding by various standard deviation increments above remote myocardium (251). Depending on the thresholding technique applied there are significant variations
in the values obtained (251,252). Indeed, whether such techniques can provide incremental benefit in the context of viability remains unclear, although some studies demonstrated higher prognostic value of the FWHM method (253). An obvious limitation is that wall-thickness, itself a highly sensitive measure of viability (254), serves as an important confounder when it comes to quantitative evaluation of LGE.

**Low-dose dobutamine**

Evaluation of contractile reserve as a marker of viability using low-dose dobutamine (eg. up to 10mcg/kg/min) is also possible with CMR. Knowledge and expertise on the technical aspects of this method is drawn from stress echocardiography, although there are practical challenges in its application in an MRI suite (255). Whether low-dose dobutamine has a higher diagnostic accuracy compared to LGE remains unclear. Wellnhofer et al (256) suggested that low-dose dobutamine was superior to delayed-enhancement in predicting improvement in wall motion recovery particularly after revascularisation, with the greatest advantage seen in myocardial segments with delayed enhancement of 1% to 74%. Direct comparison of the two methods is difficult, as these techniques evaluate “viability” from a different perspective. As already discussed, LGE provides a morphological assessment of the myocardium whereas low-dose dobutamine testing evaluates the inotropic reserve of segmental contractile function. None of these methods evaluate viability in its strict pathophysiological sense but each has unique advantages. In general terms, it is accepted that low-dose dobutamine has a high specificity in predicting segmental contractile recovery after revascularisation, whereas LGE provides the highest sensitivity
Therefore, the possibility of integrating the two techniques within a single study is potentially attractive (258).

1.4.2 Cardiovascular Magnetic Resonance and myocardial perfusion

Stress perfusion CMR is now an established method for detection and evaluation of coronary artery disease, and despite geographic variations in its use (259), it has been incorporated in clinical guidelines (22). The technique has undergone major advances over the past 30 years, attributed to improvements in imaging acquisition methods and implementation of machine learning approaches, but fundamentally relies on the basic principles of first pass perfusion, similar to its early description in 1990 (260). During stress perfusion CMR, a gadolinium-based contrast agent (GBCAs) is injected into a peripheral line and the process is registered by a dynamic series of images, often acquired in a multi-slice mode. Acquisition requires the use of ECG-gated fast pulse sequences that aim to capture the signal changes induced by the passage of contrast through the LV cavity and subsequently the myocardium (Figure 1-14).

**Figure 1-14 First pass perfusion CMR**

Injection of gadolinium contrast (in this case Gadoterate Meglumine; Dotarem) followed by saline flash. Dynamic imaging acquisition starting before contrast arrival in the RV cavity ($t_5$) and continues until after the bolus disappears from the LV cavity ($t_{25}$). In this case, cardiac motion is managed through ECG-gating and respiratory compensation is applied.
Perfusion image acquisition is based on the property of GBCAs to shorten the T1 relaxation, thereby generating myocardial signal which is reflective of tissue blood supply. Differences in myocardial signal intensity therefore become a measure of regional myocardial blood flow. The technique usually relies on a saturation-recovery pulse sequence, whereby T1 weighting and therefore differential T1 signal sensitivity is induced by a 90° magnetization preparation pulse, with signal read-out usually performed after a delay of 100-150ms (261), although a number of modifications of the pulse sequence are in use (Figure 1-15).
Figure 1-15 Perfusion CMR pulse sequences

A) Commonly used sequence with 3x 2D slices acquired per RR-interval. B) Example of 4x slices acquired over two heart beats and C) 7x slices acquired over two beats but acquisition occurs during periods of cardiac cycle with significant cardiac motion. D) 3D volume over a single RR. E) Example of a dual-sequence approach used for quantitative perfusion mapping. This involves acquisition of a low-resolution arterial input function slice prior to acquisition of myocardial perfusion imaging. Adapted from The EACVI Textbook of Cardiovascular Magnetic Resonance, Oxford University Press, September 2018.
Typically, stress perfusion CMR is performed using pharmacological vasodilating agents such as adenosine, dipyridamole and regadenoson, and rely on the physiological processes described previously (Section 1.3.2). Adenosine, a naturally-occurring endogenous purine nucleoside (262), is capable of eliciting maximal vasodilatation of both epicardial coronary conductance and myocardial resistance vessels, via their action on A2A and A2B receptors (activation of A1 and A2B receptors in splenic afferent arterioles results in vasoconstriction (263), which forms the basis of the “splenic switch” as a measure of adequate adenosine response (264)). The different vasodilatory agents vary in terms of their pharmacokinetic profiles and physiological effects (Figure 1-16). Adenosine has a short half-life (~20 seconds), which necessitates its administration in the form of an infusion (265). Regadenoson is used as an alternative agent in some centres, with perhaps a better side effect profile than adenosine due to its selective 2A receptor activation, with less bronchospasm and atrioventricular block reported (266,267). It has a different pharmacokinetic profile requiring a bolus injection and has a longer duration of action than adenosine, often requiring the use of reversal agents (268). Only a few studies compared the vasodilator efficacy between different agents, suggesting that both regadenoson and adenosine have similar impact on myocardial blood flow as assessed by CMR (269).

Although dobutamine stress first pass perfusion has been validated and considered at least non-inferior to conventional vasodilators (204–206), practical difficulties in administration, manual dose up-titration, patient monitoring and the small risk of ventricular arrhythmias have limited its use. Similar practical
challenges are encountered with exercise as a form of myocardial stress, necessitating the use of dedicated equipment (273).

Figure 1-16 Cardiovascular effects of Adenosine
SAN, sino-atrial node; AVN, atrio-ventricular node. Reproduced with permission from Layland et al JACC: Cardiovascular Interventions; 2014.
From a clinical perspective, multiple-slices of the LV myocardium are needed for a comprehensive assessment of coronary artery disease, therefore fast read-out strategies are often deployed (274) and these are combined with methods of parallel imaging (275). Improvements in imaging acquisition acceleration techniques are ongoing (276), and have been coupled with substantial improvements in spatial resolution, offering an advantage over traditional modalities of perfusion assessment such as PET and SPECT, with an in-plane resolution of 1x2mm often achievable (99).

**Semi-quantitative analysis of perfusion**

One of the main limitations of conventional stress perfusion CMR imaging relies on the reliance on visual image interpretation, which depends on a subjective comparison of stress and rest perfusion images, as well as differences within different myocardial coronary territories. These are qualitative assessments and are limited in terms of inter-observer reproducibility (277). As a result, there has been a shift towards “semi-quantitative” and subsequently “fully quantitative” perfusion CMR. Semi-quantitative techniques have largely been superseded by fully quantitative methods, but their principles – mainly based on the indicator dilution methods – formed the basis on which subsequent advances were made (278). A number of semi-quantitative techniques were originally proposed that utilised various aspects and ratios of the arterial and myocardial signal intensity (SI) curves (SI/time). Examples include the contrast enhancement ratio (CER) \((SI_{\text{peak}} - SI_{\text{baseline}})/SI_{\text{baseline}}\), the myocardial to LV upslope index (ratio of upslope SI\(_{\text{myocardium}}\) / upslope SI\(_{\text{AIF}}\)) (279), and the upslope integral (calculating the area under the myocardial signal curve (280)) (Figure 1-17). With most semi-quantitative techniques, signal curves derived from the myocardium where
adjusted by the signal intensity curves obtained from the arterial input function, thereby “normalising” for the shape of the AIF curve and the underlying haemodynamic conditions (279). More recent semi-quantitative methods eliminated the need for AIF curve estimation but instead utilise myocardial transmural signal intensity gradient (TMG), thereby exploiting the relative susceptibility of endocardial layers to reduced blood flow (281). Although these techniques provide quantitative measures such as perfusion index, specific cut offs varied between techniques and there was limited agreement with invasive indices of flow resulting from underestimation of MBF particularly at higher flows (215), limiting their clinical use.

Figure 1-17 Semi-quantitative indices of myocardial perfusion
Examples of parameters derived from arterial input function and myocardial signal intensity curves, allowing derivation of semi-quantitative indices of myocardial perfusion in CMR. From Jerosch-Herold M; JCMR 2010 (278). Reproduced under the terms of the Creative Commons CC BY license,
Principles of quantitative perfusion

A natural evolution of these semi-quantitative techniques was the refinement of fully quantitative perfusion techniques. Initially unattractive due to the need for extensive post-processing, advances in these techniques in the context of CMR paralleled improvements in speed of acquisition, computational capabilities and introduction of machine learning. A key aspect of these techniques, is that they provide an estimate of MBF (in units of ml/g/min), which is similar to other methods of quantitative blood flow estimation using microspheres and nuclear imaging (196). Full quantification of myocardial blood flow requires execution of tracer kinetic analysis, a mathematical relation between the arterial input function and myocardial signal intensity curves, based on the tracer-kinetic theory of linear and stationary systems (278) (Figure 1-18).

Figure 1-18 Schematic of the key steps of quantitative perfusion

Schematic representation of the key steps involved in quantitative perfusion. A number of tissue models are in use as discussed in the main text. Slide Adapted from Peter Kellman; EuroCMR 2019.
The methods by which this is performed has been the focus of research that spans several decades, with a number of models been proposed, with varying physiological realism (284). A fundamental principle of these methods is that the myocardial signal is regarded as the convolution of the arterial input and the myocardial tissue response to contrast administration (285). The mathematical relations deployed range from non-specific empirical models (Fermi model (286)), compartmental models (which consider that the tracer distributes instantaneously within compartments) (287), to distributed parameter models that take into account a number of physiological parameters, such as myocardial blood flow (ml/g/min), permeability-surface-area product ($PS$, ml/min/g), blood volume $V_b$ (ml/g) or plasma volume $V_p$ (ml/g), interstitial volume $V_{isf}$ (ml/g), extraction fraction $E$ and capillary transit time $T_c$ (sec). (288). Comparisons between models have been performed, with distributed parameter models often demonstrating superior performance (289,290), as these are considered to offer higher accuracy by better approximation of myocardial capillary physiology (291).

In the work presented in this thesis, the perfusion sequence deployed is based on a Blood-tissue exchange model (BTEX) originally described by Bassingthwaighte (Figure 1-19), a physiological model originally designed to describe tissue haemodynamics, but subsequently applied in the context of nuclear imaging (292). This model has been used in quantitative perfusion with $^{13}$N-Ammonia using PET and has been validated against microspheres (293).
Figure 1-19 Bassingthwaighte’s BTEX model
Schematic representation of a 4-region distributed capillary-tissue unit that describes the basis of Bassingthwaighte’s BTEX model. $F_p$, flow; $C$, concentration; $PS$, permeability surface-area product; $G$, Intra-regional reactions or metabolic consumption; $D$, axial dispersion, $V$, volume of distribution; $p$, plasma; $g$, inter-endothelial cleft or gap PS; ecl, luminal surface of endothelial cell; ec, endothelial cell; isf, interstitium; eca, antiluminal surface of endothelial cell; pc, parenchymal cell. From Bassingthwaighte et al Circulation Research 1989 (292). Reproduced with permission from Wolters Kluwer Health, Inc.

Irrespective of the method deployed to analyse the signal obtained from the blood pool and myocardium, there are aspects of myocardial perfusion using CMR, that warrant consideration, as these inform the sequence type and method of data acquisition. These also help appreciate the limitations of the data obtained in vivo. A key aspect of perfusion using gadolinium as an indicator, is the non-linear relation between contrast concentration and signal intensity (294). High concentrations of gadolinium, particularly in the LV cavity, can cause complete magnetization recovery (as well as increased T2* effects (295)), with further increases in gadolinium concentration unable to further enhance the T1-weighted
signal (295). This signal attenuation can be minimised by either using a low-dose contrast bolus or by altering the imaging sequence parameters, resulting in separate measurements of AIF and myocardial signal. Two techniques predominantly used are therefore the “dual bolus” and “dual sequence” techniques. The dual sequence is the technique deployed throughout this thesis, and is described in more detail below.

The dual bolus approach involves administration of an initial-low contrast bolus resulting in a sub-saturating concentration of contrast allowing AIF from the blood pool, followed by a higher dose used for myocardial signal detection (296). Despite good agreement with both animal models using microspheres (282) and in patients comparing with MBF derived from PET imaging (297), the technique has its own limitations. There are practical implications as the delivery of the two separate boluses is clinically more demanding in terms of the clinical workflow (296). Furthermore, given that the two acquisitions (AIF and myocardial response curves) are not simultaneous, there is potential for introducing error, for example as a consequence of breathing variability. Nevertheless, various groups have implemented a dual approach in quantitative perfusion, demonstrating incremental prognostic value to visual assessment (113).

The dual sequence perfusion mapping approach generates a fully automated, in-line perfusion maps with absolute quantification (mls/g/min of blood flow) (298). The sequence involves a saturation recovery preparation pulse as below (Figure 1-20). This separately optimises imaging acquisition for blood (arterial input function) and myocardium.
Figure 1-20 Dual-sequence myocardial perfusion

Separate low-resolution AIF and high-resolution myocardial perfusion images. Saturation recovery preparation is achieved with a 6-pulse design as this was previously shown to achieve efficient saturation (190). TS – saturation time; TD – trigger delay, R-R – duration of cardiac cycle. Reproduced from From Kellman et al, J Cardiovasc Magn Reson 19, 43 (2017) (100) under the terms of the Creative Commons Attribution 4.0 International License

This involves the acquisition of a low-resolution AIF image at the start of the R-wave and a higher resolution image acquisition of the myocardium. Typically, images are acquired for 60-90 heartbeats starting prior to bolus administration. The image readout, is a single shot using a low flip-angle FLASH for the AIF and either FLASH or b-SSFP for the myocardium. Proton density (PD) weighted images are acquired prior to contrast administration, allowing for correction of surface coil irregularities and for normalisation of the AIF and myocardial signal intensity curves, and used as an input for gadolinium concentration conversion. Image acquisition is shortened with the use of parallel imaging methods,
ultimately allowing acquisition of at least 3 myocardial perfusion short axis slices, at heart rates of up to 120 beats per minute, whilst minimizing cardiac motion and therefore reducing dark rim artefacts (299). If greater LV coverage is needed, then for rates <120bpm, acquisition of myocardial signal can be performed every other R-R interval thereby allowing 6 slices to be imaged (although this reduces the sampling points for myocardial signal by 50%, AIF remains unaltered).

A key step in quantitative perfusion is the accurate detection of the AIF signal, as this provides the key input for the subsequent mathematical modelling used to derive myocardial blood flow. A number of methods can be deployed that range from simple thresholding to eliminate background and non-enhanced structures within the field of view (FOV) based on the signal up-slope (300) to the use of a convoluted neural network-based solution to detect the LV blood pool (301). Whatever the method of identification, accurate detection of key segments of the AIF signal curve is important in subsequent curve fitting and quantitative analysis (Figure 1-21).

As highlighted in previous sections, one of the main challenges with quantitative perfusion using gadolinium (and indeed some of the tracers used in other modalities) is the lack of linearity between the signal measured from CMR and the contrast agent concentration. In this technique, signal intensity is converted to gadolinium concentration, thereby allowing common scaling between the AIF and myocardial signal (100), with a use of a look-up table based on Block signal calculation. Additional T2* correction is performed thereby minimising another source of non-linearity caused by the high contrast concentration in the blood
pool (302). Once signal is converted to gadolinium, myocardial blood flow is estimated using a blood tissue Exchange Model (BTEX) based on the original model described by Bassingthwaighte (Figure 1.10). This is a type of distributed model, that allows estimation of additional parameters. The arterial contrast delay (TA) is one of these parameters, and is the absolute time in seconds required for the gadolinium to travel from the LV blood pool (where AIF is measured) to the myocardium. This is parameter is of particular importance in patients with long coronary artery grafts, given that a differential TA may be encountered during first pass perfusion imaging in these patients, and is further evaluated in in Chapter 4 of this thesis.

**Figure 1-21 An iterative process of BTEX-derived differential equations**

*The model parameters are constantly adjusted until there minimal possible discrepancy between the estimated and measured curves is achieved, thereby*
allowing derivation of the various models components. Reproduced from Xue et al, Magn Reson Mes 2020 (300) with permission from John Wiley and Sons.

The perfusion mapping software is supported within the Gadgetron software framework (303) and enables a series of processes to be performed, including imaging reconstruction of raw k-space data and respiratory motion correction, as well as performing an iterative process for BTEX modelling. In essence, the AIF gadolinium concentration is used as the driving input function for solving the partial differential equations of the BTEX model. The resulting curve, is compared to the measured “true” perfusion gadolinium curve, with the processes being re-iterated until the best possible agreement is reached. This is performed for each myocardial pixel.

Figure 1-22 Quantitative perfusion workflow
Steps involved in generation of quantitative perfusion maps Motion correction is performed using a non-rigid image registration. Reproduced from From Kellman et al, J Cardiovasc Magn Reson 19, 43 (2017). under the terms of the Creative Commons Attribution 4.0 International License (100)

This method has already been used a number of studies, both in the context of epicardial and microvascular coronary artery disease (110,304), as well as evaluation of MBF abnormalities in various models of hypertrophy (77,78) and myocardial infiltration (305). Kotecha et al, evaluated its performance in detecting
epicardial coronary artery disease, using invasive physiology with FFR and IMR (index of microvascular resistance) as a reference standard, demonstrating good performance in identification of epicardial stenosis and differentiating between multi-vessel and microvascular dysfunction (110). A study led by the same centre, recently demonstrated that this method was superior to visual assessment in identification of multi-vessel coronary artery disease (306). Using this approach of perfusion mapping, our group previously demonstrated that quantitative evaluation of MBF and MPR independently predicted adverse cardiovascular outcomes in a large cohort of patients (80).
Role of stress perfusion CMR in stable coronary heart disease

There is a large body of evidence confirming the diagnostic accuracy of the perfusion CMR both in the research setting as well as using real world data. A number of studies, including several meta-analyses (307–309) examined the performance of stress perfusion CMR in the evaluation of significant epicardial disease, (often taken as >50-70% diameter stenosis) against coronary angiography as well as against invasively measured FFR. These suggested high diagnostic accuracy, with some demonstrating slightly superior performance at higher field strength (310). In the MR-IMPACT II trial, CMR was more sensitive in detecting coronary artery disease than Single Photon Emission Tomography (SPECT), although with lower specificity (311), thereby concluding that the two modalities had similar performance.

From a clinical perspective a number of studies have also confirmed the safety and clinical utility of perfusion CMR in terms of patient outcomes. In the CE-MARC study, perfusion CMR was a stronger predictor of major adverse cardiovascular outcomes compared to SPECT. Similarly, in a large multi-centre study of 9151 consecutive patients with known or suspected coronary artery disease, an abnormal stress CMR study was associated with increased patient mortality, which was incremental to LVEF and common clinical risk factors (312). The impact of abnormal CMR perfusion result on prognosis was also supported by a meta-analysis by Lipinski et al (128). Using data from a total of 11,636 patients and a mean follow-up of 32 months, the authors demonstrated that stress CMR can provide prognostic risk stratification of patients with known or suspected coronary disease. Recently, the US-based SPINS study reported similar findings, confirming that patients without perfusion defects on stress CMR
have low probability of adverse cardiac events, need for revascularisation and downstream costs (126).

Very few studies however compared the performance of stress CMR in a randomized controlled trial setting. The CE-MARC2 study (313) demonstrated that the use of perfusion CMR reduced the use for unnecessary angiography within 12 months when compared to NICE guideline-directed care, without any difference in adverse outcomes. The MR-INFORM trial was a comparative effectiveness study evaluating a CMR-based strategy versus a strategy using FFR, in patients with stable angina (279). The study showed that perfusion MRI was associated with a lower incidence of revascularization than the use of FFR and was non-inferior with respect to major adverse cardiac events.

Despite the large body of evidence supporting a clinical role of the use of stress perfusion CMR, its performance specifically within the context of ischaemic cardiomyopathy is less established. Gu et al, recently reported on the performance of stress CMR in patients with impaired LV function, suggesting that the presence of perfusion defects on CMR can accurately risk stratify patients with low LVEF (129). Data from patients with prior surgical revascularisation however are even more scarce. Patients with prior CABG comprise a significant proportion of patients referred for ischaemia evaluation due to symptom recurrence, but these patients have been largely excluded from landmark studies of perfusion CMR (126,311,314,315), or have been under-represented in meta-analyses (128). Only 1 study has previously evaluated the performance of
perfusion CMR in patients with prior CABG, albeit the majority of patients included were asymptomatic (157).
Chapter 2       Research hypotheses and aims

2.1 Global research hypothesis

Novel CMR methods, particularly the use of quantitative parametric mapping techniques can better characterise the pathophysiological processes that determine outcomes in patients with stable coronary artery disease, including patients with multivessel disease and left ventricular dysfunction. These methods can provide new tools for patient risk stratification and phenotyping and for evaluating the effects of treatment, including the impact of revascularisation.
2.2 Aims

The aim of this thesis was to deploy quantitative CMR techniques to understand the pathophysiological processes that determine outcomes in patients with stable coronary artery disease. The work mainly focuses on patients with advanced, multivessel coronary disease and explores novel non-invasive imaging biomarkers that can enhance disease characterisation and phenotyping. Given the central role of revascularisation in the management of these patients, this work primarily explores the impact coronary artery bypass graft surgery (CABG) on myocardial structure, function and perfusion. The specific aims of this thesis are presented below and organised by the Results Chapters

- To deploy quantitative myocardial perfusion and delayed enhancement imaging using CMR, combined with paired non-invasive anatomical imaging using CTCA to gain insights into the impact of surgical revascularisation on myocardial structure and function in patients with ischaemic cardiomyopathy.

- To investigate the performance of quantitative perfusion mapping in ischaemia evaluation of patients with prior CABG, particularly in those with left internal mammary (LIMA) grafts. Specifically, the impact of delayed contrast arrival through patent LIMA grafts. To also examine the impact of native vessel disease on myocardial perfusion in bypassed segments.

- To investigate the prognostic role of quantitative perfusion mapping in a separate cohort of patients with prior CABG, after adjusting for conventional prognostic parameters, including the extent of prior infarction. This would be the first time
that the prognostic value of quantitative myocardial blood flow estimation in patients with prior CABG is being explored.

- To develop an in-line method of pulmonary transit time (PTT) estimation during perfusion mapping with CMR, by adapting the existing quantitative perfusion technique infrastructure. This work aims to provide a novel, automated method of PTT estimation that enables its at scale evaluation and clinical adoption. To then evaluate the prognostic significance of both PTT and pulmonary blood volume (PBV) in a large patient cohort.
Figure 2-1 Summary of the 3 workstreams presented in this thesis

Chapter 3  Methods

3.1 Outline and personal contribution

This thesis contains technical development work, and a series of clinical studies. The studies carried out share a number of common CMR sequences and imaging analyses methods, and these are presented within this chapter. Additional details or deviations from routine analyses methods specific to each study are provided within the corresponding chapter. For the technical development work, the details of the methodology is outlined in the relevant chapters.

A summary of all four cohorts included in this thesis, is shown in Table 3-1. Patients were prospectively recruited for the work presented in Chapter 4, and additional details on the study set up and, recruitment are shown in this section. The data presented in Chapters 5-7 refer to retrospective analyses, therefore the details of patient selection are reported within the corresponding chapters.
<table>
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<th>Time-points / Centre</th>
<th>Follow up (months)</th>
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</tr>
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<td>n/a</td>
<td>CMR and CTCA</td>
<td>Quantitative perfusion, LGE, CTCA anatomy, 6MWT</td>
</tr>
<tr>
<td><strong>Chapter 5</strong> Patients with patent LIMA grafts</td>
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CTCA: Computed tomography coronary angiography, PTT: pulmonary transit time; PBV: Pulmonary blood volume; CABG: coronary artery bypass graft surgery, BHC: Barts Heart Centre; RFH: Royal Free Hospital; 6MWT: 6-minute walk test
The patients described in Chapter 4 comprise a prospective cohort of patients with impaired left ventricular systolic function and multivessel coronary artery disease that were listed for CABG surgery. This cohort was used for evaluation of the use of quantitative perfusion CMR for evaluating the structural and functional impact of CABG in patients with ischaemic cardiomyopathy. The study involved assessment of patients both before and 6-months after their CABG operation with paired imaging (CMR and Computed Tomography coronary angiography, CTCA). I co-designed the study and obtained the grant funding. I obtained the ethical approval from REC/HRA and local approvals between Barts Heart Centre and University College London. I recruited and performed all CMR studies, supervised the CTCA scanning and other research activities as outlined in more detail in this chapter. I created a data capture platform using Redcap to collect anonymised data and performed the data analysis (volume, LGE quantification, feature-tracking strain, mapping analysis).

For chapter 5, I conceived the idea for performing a technical analysis of quantitative perfusion imaging in patients with left internal mammary grafts, to evaluate the impact of delayed contrast transit through long grafts on quantitative perfusion indices. To confirm graft patency, patients with paired perfusion CMR and coronary angiography data were selected from the ongoing BYPASS-CTCA study (NCT03736018). I collaborated with Dr Peter Kellman to extract the arterial delay of contrast in these patients and quantified the impact of this on the performance of quantitative perfusion imaging. I collected the data and performed the statistical analysis.
For chapter 6, my aim was to explore the prognostic value of quantitative perfusion among a large cohort of patients with prior CABG. Patients with CABG-only surgery were included and follow up was available for a median of 21 months. The study utilised existing ethics allowing the use of retrospective data analysis of patients undergoing revascularisation from the Barts Revascularisation Registry (ID: 142567) Together with Dr Benjamin Dowsing I performed the imaging and clinical outcome data collection, including semi-automated LGE quantification of approximately 400 cases. I then performed the statistical analysis.

For chapter 7 I conceived the idea of exploiting the existing quantitative perfusion framework to develop a novel method of pulmonary transit time (PTT) estimation using perfusion CMR. I collaborated with Dr Peter Kellman to identify the optimal method of PTT estimation, the process of which is described in this Methods chapter. Dr Kellman subsequently led on the implementation of this as a research tool on a number of CMR scanners that are supported by the Gadgetron framework. I then used a large cohort of clinically referred patients undergoing a perfusion CMR to assess the prognostic value of PTT and PBV as an imaging biomarker, comparing it to conventional prognostic clinical and imaging parameters. The study included patients from the Barts Heart Centre and Royal Free hospitals (Barts BioResource - REC ID 14/EE/0007, Royal Free Hospital - REC ID 07/H0715/101). I collected the data and performed the data analysis.
3.2 Pre- and post CABG surgery cohort (Chapter 4)

3.2.1 Study design

A prospective observational study of subjects with coronary artery disease and impaired ventricles undergoing CABG. Using advanced cardiovascular imaging with two modalities, patients were evaluated at two time points; before and at 6 months post-surgery. The global study flowchart is shown in Figure 3-1.

\[\text{CTCA, computed tomography coronary angiography; CMR, cardiac magnetic resonance; 6MWT, 6-minute walk test; NT-pro BNP, N-terminal pro b-type Natriuretic Peptide}\]
3.2.2 Recruitment

Participants were recruited from Barts Heart Centre and all surgery and investigations were performed at the same site. Patients were approached in multiple settings, including the cardiothoracic clinic, surgical pre-assessment clinic, the cardiology and cardiothoracic wards. Participant permission was sought initially by the clinician responsible for their care and patients were provided with a dedicated patient information leaflet (PIS). The initial assessment was scheduled (in the vast majority of cases) on the same day of admission to minimize travel for patients.

3.2.3 Patient selection

Patients with multi-vessel coronary artery disease and imaging evidence of impaired LV systolic function (LVEF <50%) undergoing coronary artery bypass graft surgery were eligible for recruitment. The cohort included patients presenting with stable coronary disease as well as those with non-ST elevation acute myocardial infarction (NSTEMI). Patients presenting with ST elevation MI were excluded, as well as patients with significant left main stem disease. The complete list of inclusion/exclusion criteria is as follows: Participants unwilling/unable to provide consent, patients with conventional contraindication for CMR (non-MR conditional pacemakers/implantable defibrillators, claustrophobia, asthma/COPD of sufficient severity to make adenosine contraindicated, renal impairment (creatinine clearance <30ml/min/1.73m²), high-grade conduction disease precluding the use of adenosine, age <18 years, pregnancy, patients presenting with ST elevation MI or patients in cardiogenic shock, patients with known previous allergic reactions to gadolinium, dobutamine,
adenosine or iodinated contrast, recent acute MI judged to be an important cause of left ventricular dysfunction, patients with significant left main stem stenosis (left main stem disease of >50%) needle phobic patients that would preclude blood taking.

3.2.4 Computed Tomography Coronary angiography

All computed tomography coronary angiograms (CTCA) were carried out using a 3rd generation dual source CT scanner (Somatom FORCE, Siemens, Germany). When possible, imaging acquisition was performed prospectively using ECG-triggered high-pitch spiral scanning (FLASH) or sequential scanning protocols (prospective systolic/diastolic), depending on patient’s characteristics and heart rate. For the follow up studies post CABG, the scan was extended to include the ascending aorta from the sinuses of Valsava to the subclavian arteries, in order to visualize the grafts origins. A test bolus method was used to evaluate the contrast delay for optimising coronary and graft contrast opacification, especially in view of the degree of LV impairment (and the corresponding low cardiac output) encountered in this cohort.

A large sample of local data of prospectively gated scans for CT coronary angiograms performed at Barts Heart Centre was used to estimate the dose for the CTCA related to this study, by estimating the mean dose-length product (DLP), and by using a DLP to effective dose conversion factor of 0.027 mSv/mGycm (316). The total participant dose for the two CTCA examinations incorporated in the study protocol was estimated as approximately 15mSv. As this dose was additional to standard care, the patient information leaflet explicitly
reported the risk related to the exposure to ionising radiation. Using the adult whole population lifetime risk coefficient of 1 in 20,000 per mSv, the lifetime risk of cancer is approximately 1 in 1300 for a dose of 15 mSv. The dose used in this study (including both scans), was therefore equivalent to approximately 7 years of natural background radiation.

3.2.5 Other investigations

3.2.5.1 Blood samples

Approximately 10mls of blood were taken for research purposes at the time of the initial scans (patient’s 1st visit at the BHC Imaging department. The sample was taken before the scans were performed. Blood samples were analysed for NT-pro BNP and troponin T. A further blood sample to measure serum troponin T was taken within 48 hours post CABG to assess for evidence of peri-operative myocardial injury. A further single blood test was taken at the time of the repeat scan for NT-pro BNP.

3.2.5.2 Six-minute walk test (6MWT)

The patients completed a standard 6MWT at the two study time points. This was performed at the time of their initial scans (pre-operatively) and at the time of the repeat scans (aimed at 6 months post-CABG). The 6MWT was performed using a designated 20-meter corridor with fixed turnaround points. Blood pressure, heart rate and oxygen saturation were recorded at the start and at the end of the test. The total distance walked was recorded. Patients were instructed to walk the length of the corridor at their own pace while attempting to cover as much ground as possible in 6 min. Patients were allowed to rest on a chair during the
test, but were encouraged to resume when they felt physically able to do so. The distance covered to the nearest meter, was recorded on a dedicated proforma. In almost all cases, the same member of the research team supervised all 6MWTs to minimize variations in test execution.

3.2.5.3 Patient questionnaires and Euroscore II

The patients completed healthcare questionnaires during each visit. Questionnaires included the following: European Quality of Life EQ-5D-5L and Minnesota Living with Heart Failure Questionnaires). A license was obtained from EuroQol Research Foundation for the use of the EQ-5D-5L questionnaire. EQ-5D-5L is an instrument that evaluates the generic quality of life and includes a 20-cm visual analogue scale ranging from 0 to 100 (with higher score reflecting better health) and has been used in previous heart failure studies (317). The Minnesota Living with Heart Failure Questionnaire is an instrument that has been used as a key outcome measure in multiple studies in patients with heart failure. This patient-reported outcome can be used to determine whether a treatment for heart failure is effective for improving patients’ quality of life by reducing the adverse impact of heart failure. A formal license for its use was obtained from the University of Minnesota (USA). The European System for Cardiac Operative Risk Evaluation II (Euroscore II) was estimated for each case. Euroscore II is a well validated cardiac risk model for predicting mortality after cardiac surgery (318).

3.2.6 Study set up and impact of COVID-19

3.2.6.1 Approvals and protocol modifications
Funding for the study was obtained originally obtained from Barts Charity as part of a 1-year Clinical Research Fellowship (ID: MGU0422). It was subsequently funded from the British Heart Foundation as part of a separate Clinical Research fellowship. The study was formally initiated in May 2019, after obtaining approvals from the Regional Ethics Committee (REC), the health Research Authority (HRA) and locally at Barts Heart Centre (REC ID: 19/LO/0215).

Due to the low recruitment rate (~1-3 patients per month) in the first 3 months, an amendment to the study protocol was made in December 2019, expanding the cut off LVEF for eligibility to 50% (originally <40%). In view of the impact of COVID19, the study protocol was further amended in August 2020, to minimise the impact of the research study on the clinical workflow, which meant that only patients undergoing clinical scans would be eligible for recruitment, with additional modifications in the CMR protocol to shorten study duration (low-dose dobutamine stress was no longer performed).

3.2.6.2 Impact of COVID-19

COVID-19 has had a major impact on study feasibility. Recruitment of patients was significantly affected by the COVID-19 pandemic due to suspension of all non-COVID19 related studies at our centre on at least 2 occasions. In addition to the impact of formal suspension of prospective research activities, and the need for staff redeployment, COVID-19 had a significant impact on clinical workflows with non-urgent cardiac surgery suspended or outsourced when possible. This led to a significant reduction of patients referred for cardiac surgery at Barts Heart Centre with prioritisation of high-risk cases, therefore reducing the number of
eligible patients (Figure 3-2). Patients that would have been otherwise eligible for recruitment were outsourced to alternative cardiothoracic units to minimise waiting times and to preserve intensive care bed capacity. Similarly, a number of patients expressed the wish to avoid unnecessary exposure to a hospital setting, with a significant proportion of patients declining to enrol into the study, to return for follow up scans (~50%) or delayed their post-CABG investigations beyond the original study protocol.

Figure 3-2 Study recruitment progress
*Highlighted are the periods of formal study suspension due to COVID-19. Dotted line is a theoretical projection of recruitment based on the recruitment rate achieved in the first 8 months of activity.*

3.3 CMR protocols and key sequences used across all studies
A number of CMR sequences are deployed in this thesis, primarily aiming to provide a multifaceted evaluation of patients with ischaemic cardiomyopathy
undergoing surgical revascularisation. Some of the key sequences deployed, particularly the dual sequence perfusion mapping approach, have been described in Section 1.4.2. A brief description of additional techniques particularly related to tissue characterisation that are used in this thesis are reported here.

3.3.1 Motion-corrected bright and dark blood delayed enhancement

Infarcted myocardium is typically imaged using an inversion recovery (IR) sequence. A phase-sensitive reconstruction is currently the default method used most centres, including ours, due to its superiority over the conventional magnitude reconstructed imaging, where the performance of inversion recovery delayed enhancement is highly sensitive to the inversion time (TI) selected by the operator (319,320). A further advancement in the field of LGE imaging, was the introduction of a free-breathing, motion corrected acquisition (MOCO) (321). The method requires the use of a single-shot inversion recovery that eliminates the need for breath-holding, with averaging of multiple motion-corrected images used to recover the signal to noise ratio (SNR). Motion correction is achieved by a multiscale, subpixel intensity-based image registration as previously reported (322). MOCO-LGE has been shown to be potentially faster than breath-held LGE acquisitions and in some cases allow better imaging quality that is easier to interpret (323). This is particularly relevant in this specific cohort of patients with ischaemic cardiomyopathy, where the protocol implemented was often long (with an approximate scan duration of ~1hr associated with the protocol deployed in Chapter 4). A further technique deployed in this study is the use of a dark blood late enhancement. A number of methods of varying technical complexity are available for obtaining dark blood LGE imaging (324,325). The technique has
merits particularly in identification of subendocardial late enhancement (326), the typical feature of myocardial infarction, as it allows increased scar-to-blood contrast (Figure 1-13). This is again relevant in the context of our patient cohort. The dark blood method used in this study was reported by Kellman et al (327). In brief, the sequence uses a T2-preparation pulse to shift the null time of the myocardium relative to the blood, making it possible to choose a TI that nulls both (normal myocardium and blood) at the same time.

![Figure 3-3 Study case – Bright and dark blood](image)

**Figure 3-3 Study case – Bright and dark blood**

*Example case comparing bright (left) and dark (right) blood LGE techniques in a study patient. The large transmural inferior myocardial infarction appears very similar between the 2 techniques. There more subtle subendocardial infarction at the mid anteroseptum is better visualised with the dark blood technique.*

3.3.2 Native T1 mapping

T1 mapping involves the acquisition of a series of co-registered images at different times of T1 recovery, allowing the pixelwise illustration of an absolute T1 relaxation time through the generation of a colour-encoded map (328). T1 mapping can be used for both native (pre-contrast) and post-contrast T1 relaxation measurements. In this study, a Modified Look-Locker Inversion
recovery (MOLLI) pulse sequence is used (329). Native T1 mapping can provide quantification of the composite signal from both the myocytes and extracellular space, with oedema and interstitial space alterations representing its main biological determinants (330).

3.3.3 Post contrast T1 mapping and synthetic ECV

Post contrast T1 relaxation predominantly reflects changes in the extracellular space, however the signal obtained is susceptible to changes in a number of technical parameters, including contrast dose, magnetic field and body composition, potentially introducing confounding factors in evaluation of the extracellular space. When combined with native T1 values, contrast-enhanced T1 mapping allows the calculation of ECV (extracellular volume fraction), which can be defined as a coefficient of T1 relaxation rate (R1 = 1/T1) in tissue and blood (331),(332). It requires measurement of myocardial and blood T1 before and after administration of contrast as well as the patient’s haematocrit (Hct) value. The ECV can then be estimated with the following formula:

$$ECV = \frac{\Delta R_{1t}}{\Delta R_{1b}} \times (1-Hct).$$

Our group previously described and validated the estimation of a synthetic ECV (333) which can be calculated by estimating Hct from the longitudinal relaxation rate (R1) of blood (334) (Figure 3-4)
Figure 3-4 Native and post-contrast T1 mapping

Left: Native T1 mapping (MOLLI); Right: Post-contrast T1 mapping and synthetic ECV. There is elevation of both T1 (1144ms) and ECV (74ms) at the inferior wall, corresponding to an area of chronic myocardial infarction. There is normal T1 mapping (1031ms) and ECV (29%) in areas remote to the infarct.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>bSSFP Cine (short axis)</th>
<th>SSFP Perfusion</th>
<th>LGE PSIR Bright blood</th>
<th>LGE PSIR Dark blood</th>
<th>Native T1 (MOLLI), 5s_3s_3s</th>
<th>T2 mapping</th>
</tr>
</thead>
<tbody>
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<td>360 x 270</td>
<td>360 x 270</td>
<td>360 x 270</td>
<td>360 x 270</td>
<td>360 x 288</td>
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<td>1.4 x 1.4</td>
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<td>Prospective/Trigger</td>
<td>Prospective/Trigger</td>
<td>Prospective/Trigger</td>
<td>Prospective/Trigger</td>
</tr>
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<td>1.04 / 2.5</td>
<td>1.19 / 2.8</td>
<td>1.18 / 2.8</td>
<td>1.12 / 2.7</td>
<td>1.06 / 2.5</td>
</tr>
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<td>142 / 70</td>
<td>- / 203</td>
<td>- / 198</td>
<td>- / 167</td>
<td>- / 107</td>
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<td>16</td>
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<td>192 x 116</td>
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<td>Parallel Imaging (rate / ref scan)</td>
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<td>3 / T-PAT</td>
<td>2 / Separate</td>
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<td>Partial Fourier</td>
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<td>7/8</td>
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<td>Cardiac phases</td>
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<td>Magnetization preparation</td>
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<td>Non-selective IR</td>
<td>Non-selective IR &amp; T2 prep</td>
<td>Non-selective IR</td>
<td>T2 prep</td>
</tr>
</tbody>
</table>

PSIR: Phase-sensitive inversion recovery; bSSFP: balanced steady state free precession; TE: echo time; TR: repetition time; MOLLI: modified Look-Locker sequence; SR: Saturation Recovery; IR: Inversion Recovery; T-PAT: Temporal - Parallel Acquisition Technique

(Data shown are for the Aera 1.5T scanner)
3.4 CMR analysis

Image analysis for each study is briefly described within each Result chapter (Chapters 4-7). In this section, a more detailed description of CMR analysis that applies across the studies is presented. Where possible, machine learning approaches were deployed in imaging analysis, particularly in the context of quantitative perfusion and volume assessment.

3.4.1 Volume, function and mass analysis

Volumetric analysis for all studies was performed using a balanced steady-state free precession (bSSFP) short-axis stack cine imaging. Details of the sequence are shown in Table 3-2. In chapter 4, evaluation of left ventricular volume and mass was performed automatically, using a machine learning approach previously developed and deployed by our group. In brief, this is an automated 2D deep convoluted neural network developed for segmentation of short-axis endocardial and epicardial LV contours. The algorithm was trained on 1923 participants (recruited from 13 centres in 3 countries and represented 10 scanner models) and included a range of cardiac pathologies (eg. hypertension, myocardial infarction, dilated cardiomyopathy, models of myocardial hypertrophy) (335,336). The same technique has been applied in evaluation of maximal wall thickness in patients with hypertrophic cardiomyopathy (335) and has been validated on the VOLUMES Resource database, an open source dataset (https://thevolumesresource.com) (337). Papillary muscles were considered as part of the LV blood pool. For chapters 5, 6 and 7, left volumes and mass were assessed by manual contouring of end-systole and end-diastole in the short axis stack, and papillary muscles were again excluded from the mass
estimation. The specific method used for this analysis is identical to that reported by Petersen et al, using a large reference rage dataset derived from the UK Biobank (338).

Figure 3-5 Example of machine learning segmentation
Top: Short axis bSSFP cine showing endocardial and epicardial contour segmentation in diastole. Bottom: Segmentation of endocardial contour in peak systole. Papillary muscles are considered part of the LV blood pool.
3.4.2 Quantitative late gadolinium enhancement analysis

In Chapters 4 and 6, quantitative analysis of late gadolinium enhancement is performed, based on previously published methods (251). The analysis was performed on phase-sensitive inversion recovery (PSIR) images. The process involved reviewing all long axis LGE, contiguous short axis slices and additional through plane images to confirm or refute the presence of LGE. The LVOT and the apical slice were occasionally excluded from the analysis to avoid significant partial voluming. Subsequently, epicardial and endocardial contours were manually drawn for all short axis slices. Both the inferior and superior RV insertion point were identified. For full-with half maximum (FWHM) analysis, an area with visually the greatest signal intensity was recorded. For the assessing LGE using the +5x standard deviation technique, an area of the remote myocardium (aimed for the darkest area of myocardium throughout the whole short axis stack) was defined. Example images of LGE quantification analysis is shown in Figure 3-6, and the process was repeated for all short axis slices.
3.4.3 Strain analysis with feature tracking

In Chapter 4, analysis of global longitudinal, radial and circumferential myocardial strain was performed using CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada. This was performed using three (3) long axis views and the entire short axis stack. The process involved manual segmentation of endocardial and epicardial contours in all views, in both systole and diastole. The superior and inferior RV insertion points are also manually identified. The end-diastole and end-systole is identified for all views. The mitral valve plane was manually adjusted if necessary. Example image of strain analysis is shown in Figure 3-7.
Figure 3-7 Analysis of global longitudinal strain using Feature tracking
3.5 Developing a method for pulmonary transit time estimation

In Chapter 7, a novel method of in-line estimation of pulmonary transit time (PTT) and blood volume is implemented. Extraction of PTT was possible through modification of the existing quantitative perfusion sequence which has been described previously (Section 1.4.2) and a description of the development and validation steps is included in this section.

3.5.1 Acquisition of right ventricular arterial input function (AIF)

The initial step in our effort to obtain data on PTT was the development of an in-line method of arterial input function (AIF) sampling from either side of the pulmonary circulation. The landmarks selected to achieve this were the right and left ventricles (RV and LV). As detailed in Section 1.3.1, the single bolus, dual sequence technique deployed throughout this work, relies on the estimation of the arterial input function from the LV blood pool, taken from a basal short axis slice. Theoretically, sampling of the AIF should be as close to the input location flow of the myocardium (capillary bed), in order to meet the assumptions of the indicator dilution principle, which ideally assumes a single-input system (339). Despite this, the basal LV slice for AIF sampling is the current reference position to acquire this for a number of reasons. Firstly, sampling the AIF at the basal LV slices allows sampling from a large area of blood pool, facilitating the automated selection of voxels for signal sampling. Secondly, sampling from a large area of blood pool means that technical challenges such as gating and motion correction are easier to deal with. Beyond this, the basal LV cavity is typically free from trabeculations and papillary muscles which further minimises artefacts from these structures.
To achieve extraction of PTT, the perfusion sequence was modified (by Dr Peter Kellman) so that the right ventricular (RV) arterial input function was similarly obtained in-line from the RV blood pool. The RV was selected as the anatomical landmark from which we aimed to extract right sided AIF data as it can be reliably visualised from the basal short axis slice, mitigating the need for additional sequence acquisition and variations in slice planning. This enabled the automatic segmentation of the RV blood pool within the same image. Changes were implemented directly through the Gadgetron framework.

![Image](image_url)

**Figure 3-8 Image plane used for sampling RV and LV AIF**
*Left: 4Ch Cine; Right: Short axis slice from first pass perfusion; green line shows the cross reference between the short axis and 4Ch views.*

**3.5.2 Exclusion of re-circulation from the arterial input function**

Estimation of pulmonary transit time is based on the calculation of the time interval between the two arterial input function curves. We opted to perform the curve subtraction using the centroid of the 2 AIF curves (rather than the peak), as this was shown to be a more reliable method of estimating the transit time in
phantom experiments performed by Ugander et al (340). Beyond this, we also observed that the shape of the AIF appeared to be affected by both structural and functional pathologies involving the two ventricles, suggesting that accurate analysis of each curve would potentially allow a more accurate cardiac physiological assessment through evaluation of PTT. This observation was in agreement with historical data (341). Indeed, the indicator dilution curves were previously used for the calculation of valve regurgitation (341) as well as the estimation of intra-cardiac shunts (206). Examples of typical AIF shapes based on pathology are shown in Figure 3-9.

![Figure 3-9 Arterial input function curves in the presence of valve disease](image)

*Left: Healthy volunteer; Middle: Patient with moderate tricuspid regurgitation; Right: Patient with moderate mitral regurgitation (Unpublished data, courtesy of Peter Kellman, SCMR 2021)*

As the exact position of the centroid is affected by the entire indicator dilution curve, accurate detection of the primary curve is important. For this reason, the arterial input function curve had to be an accurate representation of the first passage of contrast, therefore different methods of mathematically excluding the re-circulation were tested (Section 1.3.7). We eventually adopted the use of a log-normal method of deriving the primary curve as shown in Figure 3-10.
Elimination of the re-circulation component of the AIF curves

Based on the indicator dilution principle (Section 1.3.6), conversion of the signal intensity to gadolinium units meant that the area under the primary curve after re-circulation was excluded (ie. extrapolated curve using a log-normal method) would correspond to the stroke volume of each ventricle. This step was necessary to allow accurate derivation of the pulmonary transit time, by estimating the time between the two centroids (vertical lines).

3.5.3 Evaluating the accuracy of AIF detection and estimation of stroke volume

Once re-circulation was eliminated and the primary first pass perfusion curve was identified, the area under each curve represented the stroke volume from each ventricle. To assess the accuracy of this method, we then compared the stroke volume derived from the integration of the left ventricular AIF curve, to the stroke volume derived in the same patient using either volumetric (conventional short axis cine imaging) or flow measured with phase contrast CMR (Figure 3-11). This process provided a degree of validation for a number of steps involved in the derivation of AIF stroke volume:

1. Automated detection of LV and RV blood pools following motion correction
b) Appropriate signal detection (avoiding oversaturation of signal particularly in the RV blood pool)

c) Conversion of signal to gadolinium concentration

d) the accuracy of the shape of the first pass AIF curves, which were subsequently used to derive the pulmonary transit time.

Figure 3-11 Validation of left ventricular stroke volume estimation using AIF

Left: Comparison between arterial input function (AIF) - derived stroke volume versus stroke volume derived from volumetric analysis. Right: AIF-derived stroke volume versus phase-contrast CMR. Data courtesy of Peter Kellman (Presented at SCMR 2021).
3.6 Data storage

Data for all studies was stored on a Barts Health NHS Trust server, within a dedicated research drive. For Chapter 4, data were collected on a dedicated proforma and was transcribed onto spreadsheets and subsequently stored on NHS computers. I set up a dedicated Research Electronic Data Capture platform (UCL REDCap) that captured non-identifiable clinical information relevant to this project. Data was validated at entry into an electronic case report form and an audit trail was maintained. Handling and storage of data, planning, assessment and quality assurance conformed to the GCP/ GDPR standards.

3.7 Statistical analysis

Data analysis was performed using SPSS software package (IBM SPSS Statistics, version 26.0). In Chapter 4, some of the data visualisation was prepared using GraphPad, Prism Version 9.1.1. The exact methodology and statistical methods used are described in details within each Chapter.
Chapter 4  Impact of surgical revascularisation in patients with ischaemic cardiomyopathy

4.1 Introduction

Coronary artery bypass graft surgery effectively relieves angina and in selected patients improves functional capacity, quality of life and survival (32). However, the benefits of CABG in the context of heart failure secondary to ischaemic cardiomyopathy is less clear. Previous studies suggested that this clinical benefit is augmented in patients with impaired LV function, but these conclusions were drawn from subset analysis of the original landmark trials (43,61) or from retrospective observational datasets (59). More recent evidence from the STICH trial confirmed a survival benefit at 10 years after surgical revascularisation among those with impaired LV function (29); an effect not identified from survival analysis at 56 months.(65).

There is therefore a degree of uncertainty with regards to the mechanisms by which coronary artery bypass surgery offers a functional and survival benefit and why its impact on mortality is not more obvious early after revascularisation (342). Importantly, it is unclear whether the physiological changes responsible for improving symptoms, functional status and survival may differ. Restoration of myocardial blood flow (MBF) is conceptually the principal objective of CABG surgery, and in clinical practice is often the process that triggers the need for revascularisation.

Beyond this, specific pathophysiological processes such as myocardial viability, graft failure, native disease progression, peri-operative injury and completeness
of revascularisation mean that physiological evaluation of the impact of surgery both at structural and functional level likely requires simultaneous consideration of these processes (Figure 4-1).

As detailed in Chapter 1 (Section 1.4), quantitative cardiac magnetic resonance (CMR) imaging can offer a comprehensive assessment of myocardial structure, function and perfusion. Similarly, CT coronary angiography has demonstrated high diagnostic accuracy in identifying graft stenosis or occlusion in patients post CABG (343), and can provide insights with regards to the anatomical extent of revascularisation at the time of CMR evaluation.

Considering the invasive nature of surgical revascularisation and the associated peri-operative risk reported even in contemporary registries (47), improved understanding of the pathophysiological impact of CABG on the myocardium and the coronary circulation is important. In this study, I deployed paired imaging techniques including quantitative perfusion CMR and CT coronary angiography, before and after CABG, to gain insights into the key processes that characterise the physiological changes following revascularisation in patients with impaired ventricles. We hypothesised that MBF augmentation would be a determinant of improvement in functional status, and that the extent of MBF augmentation would be closely associated with the degree of revascularisation achieved.
Pathophysiologica processes predictive of poor functional recovery post CABG

Potential pathological mechanisms determining functional recovery post CABG and the imaging tests and sequences available to interrogate them.

CMR – Cardiac magnetic resonance; LGE – late gadolinium enhancement imaging; ECV – extracellular volume; MOCO PSIR – motion-corrected, phase-sensitive inversion recovery; CTCA – CT coronary angiography; MPR – myocardial perfusion reserve
4.2 Methods

4.2.1 Patients and study design

This was a single-centre prospective study with paired evaluation pre and post operatively, performed at Barts Heart Centre, London, United Kingdom. The details of the study design and recruitment method, including details of inclusion and exclusion criteria are presented in Chapter 3 (Section 3.2.3). In brief, the study aimed to recruit patients with multi-vessel coronary artery disease and impaired LV systolic function (LVEF <50%) that were scheduled to undergo coronary artery bypass graft surgery. Exclusion criteria included the presence of contra-indications to CMR perfusion testing, presentation with STEMI followed by inpatient surgery, acute cardiac decompensation or evidence of significant left main stem disease.

The primary outcome measure was the improvement of functional markers at 6 months post CABG as measured by the change in distance walked in a 6-minute walk test (Section 3.2.5.2), and change in patient reported symptoms and quality of life (measured by the EQ-VAS and Minnesota Living with Heart Failure Questionnaires; Section 3.2.5.3). Secondary outcome measures included changes in left ventricular ejection fraction and wall motion score, as well as changes in global and segment myocardial blood flow indices (stress myocardial blood flow and myocardial perfusion reserve). Blood biomarkers were collected as reported in Section 3.2.5.1.
4.2.2 Cardiac magnetic resonance imaging (CMR)

All patients underwent CMR at 1.5 Tesla using the same scanner (Magnetom Aera, Siemens Healthcare Erlangen, Germany) with a 30-channel phased array receiver coil. I designed a dedicated protocol to meet the study requirements and this is summarised in Figure 4-2. Details of the typical sequence parameters are shown in Table 3-2. In brief, the protocol included standard cardiac localizers and trans-axial bright blood stacks for extracardiac anatomy evaluation and to help planning subsequent views. Long and short axis cine were acquired using a standard balanced steady-state free precession pulse sequence. T1 mapping was performed using a Modified Look-Locker Inversion recovery sequence and 3 short axis slices (basal, mid, apex) were acquired. A single mid-short axis T2 map was acquired. Adenosine was administered as per standard clinical protocols (344) (initial rate of 140 mcg/kg/min for 4 minutes, up to 175mcg/kg/min) to induce vasodilator stress. At peak stress, a gadolinium-based contrast agent (gadoterate meglumine, Dotarem, Guerbet, Paris, France) was injected at 4 mL/s at a dose of 0.05 mmol/kg. Rest perfusion was then performed after a 10min period allowing for normalization of heart rate and attenuation of the vasodilator effect of adenosine, and a further identical contrast injection was administered. Blood pressure was recorded both at peak stress and just prior to rest perfusion acquisition. Rate pressure product (RPP) was used for adjusting the comparison between the two paired CMR perfusion studies. RPP was estimated as the product of heart rate (bpm) and systolic blood pressure (mmHg) at the time of perfusion acquisition. Routine medications, including β-receptor antagonists, were not be altered
before testing. Viability was assessed using late gadolinium enhancement (and in a study subset using low dose dobutamine).
Figure 4-2 CMR protocol

SA – short axis; MOLLI – Modified Look-Locker Inversion recovery; Gd – gadolinium; EGE - early gadolinium enhancement; LGE – late gadolinium enhancement; LVOT – Left ventricular outflow tract; ECV – extracellular volume fraction. Total scan time ~ 60min. (Dobutamine was only performed for a small number of patients in the pre-op scan, in view of the protocol modification in response to the COVID-19 pandemic)
4.2.3 Cardiovascular magnetic resonance imaging analysis

Image analysis was performed using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Volume and function analysis was performed using a machine learning algorithm (336), as described in Section 3.4.1. This was particularly important in order to minimise bias in the interpretation and comparison of paired studies pre and post CABG. Mapping analysis was performed using the pixel-wise coloured maps generated inline (Figure 3-4). Both global T1 and ECV were estimated by contouring the endocardial and epicardial borders of all 3 short axis slices, using a 10% offset border to minimise blood pool contamination. Regional T2 values are obtained by drawing a region of interest (ROI) at the mid septum. If LGE (or artefact) was present in this territory, remote, “non-infarct” myocardial areas are measured.

Automated analysis of myocardial perfusion was performed entirely in-line, with both global and regional (American Heart Association, AHA) values for myocardial blood flow at rest and with stress included in the sequence output. A detailed methodology of this quantitative perfusion technique is presented in Section 1.4.2 and the technical details have been previously published (100). Myocardial perfusion reserve was calculated as the ratio of maximal stress flow to rest flow.

Wall motion was graded as normal (1), hypokinetic (2), akinetic (3), and dyskinetic (4) using a 16-segment AHA model. Viability was considered present when there was an improvement in the wall motion of at least 1 grade, except when this involved transition from dyskinesia to akinesia. Analysis of myocardial
deformation and calculation of myocardial strain was performed using the feature tracking package from CVI42 as shown in Section 3.4.3.

Qualitative analysis of late gadolinium enhancement (LGE) was performed using a 5-point scale (0 indicated no LGE, 1 indicated 1-25%, 2 indicated 26 to 50%, 3 indicated 51 to 75% and a score of 4 indicated 76-100%) (345). Viable myocardial segments were deemed those with LGE transmurality of <50%. Quantitative analysis of late gadolinium (LGE) images was performed using the full-width half maximum and 5-standard deviation methods (251) as described in Section 3.4.2.

4.2.4 Computed Tomography Coronary angiography (CTCA) analysis
Details of CTCA acquisition were presented in Section 3.2.4. CT coronary angiograms were analysed using Syngo.CT Cardiovascular Engine (Siemens Healthineers). Baseline studies were analysed for coronary artery calcium scoring performed using standardised Agatston criteria (346). Vessels with prior stenting were excluded from calcium score evaluation. Coronary anatomy analysis was performed as per clinical practice standards. Disease severity was assessed using the Society of Cardiovascular Computed Tomography (SCCT) coronary scale for stenosis severity (347). All CTCA studies were reported by the fellow and a Level 3 accredited reporter to ensure any incidental or extracardiac findings were clinically reviewed. In patients where graft failure was incidentally detected in the post-operative scans, a formal clinical referral to the cardiology team at Barts Heart Centre was made.
4.2.5 Assessment of coronary revascularisation at a segmental level

To evaluate the impact of revascularisation on myocardial perfusion indices a segmental analysis of stress MBF and MPR based on each AHA-derived myocardial territory was performed. Correlation between myocardial segments and coronary vessel anatomy was based on the AHA model using the conventional nomenclature (348). Adjustments to the coronary vessel distribution and their corresponding myocardial segments were made as needed, using data from CTCA (eg. confirmation of RCA dominance, presence of an intermediate vessel). The final designation of a coronary vessel to a CMR-derived myocardial perfusion territory was performed by visual correlation of CTCA and CMR data as shown in Figure 4-3.
Figure 4-3 Correlation of coronary anatomy and myocardial perfusion using stress first pass perfusion CMR images and maps, and CTCA images to designate coronary supply to myocardial segments.

Example case demonstrating the method for correlating myocardial perfusion segments to coronary vessels. As CMR perfusion is conventionally acquired using 3 short axis slices, the exact location of each slice was checked on long axis views and correlated to identical CTCA planes. The coronary anatomy supplying the relevant territory was then checked using CT coronary artery data.
Evaluation of whether a myocardial segment was adequately revascularized was based on recently published methodology for defining complete revascularisation (349). In brief, a coronary vessel (and its corresponding myocardial segment) was considered anatomically revascularized if all anatomically significant lesions (any lesion ≥50% severity on visual assessment on CTCA) were bypassed by a patent graft (with <50% stenosis on visual assessment).

**Figure 4-4 Completeness of revascularisation in each coronary vessel.**

*Reproduced from Ali et al. J Am Heart Assoc. 2021 May 4;10(9) under the terms of the Creative Commons CC BY license.*
4.2.6 Statistical analysis

The primary outcome measure was a change in 6-minute walk test distance that would correspond to a minimally clinically important difference (MCID). Previous studies have reported MCID to range between ~15 - 35m (350), however these studies were predominantly in pulmonary disease. In view of this, we used a distance of 30 meters, which was the figure used to calculate the sample size in CONFIRM-HF (351) and was most relevant to this study. The standard deviation of difference in 6MWT distance ranges between 70 to 100 meters (eg. 72 meters in the FAIR-HF study (317)), therefore a middle estimate of 85m was used.

The effect we wished to detect therefore corresponded to ~12% of the variance in 6MWT disease (i.e. partial r² = 0.12 or Cohen's f² = 0.15). To detect an effect of this size with 80% power at alpha = 0.05 using linear multivariable regression with 4 variables of interest and a total of 10 covariables (i.e. 6 potential confounders) we estimated that 85 participants would be needed. We also estimated that a number of patients would not be able to complete the follow up assessment at 6 months, therefore we aimed to recruit a total of 100 participants.

Continuous variables are presented as mean ± SD; categorical as absolute values and percentages. Normality was assessed using a Kolmogorov-Smirnov test. Comparison of means for continuous variables was performed using a paired Student-t test or Wilcoxon signed-rank test. Correlations were assessed using Spearman’s rank correlation coefficient. Data was analysed at a patient level (eg. using global MBF and MPR for each patient) as well as at a segmental level (eg. assessing change in MBF and MPR for each myocardial segment...
according to the 16-segment AHA model). To account for clustering and controlling for within subject dependency (e.g. 16 myocardial segments derived from a single patient), generalised linear equation models were deployed. The impact of successful revascularisation and the presence of LGE on segmental MBF was assessed by fitting these as variables in the model. In order to test whether the revascularisation effect differs between those with and without LGE, an interaction term between these variables was also included in the model. Generalised linear equation models were used to assess the impact of revascularisation on wall motion score using the same method. Statistical analysis was performed in SPSS (IBM SPSS statistics, Version 26.0). Before and after plots shown in this chapter were constructed using GraphPad, Prism Version 9.1.1.
4.3 Results

830 patients listed to undergo coronary artery bypass graft surgery were screened. 785 patients were excluded at the initial screen, mainly due to either the presence of preserved LV systolic function or the presence of left main stem disease. 45 patients were approached in clinic and undergone a second screen (Figure 4-5).

*Figure 4-5 Flow diagram showing patient screening and recruitment*

LVEF cut off was increased from <40% to <50% in December 2019. Devices include permanent pacemakers, cardiac resynchronisation therapy (CRT) and
implantable cardioverter defibrillator (ICS)s. Renal impairment was a study exclusion if eGFR <30ml/min. Other: Due to the nature of the study centre (tertiary cardiothoracic centre), some patients were transferred from district general hospital <24hrs prior to their surgical procedure, therefore it was not possible to recruit them in the study.

A total of 18 patients were recruited (83% male, mean age 62 ± 8.8 years). From these 17 have undergone a coronary artery bypass graft surgery (1 patient refused to undergo surgery after recruitment) and 9 patients completed their follow up scans. 1 patient had insertion of a permanent pacemaker and 2 patients had deterioration in renal function prohibiting participation in the study. 5 patients were lost in follow up (these either declined invitation to attend for repeat scans in order to minimise their exposure to COVID-19, or were not contactable). Among the 17 patients median time between the CMR study and operation was 1 day (IQR, 1-5days). Demographics, baseline characteristics and pre-operative evaluation details are shown in Table 4-1.
<table>
<thead>
<tr>
<th>Demographics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=18</td>
<td></td>
</tr>
</tbody>
</table>

**Demographics**
- Age, years: 62 ± 8.8
- Male (%): 15 (83%)
- BSA (m²): 2.04±0.22
- BMI (kg/m²): 31.9±7.67

**Presentation prompting referral for surgery : n(%)**
- Stable angina: 10 (55.6)
- NSTEACS: 7 (38.9)
- Other: 1 (5.6)

**Comorbidities/ Relevant past medical history**
- Stroke/TIA: 1 (5.6)
- Hypertension: 17 (94.4)
- Diabetes: 12 (66.7)
- Hyperlipidaemia: 17 (94.4)
- Atrial fibrillation: 2 (11.1)
- Renal disease (eGFR < 90): 7 (38.9)
- Family history of ischaemic heart disease: 12 (66.7)
- Previous myocardial infarction: 18 (100)
- Previous PCI: 6 (33)
- Smoking history: 9 (50)

**Medication**
- ACE-I, ARB: 18 (100)
- Calcium channel blocker: 1 (5.6)
- B-blocker: 17 (94.4)
- Statin: 18 (100)
- Antiplatelet: 18 (100)
- Diuretics: 7 (38.9)
- Nicorandil, Ranolazine, Nitrate: 9 (50)
- Mineralocorticoid receptor antagonist: 8 (44.4)

**Number of diseased vessels on coronary angiography**
- 1 vessel disease: 0
- 2 vessel disease: 1 (5.6)
- 3 vessel disease: 17 (94.4)

**LVEF on pre-op echocardiogram**
- Normal (>52%): 0
- Mildly abnormal (41-51%): 3 (16.7)
- Moderately abnormal (30-40%): 12 (66.6)
- Severely abnormal (<30%): 3 (16.7)

**NYHA classification**
- Class I: 3 (16.7)
- Class II: 7 (38.9)
- Class III: 7 (38.9)
- Class IV: 0

**CCS classification**
- CCS I: 11 (61.1)
- CCS II: 3 (16.7)
- CCS III: 3 (16.7)

**Euroscore (%)**
- 1.86±0.96

**Patient-completed questionnaires**
- MLHFQ total score: 41.9±21.5
<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D-3L total score</td>
<td>60±14.8</td>
</tr>
</tbody>
</table>

**6-minute walk test (6MWT) mean.**
- 6MWT distance covered (m)       | 365±78      |
- Hear rate at the start (bpm)     | 73±10       |
- Hear rate at the end (bpm)       | 81±10       |

**Blood sample analysis (pre-op)**
- Haemoglobin (g/dL)               | 131±12.6    |
- Haematocrit (L/L)                | 0.40±0.03   |
- Urea (mmol/L)                    | 6.6±2.6     |
- Creatinine (umol/L)              | 94.3±21.8   |
- Troponin T (ng/L)                | 19.5 ± 10.3 |
- NT-pro BNP (pg/ml)               | 1487±1439   |

* Qualitative categories of LVEF based on the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging; (352). TIA – transient ischaemic attack; PCI – percutaneous coronary intervention; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; NYHA – New York Heart Association; CCS – Canadian Cardiovascular Society Angina Classification; MLHFQ - Minnesota Living with Heart Failure Questionnaire; LVEF - Left Ventricular Ejection Fraction.
Patients recruited had significant comorbidity (12/18 had diabetes, 17/18 had hypertension and hypercholesterolaemia). All patients had a diagnosis of chronic coronary syndrome (22) at the time of study recruitment and all patients had stable symptoms. Seven patients had a history of recent non-ST elevation acute coronary syndrome (NSTEMI), and in these patients the median time between study assessment and ACS was 120 days (33,180). Most patients recruited had symptomatic heart failure based on their NYHA classification (14/18 NYHA class II/III) and the results of the MLHFQ (41.9±21.5) and EQ-VAS (60±14.8) scores. There was a high percentage of patients receiving guideline-directed medical therapy as shown in Table 4-1, with 17/18 patients receiving ACE-I/ARB, B-blockers, aspirin and statin. Nearly half of the patients were also on a mineralocorticoid receptor antagonist. No patient was receiving an angiotensin receptor neprilysin inhibitor or a sodium glucose transporter inhibitor. All patients recruited had impaired LVEF on their pre-op echocardiogram, with 15 out of 18 patients classified as having at least moderate LV impairment (LVEF ≤40%).

Six-minute walk test (6MWT) was successfully completed by all participants. Mean distance covered was 365±78m. In a univariate analysis there was an association between the distance covered and Euroscore II (B=-65.01; 95 CI -93, -36; p<0.001) (Figure 4-4-6) and NYHA classification (B=-73.31; 95 CI -112.9, -33.6; p=0.001). There was no significant association between the initial 6MWT distance covered and CCS (p=0.062), baseline LVEF (p=0.561), NT-proBNP (p=0.816), stress MBF (p=0.738), MPR (p=0.607) and total calcium score (p=0.887).
Results from the pre-operative CMR studies are shown in Table 4-2. Mean LVEF was 43.9% ±9.6. All patients had evidence of late gadolinium enhancement with 17 out of 18 patients having evidence of previous infarction in at least one coronary territory (1 patient having non-ischaemic LGE pattern). Mean stress MBF was 1.33 ± 0.46ml/g/min and mean rest MBF was 0.81 ± 0.15ml/g/min. Mean myocardial perfusion reserve was 1.75 ± 0.65. Median total calcium score (after excluding 6 vessels with prior stenting) was 922, IQR 331-2545). There was a significant association between baseline NT-pro BNP and stress MBF ($r = -0.69$, $p=0.006$) and MPR ($r=-0.68$, $p=0.007$).
Table 4-2 CMR analysis of pre-CABG studies (N=18)

<table>
<thead>
<tr>
<th>CMR parameters</th>
<th>N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDVi (ml/m²)</td>
<td>112±40</td>
</tr>
<tr>
<td>LVESVi (ml/m²)</td>
<td>66.9±40</td>
</tr>
<tr>
<td>LVSVi (ml/m²)</td>
<td>45.5±10</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>66.1±15</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>43.9±9.6</td>
</tr>
<tr>
<td>MAPSE (mm)</td>
<td>9±3</td>
</tr>
<tr>
<td>LAi (cm²/m²)</td>
<td>14.2±3.4</td>
</tr>
<tr>
<td>RVEDVi (ml/m²)</td>
<td>69±17</td>
</tr>
<tr>
<td>RVESVi (ml/m²)</td>
<td>30±10</td>
</tr>
<tr>
<td>RVSVi (ml/m²)</td>
<td>38±11</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>58±8</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>18±4</td>
</tr>
<tr>
<td>RAi (cm²/m²)</td>
<td>11±2.26</td>
</tr>
<tr>
<td>Aortic Root diameter (Level of Sinuses) (mm)</td>
<td>34±4.6</td>
</tr>
<tr>
<td>Total wall motion score (TWMS)</td>
<td>24±6.57</td>
</tr>
</tbody>
</table>

Quantitative myocardial perfusion analysis

- Stress MBF (ml/g/min) 1.33±0.46
- Rest MBF (ml/g/min) 0.81±0.15
- Myocardial perfusion reserve (MPR) 1.75±0.65

Tissue Characterisation

- Global native T1 (ms) 1052±36
- Septal native T1 (ms) 1035±30
- Blood T1 (ms) 1633±89
- Septal T2 (ms) 45±3
- Global Synthetic ECV (%) 31.7±4
- Bright Blood LGE (g) 24.8±19
- Dark Blood LGE (g) 23.6±15

4.3.1 Clinical and functional outcomes post CABG

A total of 16 patients underwent CABG-only surgery and 1 patient underwent CABG surgery with mitral valve replacement. 1 patient returned to theatre due to sternal wound wash out and 1 patient returned to theatre due to post-operative tamponade. There were no deaths in the patients operated and all operated patients were discharged home. Paired follow-up assessments post CABG were
completed in 9 patients, with median time between surgery and follow up CMR of 197 days (IQR 189, 326). There were no clinical adverse events between surgery and follow-up assessment. No patient had evidence of new myocardial infarction or new area of LGE on their repeat CMR. Among the 9 patients, 3 had evidence of vein graft failure at the follow up CTCA (3 out of 15 (20%) vein grafts), and no patient had failure of the LIMA graft.

Compared to baseline evaluation there was a significant improvement in the 6-minute walk distance completed at follow up with a 47m ± 38 (p=0.006) increase in distance covered. In univariate analyses, age (p=0.50), change in LVEF (p=0.46), number of LGE segments (p=0.241) and baseline NYHA (p=0.31) and CCS (p=0.12) classifications were not predictive of the change in distance covered. There was no association between the change in stress MBF or MPR and the degree of improvement in 6MWT distance.

There was a significant improvement in patient reported symptoms based on the EQ-VAS (pre-op 57.8±17.7 vs post-op 77.8± 20.9; mean increase 20±24.5 points; p=0.040), with higher values indicating better overall health status. There was also a trend for improvement in the MLHFF score (lower values indicating better health status), however this did not reach statistical significance (pre-op 40.9±26.7 vs post-op 24.8±24.5; p=0.053). There was no association between the improvement in the EQ-VAS score and change in LVEF (p=0.290) or change in stress MBF (P=0.683).
There was improvement in both the 6-minute walk test distance and EQ-VAS score following surgery (*p-values derived from paired student t-tests).

4.3.2 Impact of coronary artery bypass surgery on CMR parameters

Following CABG, there was a significant reduction in left ventricular diastolic volume (247.7ml ± 90.8 vs 215.9ml ± 60.8; p=0.042). There was no other significant difference in CMR volume parameters of either the LV or the RV as shown in Table 3.3. Similarly, there was no difference in LVEF (p=0.292), RVEF (p=0.218), WMS (p=0.068) or myocardial strain indices.

There was no difference in global quantitative perfusion parameters, with no significant difference in global stress MBF (pre-CABG 1.24 ± 0.46 ml/g/min vs post-CABG 1.39 ± 0.36 ml/g/min; p=0.343), global rest MBF (pre-CABG 0.70 ± 0.11ml/g/min vs post-CABG 0.67 ± 0.17ml/g/min p=0.590) or global MPR (pre-CABG 1.74 ± 0.48 vs post-CABG 2.11 ± 0.43; p=0.086). There was no difference in rate-pressure product (RPP) between stress perfusion tests before and after surgery (10,955 ±1,432 vs 11,157 ±2,896; p=0.800).
Table 4-3 CMR parameters pre and post CABG

<table>
<thead>
<tr>
<th>CMR parameter</th>
<th>Pre CABG (n=9)</th>
<th>Post CABG (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume and function analysis</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LVEDV (ml)</td>
<td>247.7 ± 90.8</td>
<td>215.9 ± 60.8</td>
<td><strong>0.042</strong></td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>136.4 ±92.7</td>
<td>105.5 ± 58.3</td>
<td>0.074</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>50 ± 18</td>
<td>53 ± 12</td>
<td>0.292</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>150 ± 40</td>
<td>160 ± 52</td>
<td>0.180</td>
</tr>
<tr>
<td>RVEDV (ml)</td>
<td>155 ± 29.8</td>
<td>148 ± 16.9</td>
<td>0.444</td>
</tr>
<tr>
<td>RVESV (ml)</td>
<td>64.7 ± 19.3</td>
<td>54.6 ± 15.6</td>
<td>0.078</td>
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<tr>
<td>RVEF (%)</td>
<td>58 ± 8</td>
<td>61 ± 8</td>
<td>0.218</td>
</tr>
<tr>
<td>Wall motion score</td>
<td>27 ± 10</td>
<td>23 ± 7</td>
<td>0.068</td>
</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>-9.4 ± 3.9</td>
<td>-9.9 ± 3.5</td>
<td>0.514</td>
</tr>
<tr>
<td>Global circumferential strain (%)</td>
<td>-13.3 ± 4.8</td>
<td>-12.5 ± 3.8</td>
<td>0.420</td>
</tr>
<tr>
<td>Global radial strain (%)</td>
<td>-18.7 ± 9.6</td>
<td>18.6 ± 6.9</td>
<td>0.965</td>
</tr>
<tr>
<td><strong>Quantitative perfusion analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress MBF (ml/g/min)</td>
<td>1.24 ± 0.46</td>
<td>1.39 ± 0.36</td>
<td>0.343</td>
</tr>
<tr>
<td>Rest MBF (ml/g/min)</td>
<td>0.70 ± 0.11</td>
<td>0.67 ± 0.17</td>
<td>0.590</td>
</tr>
<tr>
<td>Myocardial perfusion reserve</td>
<td>1.74 ± 0.48</td>
<td>2.11 ± 0.43</td>
<td>0.086</td>
</tr>
<tr>
<td>Stress rate-pressure product</td>
<td>10955 ±1432</td>
<td>11157 ±2896</td>
<td>0.800</td>
</tr>
<tr>
<td>Percentage increase in HR</td>
<td>23 (20-38)</td>
<td>20 (14-27)</td>
<td>0.063</td>
</tr>
<tr>
<td><strong>Late gadolinium enhancement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bright blood LGE (g)</td>
<td>28.9 ± 23.6</td>
<td>23 ± 14.8</td>
<td>0.261</td>
</tr>
</tbody>
</table>

Results shown as mean ± standard deviation or median (interquartile range).
4.3.3 **Impact of revascularisation on CMR parameters at segmental level**

The impact of coronary vessel revascularisation on myocardial blood flow and function was also assessed at a myocardial segmental level, with a total of 144 segments analysed (based on a 16-segment AHA model). As outlined above, successful revascularisation was assessed from follow-up CTCA using published methodology (349) Figure 4-4. At follow up, 91 (63%) segments had patent native vessels or grafts denoting successful anatomical revascularisation, whereas 53 (34%) segments were not revascularized. Reasons for incomplete revascularisation included: vein graft failure (11 segments), no graft placement (31 segments) and presence of significant native vessel stenosis distal to the graft anastomosis (11 segments). Among the non-revascularized segments, 16 (30%) had evidence of LGE and in only 9 (17%) the segment would have been considered non-viable based on pre-op imaging (LGE transmurality of ≥50%). Three-dimensional (3D) reconstructions of native and graft vessel anatomy for all patients are shown in Figure 4-8.
Figure 4-8 Coronary anatomy (3D reconstruction) post CABG
4.3.3.1 Impact of revascularisation on segmental myocardial blood flow

Segments that were successfully revascularised showed a significant increase in segmental stress MBF and MPR from baseline to post CABG. Using a generalised linear model for controlling for within subject dependency, there was a significant increase in absolute stress MBF and MPR in revascularized segments (increase in stress MBF 0.42ml/g/min, 95% CI 0.11,0.73; p=0.008; increase in MPR 0.79, 95% CI 0.50, 1.08; P≤0.001). In contrast, for non-revascularized segments, there was no change in either stress MBF (-0.15ml/g/min, 95% CI -0.38, 0.08; p=0.193) or MPR (-0.03, 95% CI -0.61,0.56; p=0.925) from baseline to post surgery.

The change in stress MBF remained significant after adjusting for the presence of LGE (p<0.001), suggesting that the difference in stress MBF observed could not be explained by differences in LGE. Furthermore, there was no significant interaction between revascularisation and LGE (p=0.10), suggesting that the impact of revascularisation was not significantly affected by the presence of LGE. Similarly, the change in absolute stress MBF was not affected by the difference in stress rate pressure product (RPP) between the paired stress perfusions tests (p=0.095). There was no significant impact of revascularisation on rest MBF (0.21ml/g/min, 95% -0.16, 0.20; p=0.823) even after adjusting for the presence of LGE.

4.3.3.2 Impact of revascularisation on myocardial wall motion

The impact of revascularisation on myocardial contractility was evaluated at a segmental level using visual wall motion score evaluation. Among the 91 revascularised segments, 21 (23.1%) had improvement in at least 1 point in their
WMS, 67 (73.6.%) had no change and 3 segments (3.3%) had deterioration in their WMS Figure 4-9. In contrast, among the 53 non-revascularized segments, 7 (13.2%) had improvement in their WMS, 44 (83%) had no change and 2 (3.8%) had deterioration in WMS. Using a generalised linear model controlling for within subject dependency, successful revascularisation did not have a significant impact on WMS change even when the model was adjusted for baseline WMS and the presence of LGE (p=0.621).

The impact of revascularisation was further evaluated based on LGE transmurality detected on pre-operative CMR. Among the 15 revascularized segments with LGE transmurality of 1%-25%, 4 (27%) showed improvement in WMS and 11 (73%) remained unchanged. Among 23 segments with 26%-50% LGE transmurality, 10 (44%) showed improvement, 12 (52%) remained unchanged and 1 (4%) segment deteriorated. Among 5 segments with transmurality of 51%-75%, 3 segments showed improvement, and 2 segments remained unchanged. A single segment with LGE transmurality of 76%-100% was revascularized and this showed improvement in contractility in the post-operative CMR study. Figure 4-9.
Figure 4-9 Impact of revascularisation and LGE on myocardial contractility

Top: Impact of myocardial revascularisation on wall motion score change based on the baseline contractility. Bottom: Impact of myocardial revascularisation on wall motion score based on pre-operative late gadolinium enhancement (LGE) transmurality. In both graphs, a proportion of conventionally-defined “non-viable” segments (LGE >50%) appear to improve their contractility following successful revascularisation.
4.4 Discussion

In this proof-of-concept analysis, we report that: 1) in patients with impaired LV function undergoing coronary artery bypass surgery a significant improvement in functional status was observed post CABG, as assessed with a 6-minute walk test and patient-reported symptoms; 2) that surgical revascularisation in patients with impaired LV function often results in only partial revascularisation of the myocardium; 3) that successful revascularisation using coronary grafts conduits results in improvement of segmental stress myocardial blood flow and perfusion reserve. 4) that there is significant heterogeneity in terms of the structural and functional impact of surgery between individual patients.

4.4.1 Changes in functional status post CABG

Studies have previously demonstrated that coronary artery bypass surgery improves patient symptoms, exercise capacity and quality of life compared to a strategy of medical therapy (353,354). Six-minute walk testing is often used as a measure of functional capacity and was shown to be associated with mortality in various disease models, including heart failure (355) and pulmonary hypertension (356) and was also shown to correlate with indices of cardiopulmonary exercise (CPEX) testing (357). Similarly, the EQ-VAS score has previously been deployed in studies in patients with both respiratory disease (358) and heart failure (359), as a global measure of health-related quality of life.

Our baseline pre-operative results (n=18) are indeed comparable to studies in similar patient cohorts. In the FAIR-HF (317) study, which evaluated the impact of intravenous iron in symptomatic patients with heart failure and reduced LVEF
(LVEF ≤45%), the distance covered at a baseline 6MWT was 274±105 meters. In a more comparable group derived from a sub-study of the original STICH trial (LVEF ≤35%; patients scheduled for CABG), the baseline 6MWT distance reported (340±117 meters) was very similar to our results (365±78 meters).

A number of both clinical variables, including the presence of respiratory pathology, diabetes, age and sex (361), as well as societal and cultural factors can affect exercise performance among patients with stable coronary artery disease (362). Adjustment for these in a multivariate analysis within our cohort was not possible in view of the sample size, therefore the analysis is limited to univariate associations. Despite this, in agreement with previous data, we demonstrate an association between pre-operative 6MWT distance and NYHA class (363). Similarly, as Euroscore II incorporates a number of clinical and imaging parameters (including LVEF and NYHA class), it is not surprising that this parameter also demonstrated a significant association with the pre-op 6MWT distance (Figure 4-4-6). A difficulty in interpreting the result of a 6MWT among patients with coronary artery disease is related to the presence of effort related symptoms. Although none of the patients tested in our study terminated the test early (either due to angina or dyspnoea), it is conceivable that patients might have regulated their effort based on their prior awareness of what level of activity would trigger symptoms.

Despite the very limited sample size used in this study, we confirmed that at a median follow up of 197 days post CABG, there was significant improvement in both 6-minute walk test distance as well as patient reported symptoms. Among
the 9 cases with paired data there was a significant increase in 6MWT distance (47m ± 38meters) post CABG. According to systematic review data, a change of 14 to 30.5 meters in a repeated 6MWT distance is likely to represent a clinically important change across multiple patient groups, including patients with coronary artery disease and heart failure (350). Although the change observed in our cohort is greater than the assumed minimal clinically importance difference (MCID)(364), it needs cautious interpretation in the context of the small sample size and the nature of the study design. In a sub-study of the STICH trial, Stewart et al (360) demonstrated that at 4 months following CABG surgery, patients increased their 6MWT by a mean of 38 meters, but no difference was observed between patients undergoing CABG and those receiving medical therapy only. Indeed, although both the pre-operative (365) and 12-month post CABG (360) change in 6MWT distance was prognostically important, the change could not be attributed to the surgery itself.

Similarly, we also identified a significant improvement in EQ-visual analogue scale score following CABG surgery. The change (mean of 20±24.5 points) is again greater than the MICD reported in previous studies, although this was primarily tested in patients with respiratory pathology (358).

There are significant limitations in the interpretation of both questionnaire-based quality of life assessments and of effort-dependent exercise tests for evaluating treatment effects. These were recently highlighted in the context percutaneous coronary intervention in the ORBITA study (42). The study, unique in its design in view of the inclusion of a sham procedure, demonstrated that there was similar
improvement in both exercise time or quality of life (using the EQ-5D-5L questionnaire) after intervention in patients with single vessel coronary artery disease and those undergoing a sham procedure. The study demonstrated the potential magnitude of a placebo effect between coronary physiology and symptoms - a feature perhaps even more prominent in the context of a major cardiovascular intervention such as CABG. The results of the ORBITA are indeed not the only evidence of the potential placebo effect on patients’ functional status. In the DEFER trial (366) (which randomized patients with stable disease with FFR ≥ 0.75 to PCI or medical therapy alone), the act of telling a patient of their FFR result (interpreted as normal coronary physiological test) resulted in a 39% relative risk reduction of chest pain (367). Similarly, in the FAME-2 study, patients not eligible for randomization due to an FFR >0.8 demonstrated a significant improvement in the CCS angina score following reassurance of a negative FFR test (368).

4.4.2 Impact of CABG surgery on myocardial blood flow

As expected, our results confirm that using quantitative perfusion CMR, patients with multi-vessel coronary artery disease and impaired cardiac function scheduled to undergo CABG surgery have low absolute stress MBF. The mean stress MBF detected in this cohort is indeed similar to the values reported by Kotecha et al (185). In their work, they showed that among 47 patients with confirmed 3-vessel disease on coronary angiography, using the same quantitative perfusion technique, the mean absolute stress myocardial blood flow was 1.32±0.47ml/g/min. Although absolute LGE quantification was not reported in their analysis, 64% of patients had a history of prior myocardial infarction.
Few studies have previously examined the impact of surgical revascularisation on absolute myocardial blood flow. Arnold et al (369), performed a validation study of 249 myocardial segments (from 28 patients) and demonstrated that rest MBF did not significantly change following revascularisation, a finding also confirmed in our study. Driessen et al (370) evaluated the impact of CABG in 18 patients (43 territories), and demonstrated a significant increase in regional stress MBF (0.66 ± 0.69ml/g/min) following CABG. In their study, patients with impaired LV function and prior myocardial infarction were excluded. Indeed most studies evaluating the impact of CABG on myocardial blood flow were performed early after surgery (370–372). As shown in this study, additional factors such as graft failure and progression of native disease even soon after the procedure are likely to have a significant impact on MBF post surgery.

To date, no other study has evaluated the prognostic impact of quantitative perfusion indices in patients post CABG. Indeed, little is known about the mechanism by which surgical revascularisation and vessel grafting impacts on prognosis, and although augmentation of MBF is conceptually a key mechanism, it might not be the main determinant of outcome. This will be the focus of investigation in Chapter 6.

4.4.3 Evaluating the success of revascularisation
Maximising complete revascularisation has been regarded as an important advantage of CABG surgery, and a key difference to percutaneous coronary intervention. It is indeed considered one of the main drivers for the difference in outcomes of CABG over PCI in patients with multi-vessel coronary artery disease
The concept of complete revascularisation was first introduced in the original landmarks studies (374), as patients who received 3 or more grafts had better survival compared to patients with <3 grafts. This notion was re-enforced by the results of the COURAGE trial, showing that reduction of residual ischaemia to <5% (by any form of revascularisation) was associated with lower mortality and incidence of myocardial infarction (134). Since then, a number of either observational or randomized controlled trials have examined the impact of the extent of revascularisation in the context of CABG, with most studies reporting higher rates of adverse events and death with incomplete (anatomical) revascularisation after CABG surgery (375). In a meta-analysis of 89 883 patients undergoing revascularisation procedures, 25 938 of whom underwent CABG, complete revascularisation (defined anatomically in 87% of studies) was associated with a 30% reduction in long term mortality (376).

A major limitation in evaluating “completeness of revascularisation” is the lack of a unifying definition, with current practice largely based on the anatomical bypassing of all epicardial vessels with a diameter ≥1.5mm and luminal reduction of at least ≥50% (377).

In this study of paired anatomical and perfusion analysis, we found that 37% of total myocardial segments assessed were not successfully revascularised at the time of follow up assessment at approximately 6 months (median interval 197 days). This includes segments supplied by grafts that have failed, the presence of significant disease distal to the anastomosis and “incomplete revascularisation” at the time of CABG. As successful revascularisation was
shown to be associated with an increase in absolute stress MBF at a segmental level within this cohort, it is reasonable to assume that the large proportion of non revascularised segments have likely contributed to the lack of significant difference in global stress MBF after surgical revascularisation.

Most studies evaluating the prognostic impact of completeness of revascularisation did so using the anatomical revascularisation success achieved intra-operatively (375). Our results confirm that additional factors such as early graft failure and native disease progression also contribute to the success of revascularisation, with the combined impact often resulting in significant percentage of myocardium remaining under-perfused.

Interpreting the clinical importance of the degree of revascularisation success seen in our study is however challenging. Incomplete revascularisation at the time of surgery, progression of native disease (either distally or proximal to the anastomosis) and graft failure may all serve as surrogates of higher disease burden and complexity, signifying a worse cardiovascular risk profile for these patients.

4.4.4 Impact of CABG surgery on myocardial structure and contractility

A number of previous studies evaluated the impact of CABG surgery on myocardial volume and function and reported an improvement in post-operative systolic function, typically measured with LVEF (378–381). Importantly however, these studies also suggested that the change in myocardial contractility was
strongly related to the degree of pre-operative adverse remodelling and baseline function.

In one of the largest studies evaluating the impact of CABG on myocardial function, Koene et al (379) evaluated 375 patients before and after surgery, and reported a reduction in LVEF among those with normal pre-operative LVEF. In contrast, both in the study by Koene et al as well as in a number of smaller observational studies, an improvement in LVEF was reported among those with impaired pre-operative LVEF (378,380). In the STICH trial, CABG surgery did not result in improvement of LVEF even among a cohort that underwent viability testing (190). Indeed, at 24 months, improvement of LVEF >10% was uncommon among patients enrolled in the STICH trial, occurring in less than 20% of the cohort (382).

Among the 9 patients undergoing paired imaging before and after CABG surgery in our study, we found no difference in global systolic function, measured with LVEF, wall motion score changes or myocardial strain indices. This is perhaps not surprising, given the small number of patients examined, and the fact that despite the original screening including patients with LVEF <50%, which was predominantly based on pre-operative echocardiographic assessment, 5 of the 9 patients with paired data had an LVEF ≥ 50% on the pre-operative CMR. Indeed, all 4 patients with LVEF <50% on the pre-operative CMR had an improvement in LVEF when assessed after CABG surgery. Furthermore, a large proportion of revascularised segments had normal contractility at baseline (42 out of 91
segments), which may partly also explain why we did not identify an association between revascularisation and segmental myocardial contractility improvement.

4.4.5 Heterogeneity in patients with ischaemic cardiomyopathy undergoing revascularisation

Another observation from this data is the significant heterogeneity among individuals with ischaemic cardiomyopathy in terms of the physiological impact of surgical revascularisation. Even within such a small cohort, the impact of surgery in terms of reverse LV remodelling, function and perfusion parameters was highly variable – and indeed in some cases striking Figure 4-10. Whether this can be attributed or predicted by specific clinical or imaging parameters remains unclear, but potentially points towards the highly complex biological variability among these individuals, both in terms of their underlying disease as well as their response to revascularisation.
Figure 4-10 Example case with significant LV remodelling post CABG

Data from a single patient showing reduction in LVEDV, and improvement in LVEF and stress myocardial blood flow post CABG (LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVM: left ventricular mass; MBF: myocardial blood flow).

4.5 Limitations

This work is limited by the small sample size. Indeed, the current results can only be viewed as hypothesis generating, as the study is underpowered to evaluate associations with either the primary or secondary outcome measures. The final number of patients recruited in this study was substantially lower from what
originally estimated from power calculations (Section 4.2.6). Beyond the impact of COVID-19 (discussed in section 3.2.6.2), there are additional characteristics specific to this patient cohort which may have contributed to the lower-than-expected recruitment. For example, a significant number of patients (~1 in 8 from initial screening) were excluded due to the presence of significant left main stem (LMS) disease. The rational for excluding patients with LMS disease was primarily based on the notion that the evidence for revascularisation in such patients substantially differs from that of multivessel disease, which may be partly the reason why studies such as ISCHAEMIA and STICH (33,65), did not randomise such patients. There were also logistic issues with recruitment, given that some patients were transferred to our centre less than 24 hours prior to their scheduled operation, resulting in insufficient time for recruitment and execution of the imaging tests. Finally, a number of eligible patients declined to participate in the study, which may partly reflect the poor functional capacity observed in these patients. Indeed, even multi-center randomised controlled studies using similar patient cohorts encountered substantial recruitment challenges (24,383). It is therefore unclear whether the results from this hypothesis generating study can be generalised to a wider unselected population of patients with multivessel coronary disease and impaired function, particularly for patients with left mainstem disease.

The improvement in 6MWT in all patients examined may not reflect real-world data, and may suggest that participants with improved functional status post CABG were more likely to return for follow up scans. This was also shown in the PREVENT IV study, where patients with worse baseline risk profile were less
likely to return for follow up imaging post CABG (384). Beyond this, the COVID-19 pandemic has been a key factor contributing to the degree of loss of follow up observed. Secondly, although the impact of revascularisation was evaluated at a segmental level by co-registering coronary anatomy (CTCA) and myocardial perfusion (CMR), the limited volumetric coverage of CMR data would have introduced error. Thirdly, the observational nature if this work is also associated with limitations that are intrinsic to the study design type. Despite this, the use of machine learning approaches for both evaluation of LV volumes and quantitative perfusion imaging (none of which involved manual input) has significantly reduced bias with regards to these analyses. Fourthly, the paired myocardial perfusion assessment using adenosine as a pharmacological stressor may have introduced differences in quantitative perfusion indices between the 2 studies. Previous work (385) using the same technique showed good repeatability of quantitative perfusion indices, particularly in terms of regional analysis.

4.6 Conclusion

In this proof-of-concept analysis, we performed detailed phenotyping of individual patients using paired CMR and contemporaneous post-operative CT coronary angiography anatomical data in order to determine successful revascularisation. Despite the small sample size, we observed a significant improvement in functional status 6-month post CABG, in terms of 6-minute walk test distance covered and patient reported status. This improvement was unrelated to the improvement in stress myocardial blood flow, with no consistent rise in global myocardial perfusion reserve post CABG. We also found that after adjusting for the presence of graft failure, progression of distal native vessel disease and
incomplete anatomical revascularisation at the time of surgery, more than a third of myocardial segments included in this study were not considered revascularised at 6 months. Finally, within successfully revascularised segments were, stress myocardial blood flow and perfusion reserve were increased.
Chapter 5  Diagnostic performance of myocardial stress perfusion MRI in patients post-surgical revascularisation

This chapter is based on a published manuscript entitled “Use of Quantitative Myocardial Perfusion Mapping by CMR for Characterization of Ischaemia in Patients with Left Internal Mammary Grafts”


5.1 Introduction

One of the key observations of the work described in Chapter 4, was that MBF in patients post CABG remains reduced, even despite achieving the degree of anatomical revascularisation intended with the use of coronary grafts. Although, the underlying mechanism of this is multifactorial and at least partly related to the pathophysiological processes described in the previous chapter, there are additional technical concerns in the use of non-invasive ischaemia testing in patients with grafts. Indeed, all non-invasive stress test methods are thought to have reduced diagnostic accuracy in identifying ischemia post CABG (386), resulting in reduced confidence in image interpretation and inconsistent impact on clinical management Table 5-1.

Coronary artery bypass surgery results in significant structural and haemodynamic alterations in the heart, which makes the evaluation of both ischaemia and absolute MBF challenging. In patients post CABG, accelerated native disease progression results in a high incidence of new total occlusions in grafted vessels (387), but whether this has an impact on MBF, particularly in the presence of patent grafts, is unclear. Similarly, variable degrees of myocardial infarction encountered in these patients complicate the interpretation of global MBF. Graft length is also of particular concern for any non-invasive test that relies on first pass perfusion using an intravenous contrast medium (Figure 5-1).
Table 5-1 Diagnostic performance of non-invasive stress tests to identify graft failure and native disease progression post CABG surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Modality</th>
<th>Type of stress</th>
<th>Time from CABG (years)</th>
<th>Number of patients</th>
<th>Study population symptom status</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitella et al (388)</td>
<td>2006</td>
<td>Echocardiography</td>
<td>Dobutamine</td>
<td>0.32</td>
<td>25</td>
<td>Asymptomatic patients</td>
<td>83</td>
<td>69</td>
</tr>
<tr>
<td>Sawada et al (390)</td>
<td>1989</td>
<td>Echocardiography</td>
<td>Exercise</td>
<td>6.3</td>
<td>41</td>
<td>Symptomatic [23] and asymptomatic [18] patients</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>Chirillo et al (391)</td>
<td>2004</td>
<td>Echocardiography</td>
<td>Dipyridamole</td>
<td>2.2</td>
<td>106</td>
<td>Patients scheduled to undergo coronary angiography</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>Elhendy et al (392)</td>
<td>1996</td>
<td>Echocardiography</td>
<td>Dobutamine</td>
<td>5.1</td>
<td>60</td>
<td>Both symptomatic [38] and asymptomatic [12] patients</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Kafka et al (393)</td>
<td>1995</td>
<td>Echocardiography</td>
<td>Exercise</td>
<td>3.6</td>
<td>182</td>
<td>Mostly asymptomatic patients (148)</td>
<td>77</td>
<td>96</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Methodology</td>
<td>Test</td>
<td>Duration</td>
<td>N</td>
<td>Main Findings</td>
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<td></td>
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<td>----------</td>
<td>----</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
<td></td>
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<tr>
<td>Crouse et al (394)</td>
<td>1992</td>
<td>Echocardiography</td>
<td>Exercise</td>
<td>7</td>
<td>125</td>
<td>Mainly symptomatic patients [96]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aloul et al (395)</td>
<td>2012</td>
<td>SPECT</td>
<td>Exercise</td>
<td>1</td>
<td>79</td>
<td>Unselected cohort prospectively assessed 1 year post CABG</td>
<td></td>
<td></td>
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<tr>
<td>Pfisterer et al (396)</td>
<td>1982</td>
<td>SPECT</td>
<td>Exercise</td>
<td>12</td>
<td>55</td>
<td>Symptomatic [26] and asymptomatic [29] patients</td>
<td></td>
<td></td>
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<tr>
<td>Khoury et al (397)</td>
<td>1997</td>
<td>SPECT</td>
<td>Adenosine</td>
<td>6.7</td>
<td>109</td>
<td>Wide range of indications for cohort selection, including &quot;periodic check-up&quot; in 31 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lakkis et al (398)</td>
<td>1995</td>
<td>SPECT</td>
<td>Exercise</td>
<td>4.2</td>
<td>50</td>
<td>30 patients with typical and 20 patients with atypical chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klein et al (399)</td>
<td>2009</td>
<td>Perfusion CMR</td>
<td>Adenosine</td>
<td>8</td>
<td>78</td>
<td>Suspicion of progression of stable angina</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Bernhart et al (400)**

- Year: 2009
- Procedure: Perfusion CMR
- Drug: Adenosine
- Dose: 1.2
- Heart Rate: 110
- Indication: Clinical indication for invasive angiography

**Klein et al (401)* 2011 Perfusion CMR Dobutamine 9.5 109 Data not available 88 96**

Dobutamine (wall motion analysis)

This is because the increased length of graft conduits plausibly results in a prolonged contrast transit time (arterial time delay, TA), potentially distorting the first pass kinetics of the contrast bolus and the subsequent estimation of myocardial blood flow in graft-subtended territories (369). This is often proposed as an explanation for the presence of perfusion defects in the LIMA territory. Evidence to support this is however lacking. In the context of quantitative perfusion, the deconvolution algorithm deployed for perfusion mapping includes assumptions about the maximum TA, meaning that a true delay in contrast delivery transit time - particularly for myocardium supplied by the long LIMA graft - may result in inaccurate estimations of MBF (402).

In this study, first pass myocardial perfusion was assessed both qualitatively (visually) and by using quantitative MBF estimation (perfusion mapping) in patients post CABG. By selecting a cohort of patients with angiographically-confirmed patent LIMA grafts to the left anterior descending (LAD) arteries and without infarction in the LIMA-LAD territory, we were able to evaluate the factors that determine myocardial blood flow in this territory, particularly the impact of native LAD total occlusion. We also evaluated the arterial time delay (TA) of contrast and assessed the impact of increasing the maximal TA programmed into the automated perfusion mapping algorithm on myocardial blood flow quantification.
Figure 5-1 Difficulties in MBF evaluation of patients with prior CABG surgery

**Top**: Summary of potential technical problems in ischaemia evaluation of patients with prior surgical revascularisation. **** Septal perforators from the mid LAD: adequacy of perfusion in this territory is unclear as the proximal LAD is occluded and LIMA attaches distally. CMR images of the same patient showing extensive area of infarction: There is extensive LGE involving both the inferior wall (RCA territory was not revascularized in this case), but subendocardial LGE also seen on the anterior wall. **Bottom**: Myocardial perfusion map of the same patient. LIMA: left internal mammary artery; LAD: left anterior descending artery; SVG: saphenous venous grafts (in this case these are SVG to D1, and SVG to OM1); CTCA: computed tomography coronary angiography.
5.2 Methods

5.2.1 Patients and study design

This was a single centre, retrospective observational study of patients with coronary artery bypass grafts undergoing stress perfusion CMR scans between October 2017 and March 2020. All patients had coronary angiograms within 60 days of CMR. Twenty-five (25) healthy volunteers with available myocardial perfusion data were included as controls, allowing comparison of the impact of TA extension on myocardial blood flow estimation between patients with grafts and healthy volunteers (controls) with unobstructed native coronaries.

The study was approved by the National Health Service Research Ethics Committee (NHS REC) and Health Research Authority (HRA) and was conducted in accordance with the Declaration of Helsinki (REC IDs 18/LO/1583 and 19/LO/0215). All subjects provided written, informed consent.

To evaluate the effect of delayed contrast arrival (TA, arterial delay) on MBF estimation within territories subtended by a LIMA graft, patients (n=38) were included in the study if they had angiographic evidence of a patent LIMA graft to the LAD (including patent anastomosis site and distal run off), and a stress perfusion CMR either prior to or within 60 days of coronary angiography (35/38 invasive angiography, 3/38 with CT coronary angiography). The clinical indication for all scans was progression of coronary disease and evaluation for myocardial ischaemia. Patients with recent ST-elevation myocardial infarction were excluded and only patients with a LIMA graft anastomosed to the native LAD were included, allowing a focused analysis of myocardial territories with minimal variability in
coronary distribution (American Heart Association (AHA) model territories 1,2,7,8,13,14) (403). To avoid other causes of low myocardial perfusion, patients with cardiac amyloid, hypertrophic cardiomyopathy or late gadolinium enhancement (LGE) in the LIMA-LAD myocardial segments were excluded.

5.2.2 Adenosine stress perfusion CMR

CMR studies were carried out on a 1.5T (Aera) or 3T scanner (Prisma, Siemens Healthineers, Erlangen, Germany). Scans were performed in accordance with published recommendations (404) with patients refraining from caffeine for 24hrs hours prior to the scan. Pharmacological stress was delivered with adenosine infusion at a rate of 140mg/kg/min for 4 min with a further 2 minutes at 175mg/kg/min if there was evidence of insufficient stress (heart rate response <10 beats per minute and absence of symptoms). Image acquisition was performed over 60 heartbeats and a bolus of 0.05 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Paris, France) was administered at 4 ml/s. Basal, mid-ventricular, and apical short-axis first pass perfusion images were acquired. The sequence was then run at rest allowing measurement of rest MBF and estimation of myocardial perfusion reserve (MPR) [MPR = MBF_{stress}/ MBF_{rest}].

5.2.3 Quantitative Myocardial perfusion mapping

Myocardial perfusion maps were acquired using a single-bolus, dual sequence as previously described (100). This involves the simultaneous acquisition of a low-resolution arterial input function (AIF) and a high-resolution myocardial perfusion acquisition. In-line automatic reconstruction and post processing is executed within the Gadgetron software framework (303). Myocardial blood flow
(MBF, ml/g/min) is calculated on a pixel-wise basis in high-resolution images. As detailed in Section 1.4.2, the process is based on a blood tissue exchange (BTEX) model, a physiological model describing the interaction between properties of the blood, the interstitium and capillary vessel walls, and requires solving of a series of partial differential equations. This process, incorporates the estimation of the arterial time delay (TA) between bolus arrival in the LV cavity and the pixel of interest. This is achieved by searching for the best fit function for each myocardial pixel over a period of 0 to 2.5 seconds, in 0.5 second steps. The TA is programmed with a 2.5 second maximum threshold as the standard default, as this has been found to cause minimal TA saturation and minimises perfusion map computation time (<90 seconds) across the general patient population.

To evaluate whether the 2.5 second threshold in TA resulted in saturation of estimation of TA and subsequent underestimation of MBF in patients with LIMA grafts, the myocardial perfusion maps were re-processed using a longer arterial time delay (TA) threshold up to 5 seconds. In a separate analysis, the actual TA selected by the perfusion algorithm was noted, allowing comparison between CABG patients and healthy volunteers.

5.2.4 Image analysis

Scans were analysed visually by experienced CMR operators (attending cardiovascular imaging consultants with >5 years CMR experience) for clinical purposes. Offline analysis was performed for evaluation of cardiac volumes, function and presence of late gadolinium enhancement using commercial software (cvi42, Circle Cardiovascular Imaging, Canada).
First pass perfusion images were initially analysed qualitatively with a visual LIMA-LAD perfusion defect defined as an inducible perfusion defect (reduced relative signal intensity) in at least one segment from American Heart Association model territories 1,2,7,8,13,14. Quantitative analysis of myocardial perfusion (stress, rest and calculated MPR by myocardial segment) was fully automated with no manual operator adjustment. Perfusion maps were automatically segmented using a convolutional neural network (CNN) approach with some older studies re-processed post hoc to ensure that a standardised automated analysis algorithm was used (300).

5.2.5 Statistical Analysis

Statistical analysis was performed in SPSS (IBM SPSS statistics, Version 26.0). All continuous variables were tested for normal distribution (Shapiro-Wilk test). Continuous variables are presented as mean ± SD; categorical as absolute values and percentages. Comparison of means for continuous variables was performed using a Student-t test or Mann-Whitney U test, and categorical variables were tested with χ² test. Comparison of MBF between conventional (TA=2.5s) and increased arterial delay (TA=5s) for each case was performed with Wilcoxon signed-rank test. Pre-specified variables considered likely to predict myocardial blood flow were analysed in a univariable regression analysis. Multivariable linear regression was then performed using variables significantly associated with MBF and MPR as well as important clinical and imaging variables (e.g. diabetes mellitus and left ventricular ejection fraction) regardless of strength of univariable associations. A bilateral p value<0.05 was considered statistically significant.
5.3 Results

A total of 38 patients with patent LIMA grafts and no LGE in the LIMA-LAD territory were included. Baseline characteristics including comorbidities and clinical indications for perfusion CMR are shown in Table 5-2. Median age was 60 years (IQR 60-73). Median time between CABG and coronary angiography was 5 years (IQR 2-11). In 30 (79%) patients, perfusion CMR was performed before coronary angiography and in 8 cases (21%) after (median 42 days, IQR 36-48). All cases were deemed to have achieved adequate stress response during perfusion.

By qualitative (visual) assessment, a perfusion defect in LIMA-LAD territory was reported in 27 out of 38 cases (71%) by clinical reporters blinded to the study details. This was despite all patients having patent LIMA grafts, no anastomotic stenosis, good distal LAD run off, and no LAD territory infarction (Figure 5-2). Among patients with perfusion defects in the LIMA-LAD territory on visual assessment, 18 (66%) were managed medically, 1 patient had percutaneous coronary intervention (PCI) to the native LAD and 8 (30%) underwent PCI in myocardial segments not supplied by the LIMA-LAD (these patients had additional perfusion defects in other territories).

Stress myocardial blood flow in the LIMA-LAD territory was lower in patients with inducible perfusion defects on visual qualitative assessment, compared to those deemed to have no perfusion defects (1.45±0.45 ml/g/min, vs 2.12±0.43ml/g/min, p<0.001).
**Figure 5-2 Patent LIMA and perfusion**

Study patient with angiographically confirmed patent LIMA to LAD and evidence of inducible perfusion defect in basal and mid LIMA - native LAD subtended territories with no infarction on late gadolinium imaging. Images shown are short axis views from base to apex (left to right). Top row (A): First pass perfusion imaging with adenosine stress, demonstrating qualitatively a perfusion defect in the basal to mid (but not apical) LAD territory. There is a second lateral perfusion defect. Middle row (B): Perfusion mapping showing quantitatively reduced peak MBF in these territories. (e.g. MBF in mid antero-septum is 0.85ml/g/min, MBF in apical septum is 1.65ml/g/min). (C): Bullseye plot of stress MBF in each AHA segment. Bottom row (D): Late gadolinium images showing no infarction. (E,F): Coronary angiography demonstrating patent LIMA graft (E) and anastomosis site (F) with good distal run off. Reproduced from Seraphim et al, JCMR 2021 under the terms of the Creative Commons CC BY license.
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients with previous CABG</th>
<th>Healthy volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=38</td>
<td></td>
<td>N=25</td>
</tr>
<tr>
<td>Age, years (median, IQR)</td>
<td>66(60-73)</td>
<td>34(30-43)</td>
</tr>
<tr>
<td>Sex, n (% male)</td>
<td>33(87)</td>
<td>13(52)</td>
</tr>
<tr>
<td>BSA, m$^2$ (median, IQR)</td>
<td>1.9(1.7-2.0)</td>
<td>2.0(1.8-2.0)</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>21(55)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>37(97)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>33(87)</td>
<td></td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-blockers, n (%)</td>
<td>30(79)</td>
<td></td>
</tr>
<tr>
<td>CCB, n (%)</td>
<td>9(24)</td>
<td></td>
</tr>
<tr>
<td>ACE-I/ ARB, n (%)</td>
<td>34(90)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelets, n (%)</td>
<td>37(97)</td>
<td></td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>24(63)</td>
<td></td>
</tr>
<tr>
<td>Atypical chest pain / dyspnoea</td>
<td>9(24)</td>
<td></td>
</tr>
<tr>
<td>NSTEACS*</td>
<td>5(13)</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary artery bypass graft</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from CABG, years (median, IQR)</td>
<td>5(2-11)</td>
<td></td>
</tr>
<tr>
<td>Total number of grafts per patient, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single graft (LIMA to LAD)</td>
<td>1(3)</td>
<td></td>
</tr>
<tr>
<td>2 x grafts</td>
<td>4(10)</td>
<td></td>
</tr>
<tr>
<td>3 x grafts</td>
<td>23(61)</td>
<td></td>
</tr>
<tr>
<td>4 x grafts</td>
<td>10(26)</td>
<td></td>
</tr>
<tr>
<td>Vein grafts per patient, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1x vein graft</td>
<td>6(16)</td>
<td></td>
</tr>
<tr>
<td>2x vein grafts</td>
<td>21(55)</td>
<td></td>
</tr>
<tr>
<td>3x vein grafts</td>
<td>10(26)</td>
<td></td>
</tr>
<tr>
<td><strong>CMR parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDVi, ml/m$^2$</td>
<td>68±12</td>
<td>77±15</td>
</tr>
<tr>
<td>Metric</td>
<td>Value 1</td>
<td>Value 2</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>54±13</td>
<td>52±10</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62±8</td>
<td>66±4</td>
</tr>
<tr>
<td>Global stress MBF, ml/g/min</td>
<td>1.54 ±0.47</td>
<td>2.82 ±0.61</td>
</tr>
<tr>
<td>Global rest MBF, ml/g/min</td>
<td>0.82 ±0.21</td>
<td>0.90 ±0.24</td>
</tr>
<tr>
<td>Global MPR</td>
<td>1.94 ±0.63</td>
<td>3.22 ±0.63</td>
</tr>
<tr>
<td>LIMA-LAD (or LAD) stress MBF, ml/g/min</td>
<td>1.65 ±0.54</td>
<td>3.04 ±0.69</td>
</tr>
<tr>
<td>LIMA-LAD (or LAD) rest MBF, ml/g/min</td>
<td>0.88 ±0.22</td>
<td>1.04 ±0.30</td>
</tr>
<tr>
<td>LIMA-LAD (or LAD) MPR</td>
<td>1.92 ±0.64</td>
<td>3.04 ±0.65</td>
</tr>
</tbody>
</table>

BSA – body surface area, CCB – Calcium Channel blocker; ACE-I – Angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; LVEDV – left ventricular end-diastolic volume; LVM -Left ventricular mass; LVEF – left ventricular ejection fraction; NSTEACS – non-ST elevation acute coronary syndrome; *CMR performed for evaluation of bystander disease after coronary angiography.
5.3.1 Predictors of myocardial blood flow in the LIMA-LAD territory

A number of prespecified clinical and imaging variables were included in a univariable regression analysis to determine the predictors of stress myocardial blood flow in the LIMA-LAD territory. These included age, sex, presence of native LAD total occlusion (proximal to the LIMA insertion), diabetes mellitus, LV mass index (LVMi), LVEF, and use of b-blockers. Amongst these, total occlusion of the native LAD proximal to the anastomosis of the LIMA (evaluated in a binary fashion; present or absent) was a strong predictor of both stress MBF ($B=-0.41, 95\% \ CI \ -0.73, -0.099; \ p=0.014$) (Table 5-3) and MPR ($B=-0.56; 95\% \ CI \ -0.95, \ -0.17; \ p=0.005$); (Table 5-4) in this territory, and remained significant in multivariable analyses.

Table 5-3 Predictors of stress MBF in the LIMA-LAD territory

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Univariate Predictors</th>
<th>Multivariate Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>B         -0.02</td>
<td>95% CI -0.04 - (-0.001)</td>
</tr>
<tr>
<td>Native LAD occlusion</td>
<td>B         -0.47</td>
<td>95% CI -0.79 - (-0.15)</td>
</tr>
<tr>
<td>LVEF</td>
<td>B         -0.02</td>
<td>95% CI -0.04 - 0.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>B         -0.18</td>
<td>95% CI -0.53 - 0.18</td>
</tr>
<tr>
<td>LVMi</td>
<td>B         -0.01</td>
<td>95% CI -0.02 - 0.01</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>B         -0.31</td>
<td>95% CI -0.83 - 0.21</td>
</tr>
<tr>
<td>Beta - blockers</td>
<td>B         0.30</td>
<td>95% CI 0.016 - 0.76</td>
</tr>
</tbody>
</table>

*Bold* $p$-values are statistically significant, *LIMA-LAD territory (average of stress MBF in myocardial segments 1,2,7,8,13,14)*
Table 5-4 Predictors of MPR in the LIMA-LAD territory

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Univariate Predictors</th>
<th>Multivariate Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>-0.05 - (-0.003)</td>
</tr>
<tr>
<td>Native LAD occlusion</td>
<td>-0.63</td>
<td>-1.00 - (-0.25)</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.01</td>
<td>-0.04 - 0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.14</td>
<td>-0.57 - 0.29</td>
</tr>
<tr>
<td>LVMi</td>
<td>-0.01</td>
<td>-0.02 - 0.01</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>-0.22</td>
<td>-0.41 - 0.86</td>
</tr>
<tr>
<td>Beta - blockers</td>
<td>0.20</td>
<td>-0.36 - 0.76</td>
</tr>
</tbody>
</table>

**Bold** p values are statistically significant; LAD - Left anterior descending artery; LVEF - left ventricular ejection fraction; LVMi – left ventricular mass index

5.3.2 Impact of native LAD CTO on LIMA-LAD territory perfusion

Stress MBF in the LIMA-LAD territory (MBF averaged in segments 1,2,7,8,13,14) was lower in cases with total occlusion of the native LAD compared to cases where the LAD was significantly stenosed but not completely occluded (mean MBF 1.43 ± 0.39 ml/g/min, vs 1.90 ± 0.58 ml/g/min; p=0.005) (Figure 5-3). A comparison of stress myocardial blood flow between the basal (AHA 1,2), mid (7,8) and apical (13,14) LAD territory segments showed that native LAD CTO was associated with MBF reductions in basal (1.47 ± 0.44ml/g/min vs 2.07 ±0.64; p=0.002), and mid segments (1.29 ± 0.34 ml/g/min vs 1.75 ± 0.60 ml/g/min; p=0.006) but not apical segments (1.52 ± 0.49 ml/g/min vs 1.87 ± 0.60; p=0.057) (Figure 5-4).
Figure 5-3 Impact of native LAD occlusion on MBF
Box plot showing stress MBF in the LIMA-LAD territory (AHA segments 1,2,7,8,13,14) depending on native LAD status. Error bars represent 95% CI. In all cases the LIMA graft was patent. Total occlusion of the native LAD was associated with significant reduction in stress MBF. Reproduced from Seraphim et al, JCMR 2021 under the terms of the Creative Commons CC BY license.

Figure 5-4 Impact of native LAD occlusion at different myocardial levels
Stress MBF within the LIMA – LAD territory in each myocardial level (basal, mid, apex). Total occlusion of the native LAD was associated with a reduction in peak
MBF of the basal and mid-but not apical LAD segments. Reproduced from Seraphim et al, JCMR 2021 under the terms of the Creative Commons CC BY license.

5.3.3 Impact of re-processing quantitative perfusion maps with increased arterial contrast delay (TA) on myocardial blood flow estimation

Raw data from myocardial stress perfusion were re-processed using a prolonged arterial contrast delay (maximal TA threshold 5 seconds) and were compared to the data obtained using a default arterial contrast delay (TA threshold 2.5 seconds). Prolonging the arterial contrast delay threshold to 5 seconds resulted in a small, but statistically significant increase in global myocardial flow at stress (0.05 ml/g/min, IQR 0.02-0.08; p<0.001) and rest (0.06 ml/g/min, IQR 0.04-0.09; p<0.001). Similar changes were observed in the LIMA-LAD territory Table 5-5. Global Myocardial perfusion reserve (MPR) was slightly reduced when TA was increased to 5 seconds (-0.05, IQR -0.11-0.00; p<0.001), as the extension of TA resulted in a proportionally greater increase in rest compared to stress flow (MPR = MBF_{stress}/ MBF_{rest}). To further examine whether arterial contrast delay has a greater impact on MBF of territories supplied only by the LIMA graft, a sub-analysis of cases with patent LIMA grafts and total occlusion of the native LAD was performed. Presence of native LAD CTO did not result in more profound effect of TA prolongation on the estimated MBF in the LIMA-LAD territory.

To evaluate whether the observed differences in MBF caused by study re-processing using a longer TA were likely to be dependent of the presence of graft, 25 healthy volunteers (HV) perfusion scans were also reprocessed after extending TA from 2.5 to 5 seconds. Baseline characteristics and CMR
parameters of healthy volunteers are shown in Table 5-2. Healthy volunteers also had a small but significant increase in global MBF at both stress (0.01ml/g/min, IQR 0.00-0.03, p<0.001) and rest (0.09ml/g/min, IQR 0.06-0.11, p<0.001).

The average arterial delay (TA) selected from the MBF estimation algorithm within the LIMA-LAD (in CABG patients) or LAD territories (in healthy volunteers) was also assessed (Figure 4.4). At stress, the selected TA (arterial delay, seconds) was longer for patients with LIMA grafts (1.7 seconds, IQR 1.2-1.9) compared to healthy controls (0.71 seconds, IQR 0.62-0.87; p<0.001). Similarly, extending the TA from 2.5 to 5 seconds resulted in a higher absolute (0.01ml/g/min, IQR 0.00-0.01 vs 0.05ml/g/min, IQR 0.01-0.09, p<0.001) and percentage (0.2%, IQR 0.02-0.67 vs 3.4%, IQR 0.53-5.94; p<0.001) increase in stress MBF in patients with LIMA grafts compared to healthy volunteers.
Figure 5-5 Measured arterial delay and its impact in MBF estimation

**Top:** The average arterial delay (TA) within the LIMA/LAD territory (AHA 1, 2, 7, 8, 13, 14) was higher in patients with grafts (previous CABG) compared to healthy volunteers (unobstructed native vessels). The TA shown is the average TA within AHA territories (1, 2, 7, 8, 13, 14). At stress, the selected TA (arterial delay, seconds) was longer for patients with LIMA grafts (median 1.70 seconds, IQR 1.20-1.91) compared to healthy controls (median 0.71 seconds IQR 0.62-0.87; p<0.001).

**Bottom:** The percentage increase in estimated stress MBF in the same territory (AHA 1, 2, 7, 8, 13, 14) caused by extending the maximum allowable TA from 2.5 to 5 seconds was 0.2% (IQR 0.02-0.67) for healthy volunteers and 3.4% (IQR 0.53-5.94) for patients with grafts (p<0.001). Reproduced from Seraphim et al, JCMR 2021 under the terms of the Creative Commons CC BY license.
Table 5-5 Absolute change in MBF and MPR after increasing TA from 2.5 to 5 seconds

All CABG cases (n=38)

<table>
<thead>
<tr>
<th>Myocardial territory</th>
<th>Change in stress MBF (ml/g/min)</th>
<th>P value</th>
<th>Change in rest MBF (ml/g/min)</th>
<th>P value</th>
<th>Change in MPR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>0.05 (0.02-0.08)</td>
<td>&lt;0.001</td>
<td>0.06 (0.04-0.09)</td>
<td>&lt;0.001</td>
<td>-0.06 (-0.11-(-0.01))</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LIMA-LAD</td>
<td>0.05 (0.01-0.09)</td>
<td>&lt;0.001</td>
<td>0.05 (0.03-0.08)</td>
<td>&lt;0.001</td>
<td>-0.05 (-0.10-0.00)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Sub-analysis of CABG cases with totally occluded native LAD (n =20)

| LIMA-LAD             | 0.06 (0.00-0.09)                | <0.001  | 0.05 (0.03-0.11)             | <0.001  | -0.03 (-0.08-0.00) | 0.063   |

Healthy volunteers (n=25)

| Global               | 0.01 (0.00-0.03)                | <0.001  | 0.09 (0.06-0.11)             | <0.001  | -0.25 (-0.35-(-0.20)) | <0.001 |
| LAD                  | 0.01 (0.00-0.01)                | 0.001   | 0.06 (0.05-0.09)             | <0.001  | -0.18 (-0.26-(-0.12)) | <0.001 |

Results shown as median and interquartile range. Reproduced from Seraphim et al, JCMR 2021 under the terms of the Creative Commons CC BY license.
5.4 Discussion

This study confirms that perfusion defects in the LAD territory are common in patients referred for perfusion CMR despite LIMA to LAD graft patency and no infarction, that these defects are predominantly located in the basal and mid rather than apical segments and are associated with native vessel chronic total occlusions. Finally, the arterial time delay (TA) may be longer after LIMA grafting (reflecting arterial transit time) resulting in slight MBF underestimation, but this is not sufficient to explain the degree of flow reduction and hence the perfusion defects. Together these findings suggest that LAD territory inducible perfusion abnormalities are commonly seen in patients with LIMA grafts and are largely due to ongoing abnormalities of myocardial perfusion related to proximal native LAD disease, rather than due to technical limitations related to contrast delay associated with grafts.

Ischemia evaluation in patients with prior CABG is challenging. The complexity of coronary anatomy, the presence of competitive flow, well-developed collateral systems, retrograde blood flow and prior infarction impacting blood flow ascertainment complicate both the interpretation of functional tests and subsequent revascularisation decisions. Previous studies using positron emission tomography (PET) (405), single photon emission computed tomography SPECT (406) and CMR perfusion (399,400) in patients post CABG, deployed either qualitative or semiquantitative methods to evaluate the impact of coronary graft physiology on myocardial blood flow. Compared to patients with native vessel coronaries, these studies reported reduced diagnostic performance in patients with grafts (399,400). Indeed, patients with prior CABG surgery were
excluded from large trials evaluating the diagnostic accuracy of perfusion CMR (315). Recently, stress CMR using visual (qualitative) assessment demonstrated good discriminative prognostic value in patients after CABG, albeit in a cohort of largely asymptomatic patients (407).

5.4.1 Myocardial perfusion mapping and underlying coronary anatomy in LIMA graft subtended territories

Myocardial blood flow is governed by processes beyond epicardial coronary flow, including microvascular function (110) and the underlying myocardial architecture. Our data suggest that even in patients with good flow to distal LAD territory via patent LIMA grafts, the main determinants of stress MBF within the LAD subtended myocardial segments were not aspects that affect microvascular function (eg. age, diabetes), but the severity of the underlying native LAD. As one might expect, the impact of native LAD CTO was greatest basally with a gradient, having little effect apically (Figure 5-4).

Despite the excellent long term patency of LIMA grafts and their association with improved prognosis, imaging evidence of myocardial ischemia in the LIMA-LAD territory post CABG is not uncommon (408). Correlation of these functional imaging abnormalities with significant anatomical lesions in the LIMA or distal LAD territories however is variable. In a study using SPECT (409) for evaluation of ischemia in the LIMA-LAD territory, half of the patients with detectable ischemia in this territory had no evidence of LIMA graft or anastomosis stenosis on angiography. Importantly, prognosis between those with or without LIMA graft stenosis but perfusion defects in the LIMA-LAD territory was similar. In the same
study, the authors proposed the mismatch between LAD and LIMA diameters at the anastomotic site as a potential mechanism for their findings, although data on native LAD patency was not provided.

A concern with the use of any first pass perfusion imaging technique in patients with CABG is the increased transit delay in the dynamic contrast delivery to tissue through long graft conduits (410). Using model-independent deconvolution analysis, Arnold et al (369), demonstrated that in the context of rest perfusion, despite a short delay associated with contrast arrival and the resulting increased contrast dispersion particularly involving the internal mammary arterial (IMA) graft, estimation of MBF was not systematically underestimated in graft subtended myocardial territories. Similarly, using semiquantitative perfusion parameters Kelle et al (402) showed that grafted and native vessel myocardium shared similar contrast kinetics, despite a short delay in contrast arrival in grafted territories.

To address the impact of delayed contrast arrival time on quantitative perfusion, we focused our analysis on a specific model, consisting of patients with a patent LIMA graft to the LAD and with no CMR evidence of myocardial infarction within the LAD territory. We showed that sequence adjustment to accommodate a longer contrast arrival time resulted in a small increase in absolute flow (both at rest and stress), but this could not account for the extent of MBF reduction seen in these territories. Indeed, in agreement with previous semiquantitative data (402), TA prolongation resulted only in a small increase in MBF in the LIMA-LAD myocardial segments (median increase in stress MBF 3.4%). This was similar even in cases where the native LAD was completely occluded, a situation that is
theoretically expected to unmask any delay in contrast arrival via the LIMA graft. Importantly, increasing the TA search window to 5 seconds would double computational time (as the best TA value is searched and selected for each myocardial pixel), and is unlikely to result in re-classification of a myocardial segment as having normal MBF.

To further assess whether the increase in MBF observed by extending the allowable TA was related to the presence of grafts, a healthy volunteer cohort was used for comparison. Despite a small, but significant increase in the LAD territory MBF in healthy volunteers, both the absolute and percentage increase in MBF at stress among healthy volunteers was less than the increase observed in patients with grafts following TA extension (Figure 5-5). However, the possibility of unmeasured confounders within the groups contributing to this observation cannot be excluded.

5.4.2 Study Limitations

Firstly, our study is limited by the small sample size and retrospective nature of data collection. However, the use of objective artificial intelligence approach to segmentation reduces bias in data analysis. Secondly, although total native LAD occlusion was evaluated in a binary manner to maintain simplicity (present or absent), coronary collaterals that are often present in these were not systematically evaluated. Thirdly, our study focused on myocardial territories usually subtended by the LIMA graft and native LAD, therefore our findings cannot be assumed to apply to other territories, particularly those supplied by vein grafts. Indeed, differential vasomotor response between arterial and vein
grafts during vasodilator stress was previously proposed (411), but evaluation of this was beyond the scope of this study. Furthermore, variable amount of LGE in territories outside the defined LIMA-LAD segments would make interpretation of MBF in these territories challenging. Fourthly, our technical analysis specifically considered the arterial delay of contrast through the LIMA graft conduit, and did not consider additional dispersion or broadening of the arterial input function. Although the effect of long conduits such as the LIMA graft on contrast dispersion was previously thought to be small (369), its impact on absolute myocardial blood flow estimation warrants further evaluation.

5.5 Conclusion

Perfusion defects in myocardial territories supplied by the LIMA and native LAD are commonly seen using stress perfusion CMR, despite the presence of patent LIMA grafts. These data indicate that perfusion abnormalities are related to the presence or absence of proximal native LAD occlusion rather than due to technical limitations resulting from the delayed contrast arrival via the LIMA grafts. Complete occlusion of the native LAD is shown to be a key determinant of myocardial blood flow in these territories, particularly in the more proximal myocardial segments. This, combined with the observed base to apex gradient suggests that despite LIMA patency, in many patients revascularization of the proximal LAD territory may be incomplete.
Chapter 6 Prognostic value of quantitative myocardial perfusion CMR in patients with prior surgical revascularisation

This chapter is based on the following manuscript published in the Journal of the American College of Cardiology

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Quantitative Myocardial Perfusion Predicts Outcomes in Patients with Prior Surgical Revascularization

Journal of the American College of Cardiology

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6.1 Introduction

The way by which surgical revascularisation improves patient symptoms and outcomes is not entirely clear, and a number of different mechanism have been proposed (53). Augmentation of myocardial blood flow (MBF) is however conceptually a fundamental aim of surgery. The work in the previous chapters (Chapters 4 and 5) focused on the impact of coronary artery bypass graft surgery on the myocardium and specifically investigated factors that determine myocardial blood flow post procedure. However, despite extensive research on the impact of revascularisation on prognosis, evidence evaluating the impact of MBF indices on patient outcomes following surgical revascularisation is lacking.

Stress perfusion cardiac magnetic resonance imaging (CMR) imaging has high diagnostic accuracy for the detection and characterisation of myocardial ischaemia in native vessel disease (314,315) and predicts adverse cardiovascular outcomes (126,412). Recent work has demonstrated that qualitative (visual) assessment of first pass perfusion with CMR can predict outcomes in patients post CABG (157), however the diagnostic accuracy of qualitative assessment in this patient population is known to be reduced (400). Importantly, visual detection of ischaemia may fail to capture additional pathophysiological processes that may contribute to adverse clinical outcomes in these patients.

As discussed in the previous sections, myocardial perfusion mapping permits quantitative evaluation of myocardial blood flow (MBF), and is increasingly being deployed for detection of both epicardial and microvascular coronary disease
It has demonstrated superior diagnostic performance compared to qualitative assessment (413), enabling global and segmental MBF evaluation even in the presence of multivessel coronary artery disease (414). Importantly, quantitative perfusion with CMR (80) and Positron Emission Tomography (PET) (144) was also shown to independently predict outcomes, with a prognostic benefit incremental to established imaging biomarkers. In these studies, patients with prior CABG were either excluded or under-represented.

The prognostic utility of quantitative MBF assessment in patients post CABG, a technically complex disease model for perfusion evaluation, has not been previously examined. In this Chapter, I therefore aimed to investigate whether evaluation of stress myocardial blood flow using perfusion mapping CMR in patients with prior CABG would be independently associated with adverse outcomes.

### 6.2 Methods

#### 6.2.1 Patients and study design

This was a single centre retrospective cohort study of consecutive patients with prior coronary artery bypass graft surgery, clinically referred for a myocardial perfusion cardiac MRI at Barts Heart Centre, London, between September 2016 to December 2020. Patients with underlying cardiomyopathies known to affect myocardial perfusion (cardiac amyloidosis, hypertrophic cardiomyopathy) and those with less than 6-months of follow-up available were excluded. Comorbidities and clinical events were retrieved from electronic patient records and the National Health Service Spine portal. Patient comorbidities recorded
were history of previous percutaneous coronary intervention (PCI, any time prior to the CMR study), hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, stroke or transient ischemic attack and history of smoking. The primary outcome was a composite of death and major adverse cardiovascular events (MACE) that included non-fatal myocardial infarction and late coronary revascularization (>90 days post CMR). Patients undergoing revascularisation within 90 days after CMR were excluded from the analysis to prevent the inclusion of events occurring as a result of the perfusion CMR. To further evaluate the possible impact of the CMR study on outcomes, a sub-analysis of clinical outcomes was also performed after excluding cases undergoing revascularisation within 180 days of the CMR study. Data on the cause of death was not available for the majority of patients, therefore data on cardiovascular death is not presented. Time-to-MACE was defined as the period from the CMR study date to the occurrence of the first MACE, death or censoring at the end of the follow-up period. Data were collected as part of the Barts Revascularisation Registry with prior approval from the Barts Health NHS Trust Institutional Review Board (study ID: 142567). This was a single centre registry that aimed to improve understanding of the characteristics and outcome predictors of patients with coronary artery disease, particularly in the context of revascularisation. Any patient 16 years of age or older undergoing revascularisation (surgical or percutaneous) at Barts Heart Centre, was eligible to be included in the registry. The registry specifically allowed evaluation of patients undergoing CABG and enabled the assessment of the diagnostic performance of invasive and non-invasive tests (including cardiac MRI), as well as the association of clinical and imaging biomarkers with clinical outcomes. All data was clinically acquired, and no patients were contacted for research
purposes. In view of the study design, informed consent was not required. Ethical approval was also in place from East of England (Cambridge Central) National Research Ethics Service Committee (21/EE/0037) for collection and use of deidentified CMR and outcome data from clinical patients for research registries.

6.2.2 Cardiovascular magnetic resonance scans

All patients included underwent stress perfusion CMR at 1.5T (Aera) or 3.0T (Prisma, Siemens Healthineers, Erlangen, Germany). The imaging protocol included cine imaging, stress and rest perfusion followed by late gadolinium enhancement. Stress and rest first pass myocardial perfusion was performed, using adenosine as pharmacological stressor. The myocardial perfusion sequence is a single-bolus, dual sequence previously described (100). Basal, mid-ventricular, and apical short-axis perfusion images were acquired at both stress and rest. Image acquisition was performed over 60-90 heartbeats. A bolus of 0.05 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Paris, France) was administered at 4 ml/s during both maximal hyperemia and subsequently at rest. The resulting perfusion maps were generated automatically, in-line with each pixel of myocardium encoding myocardial blood flow expressed in ml/g/min. The quantitative perfusion technique incorporates a machine learning approach for myocardial segmentation (300), allowing derivation of both global and segmental MBF based on the 16-segment AHA model.

6.2.3 CMR image analysis

Scans were analysed using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Myocardial volume and
mass analysis were derived from short axis stack cine images (415). First pass perfusion images were analysed visually by CMR operators (attending cardiovascular imaging consultants with >5 years CMR experience) blinded to the study outcome results. A perfusion defect was defined as an inducible perfusion defect (reduced relative signal intensity) in at least one myocardial segment, that extended beyond any area of late gadolinium enhancement uptake. Quantitative analysis of myocardial perfusion was performed in-line with no manual operator adjustment. Global MBF was derived as the average of all myocardial pixels, with global MPR representing the ratio of stress MBF / rest MBF. In view of the high infarct burden in the cohort and the known association between MBF and infarct scar, a further analysis of global MBF and MPR was performed by excluding myocardial segments with evidence of late gadolinium enhancement (LGE) Figure 6-1.
Figure 6.1 Stress MBF after excluding myocardial segments with LGE

Analysis of stress myocardial blood flow (MBF) after excluding myocardial segments with LGE. *First pass perfusion imaging of basal, mid apical short axis slices (A). Quantitative perfusion mapping (B) generated in-line, with both global and segmental MBF (C). Segments with LGE (D) are identified and subsequently excluded from the estimation of global MBF as shown in (E).*
Similarly, given the expected association between LGE and prognosis, the total number of myocardial segments with LGE were recorded. Viability was defined as LGE transmurality $\geq 50\%$. Semi-automated quantitative evaluation of LGE was also performed from the LV short-axis stack LGE (phase-sensitive inversion) images, using two different signal intensity thresholding methods (full-width half maximum (FWHM) and 5 standard deviations (SD) above remote myocardium) as previously described (253). LGE was expressed as a percentage of total LV mass. Myocardial segments with artefacts were manually excluded from the quantitative LGE analysis.

6.2.4 Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range (IQR)) depending on normality. Normality was assessed using a Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using a two-tailed unpaired Student’s $t$-test or a Mann-Whitney U test, and with a $\chi^2$ test or Fisher’s exact test for categorical variables. Multivariate linear regression models were used to evaluate predictors of stress MBF. Cox proportional hazard regression analyses were performed with adjustment for covariates including age, sex, time from original CABG surgery, left ventricular ejection fraction (LVEF), extent of late gadolinium enhancement (both as global LGE as well as number of non-viable segments), diabetes mellitus, and previous history of PCI. The proportional hazards assumption was checked using Schoenfeld residuals. A sensitivity analysis was also performed to obtain Firth’s bias-adjusted estimates to ensure there was no bias in the estimated coefficients.
due to the relatively low event rates. Results were similar to the original models. Survival curves were constructed according to the Kaplan-Meier method compared using log-rank tests based on the mean value of stress MBF and MPR in this population. A p-value<0.05 was considered significant. Analysis was performed using SPSS software package (IBM SPSS Statistics, version 27.0).

6.3 Results

6.3.1 Cohort description and characteristics

A total of 390 patients with previous CABG surgery and adenosine stress CMR perfusion were available. 13 patients were excluded due to lack of follow up, 17 were excluded due to erroneous quantitative perfusion data (inappropriate slice planning, timing of contrast injection, perfusion map quality). 3 patients were excluded due to a diagnosis of hypertrophic cardiomyopathy. 16 patients underwent revascularisation within 90 days of perfusion CMR and were therefore censored. A total of 341 patients were included in the final analysis.

Median age was 67 (60-75) years, 86% were male. The clinical indications for the perfusion scan included: presence of typical angina symptoms in 164 (48%) patients, dyspnoea in 54 (16%), atypical symptoms in 29 (9%) and in 94 cases (28%) patients referred for risk stratification (asymptomatic from cardiac perspective). Median time interval between the CMR study and CABG surgery was 9 years (3-15). Comorbidities and cardiovascular risk factors were reflective of the population studied, with 190 (56%) patients having a history of diabetes mellitus and 173 (51%) patients having history of previous percutaneous coronary intervention (PCI). The median LVEF across the cohort was 61% (50-
68%) and 256 (75%) of patients had evidence of late gadolinium enhancement in at least one myocardial segment. Baseline characteristics, including additional details of CMR parameters are summarized in Table 6-1

Table 6-1 Baseline demographics and characteristics of patients with prior coronary artery bypass graft (CABG) surgery

<table>
<thead>
<tr>
<th>Patients with previous CABG (n=341)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Male, n</td>
</tr>
<tr>
<td>BSA, m²</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Co-morbidities/ Risk factors, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Previous stroke / TIA</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Previous PCI</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
</tr>
<tr>
<td>Interval between CABG and CMR study (years)</td>
</tr>
<tr>
<td>LIMA to LAD graft, n (%)</td>
</tr>
<tr>
<td>Indication for stress CMR, n (%)</td>
</tr>
<tr>
<td>Typical chest pain</td>
</tr>
<tr>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Atypical symptoms</td>
</tr>
<tr>
<td>Risk stratification (asymptomatic)</td>
</tr>
</tbody>
</table>
### CMR parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDVi, ml/m²</td>
<td>75 (65 – 92)</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>57 (48 – 66)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61 (50 - 68)</td>
</tr>
<tr>
<td>Visual perfusion defect (qualitative), %</td>
<td>240 (70)</td>
</tr>
<tr>
<td>Stress MBF, ml/g/min</td>
<td>1.49 (1.18 - 1.90)</td>
</tr>
<tr>
<td>Rest MBF, ml/g/min</td>
<td>0.74 (0.60 - 0.88)</td>
</tr>
<tr>
<td>Myocardial perfusion reserve (MPR)</td>
<td>2.03 (1.63 - 2.57)</td>
</tr>
<tr>
<td>Stress MBF with LGE segments excluded</td>
<td>1.51 (1.22-1.93)</td>
</tr>
<tr>
<td>Rest MBF with LGE segments excluded</td>
<td>0.74 (0.60-0.90)</td>
</tr>
<tr>
<td>MPR with LGE segments excluded</td>
<td>2.05 (1.63 - 2.62)</td>
</tr>
</tbody>
</table>

### LGE analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGE present at least in 1 segment (n, %)</td>
<td>256 (75)</td>
</tr>
<tr>
<td>LGE as % of global myocardium (FWHM)</td>
<td>9.3 (0 - 17)</td>
</tr>
<tr>
<td>LGE as % of global myocardium (5x +SD)</td>
<td>8.6 (0 – 18.7)</td>
</tr>
</tbody>
</table>

BSA, body surface area; BMI, body mass index; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; LIMA, left internal mammary artery; LAD, left anterior descending artery; CABG, coronary artery bypass graft surgery; LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; LGE, late gadolinium enhancement. Results shown as mean ± SD or median (IQR). a LIMA data available for 292 patients.
6.3.2 Predictors of stress MBF and MPR in patients post CABG

Median stress myocardial blood flow was 1.49 (1.18-1.90) ml/g/min, and median myocardial perfusion reserve (MPR) was 2.03 (1.63-2.57). Both stress MBF and MPR were significantly reduced in patients with an inducible visual perfusion defect compared to those without (stress MBF 1.44 ml/g/min, IQR 1.13-1.77 versus 1.73 ml/g/min, IQR 1.29-2.06 p<0.001), (MPR 1.99, IQR 1.59-2.41 versus 2.21, IQR 1.70-2.77, p=0.007). Similar differences between those with and without visual perfusion defects were obtained when only LGE-free segments were included in the estimation of global stress MBF and MPR (p<0.001 and p=0.007 respectively).

In a multivariate regression analysis (Table 6-2), stress MBF was independently associated with age (B=-0.24, p<0.001), gender (female sex, B=0.10, p=0.045) and the amount of global LGE expressed as percentage of total myocardium (B=-0.19, p=0.003). In a multivariate regression analysis of predictors of myocardial perfusion reserve (Table 6-3), only age (B=-0.28, p<0.001) and the presence of diabetes mellitus (B=-0.18, p<0.001) were found to be independently associated with MPR.
### Table 6-2 Multivariable regression model of predictors of stress MBF in patients with prior CABG

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Standardized B</th>
<th>β (unstandardized)</th>
<th>95% CI of β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.245</td>
<td>-0.013</td>
<td>-0.018 to -0.007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.104</td>
<td>0.149</td>
<td>0.003 to 0.295</td>
<td>0.045</td>
</tr>
<tr>
<td>Global LGE (%)(^a)</td>
<td>-0.191</td>
<td>-0.008</td>
<td>-0.013 to -0.006</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>-0.095</td>
<td>-0.094</td>
<td>-0.195 to 0.010</td>
<td>0.066</td>
</tr>
<tr>
<td>Time since CABG surgery (years)</td>
<td>-0.079</td>
<td>-0.005</td>
<td>-0.012 to 0.002</td>
<td>0.174</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>-0.028</td>
<td>0.027</td>
<td>-0.129 to 0.075</td>
<td>0.599</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.109</td>
<td>0.004</td>
<td>-0.002 to 0.010</td>
<td>0.179</td>
</tr>
<tr>
<td>LVEDVi (ml/m(^2))</td>
<td>0.060</td>
<td>0.001</td>
<td>-0.002 to 0.004</td>
<td>0.413</td>
</tr>
</tbody>
</table>

\(^a\)5x SD thresholding method; LVEF left ventricular ejection fraction; CABG Coronary artery bypass graft surgery; LVEDVi, left ventricular end-diastolic volume index; LGE, late gadolinium enhancement; PCI, percutaneous coronary intervention
Table 6-3 Multivariate regression analysis of predictors of myocardial perfusion reserve (MPR) in patients post CABG

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Standardized Beta</th>
<th>β (unstandardized)</th>
<th>95% CI of β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.283</td>
<td>-0.019</td>
<td>-0.027 to -0.011</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>-0.180</td>
<td>-0.241</td>
<td>-0.380 to 0.101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>-0.071</td>
<td>-0.136</td>
<td>-0.339 to 0.066</td>
<td>0.185</td>
</tr>
<tr>
<td>Global LGE (%)*</td>
<td>-0.037</td>
<td>-0.002</td>
<td>-0.009 to -0.005</td>
<td>0.582</td>
</tr>
<tr>
<td>Time since CABG surgery (years)</td>
<td>-0.074</td>
<td>-0.006</td>
<td>-0.016 to 0.004</td>
<td>0.217</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>-0.116</td>
<td>-0.006</td>
<td>-0.014 to 0.002</td>
<td>0.168</td>
</tr>
<tr>
<td>LVEDVi (ml/m²)</td>
<td>-0.114</td>
<td>-0.003</td>
<td>-0.007 to 0.001</td>
<td>0.132</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>-0.022</td>
<td>-0.029</td>
<td>-0.171 to 0.113</td>
<td>0.688</td>
</tr>
</tbody>
</table>

*5xSD thresholding method
LVEF left ventricular ejection fraction, CABG Coronary artery bypass graft surgery, LVEDVi, left ventricular end-diastolic volume index; LGE, late gadolinium enhancement; PCI, percutaneous coronary intervention
6.3.3 Predictors of MACE and all-cause mortality

Over a median period of 638 days (IQR 367, 976) there were 85 events, in 81 (24%) patients. These included 24 (7%) myocardial infarctions, 36 (10%) late revascularisations and 25 deaths (7%). Patients with events (death or MACE) had lower stress MBF (1.30ml/g/min; IQR 1.05-1.73; versus 1.54ml/g/min; IQR 1.26-1.96; p< 0.001) and lower MPR (MPR1.96, IQR 1.56-2.33 versus 2.09, IQR 1.67-2.61; p=0.038) compared to those without events. Similar differences were observed when stress MBF was estimated after excluding segments with LGE (p=0.002). Patients who reached the primary end-point more frequently had a visual perfusion defect (83% vs 66%, p<0.001), had longer period since CABG surgery (p=0.037) and more frequently had a history of previous or PCI (p=0.003). Detailed comparison between the groups is shown in Table 6-4. Univariate associations between parameters and the primary end-point are shown in Table 6-5.
Table 6-4 Patient characteristics in relation to the primary outcome

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Death or MACE (n=81)</th>
<th>No death or MACE (n=260)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years,</td>
<td>68 ± 10</td>
<td>67 ± 10</td>
<td>0.165</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>76 (94)</td>
<td>218 (84)</td>
<td><strong>0.023</strong></td>
</tr>
<tr>
<td>BSA, kg/m²</td>
<td>1.9 (1.8-2.1)</td>
<td>1.9 (1.7-2.1)</td>
<td>0.269</td>
</tr>
<tr>
<td>Time since CABG surgery (years)</td>
<td>10 (6-17)</td>
<td>8 (3-15)</td>
<td><strong>0.037</strong></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>41 (51)</td>
<td>149 (57)</td>
<td>0.290</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71 (88)</td>
<td>236 (91)</td>
<td>0.414</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>73 (90)</td>
<td>228 (88)</td>
<td>0.553</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>53 (65)</td>
<td>120 (46)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (9)</td>
<td>30 (12)</td>
<td>0.464</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2 (2)</td>
<td>19 (7)</td>
<td>0.182</td>
</tr>
<tr>
<td>Smoking history</td>
<td>30 (37)</td>
<td>75 (29)</td>
<td>0.163</td>
</tr>
<tr>
<td>Cardiovascular Magnetic Resonance parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDVi, ml/m²</td>
<td>75 (65-94)</td>
<td>75 (65-91)</td>
<td>0.743</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>60 (43-67)</td>
<td>61 (50-68)</td>
<td>0.383</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>61 (52-68)</td>
<td>56 (48-66)</td>
<td>0.051</td>
</tr>
<tr>
<td>Any late gadolinium enhancement, n (%)</td>
<td>67 (83)</td>
<td>189 (73)</td>
<td>0.069</td>
</tr>
<tr>
<td>Myocardial segments with LGE, n</td>
<td>3 (1-5)</td>
<td>3 (0-5)</td>
<td>0.445</td>
</tr>
<tr>
<td>Global LGE (% , 5xSD)</td>
<td>9.6 (2.4-17.3)</td>
<td>7.9 (0-19.3)</td>
<td>0.319</td>
</tr>
<tr>
<td></td>
<td>Global LGE (%, FWHM)</td>
<td>10.3 (3.5-17.7)</td>
<td>9.2 (0-16.85)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>Global Stress MBF, ml/g/min</td>
<td>1.30 (1.05-1.73)</td>
<td>1.54 (1.26-1.96)</td>
</tr>
<tr>
<td></td>
<td>Global MPR</td>
<td>1.96 (1.56-2.33)</td>
<td>2.09 (1.67-2.61)</td>
</tr>
<tr>
<td></td>
<td>Stress MBF of segments without LGE</td>
<td>1.39 (1.07-1.79)</td>
<td>1.57 (1.26-1.98)</td>
</tr>
<tr>
<td></td>
<td>MPR of segments without LGE</td>
<td>2.02 (1.60-2.44)</td>
<td>2.07 (1.68-2.71)</td>
</tr>
<tr>
<td>Visual perfusion defect</td>
<td>69 (83)</td>
<td>171 (66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**MACE** - defined as myocardial infarction or unplanned coronary revascularization. BSA, body surface area; BMI, body mass index; TIA, transient ischemic attack; PCI percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; LGE late gadolinium enhancement. Results presented as medians (IQR), means (± SD) or n (%). *p*-values <0.05 shown in bold.
Table 6-5 Univariate Cox Regression analysis of associations with death or MACE

<table>
<thead>
<tr>
<th>Univariates</th>
<th>P Value*</th>
<th>Hazard Ratio (HR)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.156</td>
<td>1.016</td>
<td>0.994</td>
<td>1.038</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.140</td>
<td>0.720</td>
<td>0.465</td>
<td>1.114</td>
</tr>
<tr>
<td>Rest MBF (ml/g/min)</td>
<td>0.255</td>
<td>0.567</td>
<td>0.213</td>
<td>1.508</td>
</tr>
<tr>
<td>Global LGE (%)</td>
<td>0.494</td>
<td>1.006</td>
<td>0.989</td>
<td>1.023</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.334</td>
<td>0.922</td>
<td>0.977</td>
<td>1.008</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.043</td>
<td>0.393</td>
<td>0.159</td>
<td>0.972</td>
</tr>
<tr>
<td>Time from surgery (years)</td>
<td>0.009</td>
<td>1.035</td>
<td>1.009</td>
<td>1.062</td>
</tr>
<tr>
<td>Presence of LGE</td>
<td>0.025</td>
<td>1.943</td>
<td>1.088</td>
<td>3.474</td>
</tr>
<tr>
<td>Visual perfusion defect</td>
<td>0.001</td>
<td>2.760</td>
<td>1.494</td>
<td>5.099</td>
</tr>
<tr>
<td>Stress MBF (ml/g/min) †</td>
<td>&lt;0.001</td>
<td>3.278</td>
<td>1.398</td>
<td>3.703</td>
</tr>
<tr>
<td>Myocardial perfusion reserve †</td>
<td>0.021</td>
<td>1.550</td>
<td>1.067</td>
<td>2.252</td>
</tr>
</tbody>
</table>

* Significant univariate associations (p<0.05) are shown in bold, †HR for 1 ml/g/min or 1 unit decrease in these parameters

Multivariate cox proportional hazard analysis demonstrated that both stress MBF and MPR independently predicted death and MACE, after adjusting for a number of parameters including age, sex, amount of global LGE (using either FWHM or 5xSD method), left ventricular ejection fraction, diabetes and history of previous PCI. The adjusted hazard ratio (HR) for 1 ml/g/min decrease in stress MBF was 2.56 (95% CI, 1.45-4.35) and for 1 unit decrease in MPR the adjusted hazard ratio (HR) was 1.61 (95% CI, 1.08-2.38). In a standardised hazard model, the effect of stress MBF was found to be greater than MPR for death or MACE (standardized HR for a 1 SD decrease in stress MBF and MPR, 1.59 versus 1.35 respectively) (Table 6-6). Additional models are shown in Table 6-7. Kaplan Meier event-free survival estimates are shown in Figure 6-2.
Table 6-6 Cox Proportional Hazard Models for stress MBF and MPR as predictors of death or MACE

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Death or MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stress myocardial blood flow (MBF)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) per 1x SD per increase</td>
<td>1.49 (1.18-1.92)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) per 1x SD per increase</td>
<td>1.59 (1.20-2.08)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model \textit{Chi-square} value</td>
<td>26.25</td>
</tr>
<tr>
<td><strong>Myocardial Perfusion Reserve (MPR)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) per 1x SD per increase</td>
<td>1.33 (1.04-1.69)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) per 1x SD per increase</td>
<td>1.35 (1.05-1.75)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.020</td>
</tr>
<tr>
<td>Model \textit{Chi-square} value</td>
<td>20.9</td>
</tr>
</tbody>
</table>

\textit{MACE (myocardial infarction and coronary revascularization). Model for was adjusted for age, sex, left ventricular ejection fraction (LVEF), diabetes, history of previous PCI and global LGE (5x SD method used in this model).}
### Table 6-7. Additional multivariable Cox Regression Analysis models of association between stress MBF and the primary end-point (death or MACE)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>95% CI for HR</th>
<th>95% CI for HR</th>
<th>95% CI for HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.985, 1.034</td>
<td>0.985, 1.034</td>
<td>0.985, 1.034</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.458, 1.166</td>
<td>0.458, 1.166</td>
<td>0.458, 1.166</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.981, 1.025</td>
<td>0.981, 1.025</td>
<td>0.981, 1.025</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.404, 1.008</td>
<td>0.404, 1.008</td>
<td>0.404, 1.008</td>
</tr>
<tr>
<td>Global LGE (%)</td>
<td>0.972, 1.018</td>
<td>0.972, 1.018</td>
<td>0.972, 1.018</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1.031, 2.658</td>
<td>1.031, 2.658</td>
<td>1.031, 2.658</td>
</tr>
<tr>
<td>Global stress MBF (ml/g/min)</td>
<td>1.456, 4.367</td>
<td>1.456, 4.367</td>
<td>1.456, 4.367</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.986, 1.035</td>
<td>0.986, 1.035</td>
<td>0.986, 1.035</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.68, 1.092</td>
<td>0.68, 1.092</td>
<td>0.68, 1.092</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.976, 1.022</td>
<td>0.976, 1.022</td>
<td>0.976, 1.022</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.391, 0.973</td>
<td>0.391, 0.973</td>
<td>0.391, 0.973</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>0.888, 2.276</td>
<td>0.888, 2.276</td>
<td>0.888, 2.276</td>
</tr>
<tr>
<td>Global stress MBF (ml/g/min)</td>
<td>1.129, 3.378</td>
<td>1.129, 3.378</td>
<td>1.129, 3.378</td>
</tr>
<tr>
<td>Visual perfusion defect</td>
<td>1.221, 4.377</td>
<td>1.221, 4.377</td>
<td>1.221, 4.377</td>
</tr>
<tr>
<td>Number of segments with ≥50% LGE</td>
<td>0.856, 1.131</td>
<td>0.856, 1.131</td>
<td>0.856, 1.131</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.987, 1.036</td>
<td>0.987, 1.036</td>
<td>0.987, 1.036</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.173, 1.105</td>
<td>0.173, 1.105</td>
<td>0.173, 1.105</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.988, 1.026</td>
<td>0.988, 1.026</td>
<td>0.988, 1.026</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.383, 0.954</td>
<td>0.383, 0.954</td>
<td>0.383, 0.954</td>
</tr>
<tr>
<td>Presence of LGE</td>
<td>0.862, 3.130</td>
<td>0.862, 3.130</td>
<td>0.862, 3.130</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>0.866, 2.217</td>
<td>0.866, 2.217</td>
<td>0.866, 2.217</td>
</tr>
<tr>
<td>Global stress MBF (ml/g/min)</td>
<td>1.094, 3.236</td>
<td>1.094, 3.236</td>
<td>1.094, 3.236</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.981, 1.032</td>
<td>0.981, 1.032</td>
<td>0.981, 1.032</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.173, 1.105</td>
<td>0.173, 1.105</td>
<td>0.173, 1.105</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.399, 0.985</td>
<td>0.399, 0.985</td>
<td>0.399, 0.985</td>
</tr>
<tr>
<td>Time since CABG (years)</td>
<td>0.978, 1.038</td>
<td>0.978, 1.038</td>
<td>0.978, 1.038</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>0.866, 2.269</td>
<td>0.866, 2.269</td>
<td>0.866, 2.269</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Global stress MBF</td>
<td>0.020</td>
<td>1.848</td>
<td>1.101</td>
</tr>
<tr>
<td>(ml/g/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual perfusion defect</td>
<td>0.009</td>
<td>2.339</td>
<td>1.238</td>
</tr>
</tbody>
</table>

**Model 5 – Chi-square: 31.9**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.431</td>
<td>1.010</td>
<td>0.985</td>
<td>1.036</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.077</td>
<td>0.430</td>
<td>0.169</td>
<td>1.095</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.885</td>
<td>0.998</td>
<td>0.976</td>
<td>1.021</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.038</td>
<td>0.615</td>
<td>0.389</td>
<td>0.974</td>
</tr>
<tr>
<td>Global LGE (%, FWHM)</td>
<td>0.576</td>
<td>0.995</td>
<td>0.972</td>
<td>1.018</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>0.103</td>
<td>1.655</td>
<td>1.031</td>
<td>2.658</td>
</tr>
<tr>
<td>Global stress MBF</td>
<td>0.008</td>
<td>2.519</td>
<td>1.475</td>
<td>4.367</td>
</tr>
<tr>
<td>(ml/g/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual perfusion defect</td>
<td>0.013</td>
<td>2.237</td>
<td>1.183</td>
<td>4.232</td>
</tr>
</tbody>
</table>

To assess whether the association of stress MBF and MPR with outcomes is significantly confounded by the presence of LGE, a further analysis was performed using global stress MBF and global MPR derived only from segments without LGE. Both stress MBF and MPR remained predictive of death or MACE after adjusting for the same parameters shown in Table 6-6 (adjusted hazard ratio (HR) for 1 ml/g/min increase in stress MBF was 0.45 (95% CI, 0.27–0.74; p =0.002) and for 1 unit increase in MPR the adjusted hazard ratio (HR) is 0.67 (95% CI, 0.47-0.97; p=0.032)). Similarly, to further evaluate whether the prognostic impact observed was mainly driven by revascularisations triggered by the CMR study itself, a further analysis was performed by excluding cases undergoing revascularisation within 12 months following the CMR study. In this model, stress MBF remained independently predictive of death and MACE (Table 6-8).
Table 6-8. Multivariable Cox Regression Analysis models of association between stress MBF and the primary end-point after censoring cases undergoing coronary revascularisation within 12-months of CMR

<table>
<thead>
<tr>
<th>Predictors</th>
<th>95% CI for HR</th>
<th>95% CI for HR</th>
<th>95% CI for HR</th>
<th>95% CI for HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.066</td>
<td>1.030</td>
<td>0.998</td>
<td>1.063</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.070</td>
<td>0.262</td>
<td>0.061</td>
<td>1.118</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.876</td>
<td>0.998</td>
<td>0.972</td>
<td>1.024</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.646</td>
<td>0.871</td>
<td>0.483</td>
<td>1.570</td>
</tr>
<tr>
<td>Global LGE (%)</td>
<td>0.910</td>
<td>1.002</td>
<td>0.975</td>
<td>1.029</td>
</tr>
<tr>
<td>Global stress MBF (ml/g/min)</td>
<td><strong>0.043</strong></td>
<td><strong>2.032</strong></td>
<td><strong>1.022</strong></td>
<td><strong>4.049</strong></td>
</tr>
</tbody>
</table>
Figure 6-2 Kaplan Meier curves according to stress MBF and MPR.

Event-free survival curves for death and major adverse cardiovascular events (non-fatal myocardial infarction and unplanned revascularization) according to stress MBF and MPR. Lower stress MBF and MPR were associated with higher rates of events.
6.4 Discussion

The main finding of this study is that myocardial stress MBF and MPR independently predict all-cause mortality and adverse cardiovascular outcomes (myocardial infarction and late revascularisation) in patients with prior CABG, beyond established cardiovascular risk factors and imaging biomarkers. The association of stress MBF with prognosis is independent of the presence of regional ischaemia during stress on visual assessment.

6.4.1 Predictors of myocardial blood flow in patients post-surgical revascularisation

Very few studies have previously evaluated stress MBF post CABG and these were predominantly performed in asymptomatic patients, soon after surgery (172,370,371). Despite differences in imaging modalities and quantification techniques, our stress results are in comparable to these studies. Using $^{15}$O-water PET, Aikawa et al (371) reported a median stress MBF of 1.49ml ml/g/min in patients assessed 6-months post CABG. As expected, we found that compared to patients with similar clinical presentations but with un-grafted native vessels (414,416), patients with prior CABG had lower stress MBF. This provides evidence that quantitative perfusion cut offs cannot be extrapolated from studies on native vessel disease. There are however a number of considerations in relation to absolute MBF estimation following surgical revascularisation that warrant discussion. Patients with prior-CABG not only have advanced epicardial coronary and microvascular disease, but also have greater atherosclerotic burden, itself a determinant of myocardial blood flow (417). Consequently, even if revascularisation is achieved with anatomical lesion bypassing following surgery, myocardial blood flow is not necessarily restored to normal levels (370).
Furthermore, a number of studies reported accelerated progression of native vessel disease post CABG (387), a process shown to contribute to reduction in MBF irrespective of graft patency (418). Contemporary data would also suggest that a significant rate of vein graft failure would have been encountered in our cohort (419), considering the interval between CABG surgery and CMR in our study (median of 9 years). As in previous cohorts of patients post CABG (157), our study includes a large proportion of patients with prior infarction, with 203 (73%) patients having evidence of LGE. Quantitative evaluation of LGE was shown to be an independent predictor of stress MBF in our cohort, which is in agreement with previous studies demonstrating reduced MBF in areas of infarction (420). Evidently, this is likely to contribute to the low stress MBF seen in these patients.

6.4.2 Association of quantitative perfusion indices with MACE

With a progressive decline in acute mortality from CABG surgery and parallel improvements in medical pharmacological therapy, patients with prior CABG represent a common clinical challenge. These patients have advanced coronary atherosclerotic disease and remain at a high risk for symptom recurrence and adverse cardiovascular events. Up to 30% are expected to undergo clinically-driven angiography within 10-years (421), and up to 13% of post CABG patients will undergo repeat revascularisation during the same period (422).

A number of studies across different modalities including nuclear (148,156), echocardiography (142) and more recently CMR (157), have demonstrated a prognostic role of ischaemia detection in patients with prior CABG. Pen et al (156)
evaluated 953 patients with prior CABG using Rb-82 MPI or hybrid PET/computed tomography and reported that visual estimation of summed stress score (SSS) independently predicted all-cause mortality and cardiac death. Kinnel et al (157) recently demonstrated that detection of ischaemia using stress CMR predicted cardiovascular death or non-fatal myocardial infarction. In this study, the majority of patients were asymptomatic (67%) and ischaemia was detected on visual assessment.

To our knowledge, no previous study evaluated the prognostic value of quantitative MBF estimation in patients with prior CABG. Quantitative perfusion mapping has been shown to offer incremental value in evaluating the extent of coronary artery disease even in complex disease models, including multivessel coronary disease (414). Importantly, both stress MBF and MPR were previously shown to independently predict outcomes in the context of native coronary artery disease using CMR (80,81) and PET (144,423) and the current study suggests that a similar prognostic value is maintained in patients with prior CABG.

Different physiological mechanisms by which CABG exerts a prognostic impact have been proposed (53), but their relevant contribution on outcomes remain unclear. Extrapolating from PCI data, studies suggested that the prognostic benefit of an adequate post-PCI fractional flow reserve (FFR) is likely mediated by augmented myocardial perfusion (424). Restoration of myocardial blood flow is therefore conceptually the principal mechanism by which CABG impacts on prognosis, both through anatomical lesion bypassing and from collateralisation of distal coronary territories (53). Despite this, indices of myocardial blood flow are
also associated with both the extent of atherosclerotic burden (425), itself a
predictor of hard clinical end-points, (426) as well as microvascular health. It is
therefore likely that both factors will have an impact on MBF post-surgical
revascularisation; a prognostic effect that is potentially undetected with
conventional methods of qualitative ischaemia testing.

This study provides evidence that both absolute stress MBF and MPR post CABG
encode prognostic information, likely through a combination of parameters that
determine blood flow, including the reflection of coronary disease burden. Indeed,
the finding that MBF and MPR predict events independent of the presence of a
visual perfusion defect point towards additional contributing mechanisms, beyond
the presence of epicardial coronary artery disease.

6.5 Limitations
There are a number of limitations that warrant consideration. The study is limited
by the small sample size and its retrospective single-centre design. This
precludes evaluating associations of perfusion indices with individual end-points.
This is however the largest cohort of post CABG patients undergoing quantitative
perfusion imaging across all imaging modalities, and provides novel data on the
prognostic role of quantitative perfusion indices in this population. Despite its
retrospective design, quantitative perfusion mapping was performed entirely in-line,
with no user input, significantly reducing the potential for bias. According to
our findings, stress MBF was dependent on age, gender and the extent of LGE,
but was less affected by conventional cardiovascular risk factors such as
hypertension and diabetes. However, the high prevalence of these risk factors in
our post CABG population (56% had diabetes; 90% hypertension), is likely to have reduced the study’s power to detect such associations. Furthermore, the lack of MBF data immediately post CABG surgery as well as the lack of contemporary anatomical data for each patient makes it difficult to draw conclusions about the mechanism of reduced MBF in this cohort (eg. incomplete revascularisation vs CAD progression/graft failure). However, the results reported are reflective of real-world clinical practice, with significant variability between the original surgery and the time of ischaemia evaluation. Finally, there are technical challenges related to the use of first pass perfusion in patients with prior CABG (contrast dispersion, vasomotor differences between venous and arterial grafts) that may have an impact on absolute MBF quantification. Previous studies however examined the diagnostic performance of quantitative perfusion in the context of CABG and provided reassuring results (369,402,418). Our cohort included predominantly symptomatic patients (71%), therefore the clinical utility or prognostic value of routine use of quantitative perfusion imaging in asymptomatic patients post CABG cannot be supported by this data.

6.6 Conclusion
In this cohort of consecutive, clinically referred patients with prior CABG, both stress MBF and MPR independently predicted all-cause mortality and adverse cardiovascular events. Their prognostic effect is independent of the presence of ischaemia on visual assessment or the extent of previous infarction. These results suggest that quantitative perfusion may offer additional insights into the pathophysiological processes that determine outcomes post CABG, including its
mechanistic impact on coronary blood flow, and should be further evaluated in prospective studies across different imaging modalities.
Chapter 7       Prognostic value of Pulmonary Transit Time and Pulmonary Blood Volume estimation using myocardial perfusion CMR

This chapter is based on the following published manuscript:


Prognostic Value of Pulmonary Transit Time and Pulmonary Blood Volume Estimation Using Myocardial Perfusion CMR.

doi: 10.1016/j.jcmg.2021.03.029
7.1 Introduction

The pulmonary circulation is inextricably linked with cardiac physiology, but our understanding of the cardiopulmonary axis in various disease states is limited. Use of non-invasive imaging biomarkers as surrogate indicators of cardiopulmonary status may facilitate risk stratification and outcome prediction, potentially contributing to personalised clinical care.

Pulmonary transit time (PTT) and pulmonary blood volume (PBV) are physiological parameters reflective of cardiopulmonary haemodynamics (427). Both are known to be altered in various disease states, including heart failure (210,428), pulmonary hypertension (218,429) and chronic lung disease (430), and to correlate with structural, functional and biochemical parameters of pulmonary (431) and cardiac function (214). Pulmonary transit time, defined as the time interval for a contrast bolus to pass from the right-sided to left-sided circulation, and PBV (the product of PTT and cardiac output (CO)), correlate with established prognostic biomarkers, including right and left ventricular (LV) ejection fraction (209,432), markers of LV diastolic function (210,217), brain natriuretic peptide (BNP) levels (209,216), and pulmonary vascular resistance (429). Importantly, a small number of studies suggested an independent prognostic utility of PTT and PBV in specific disease models (210,218,433).

Despite extensive research supporting a clinical utility of PTT and PBV (Section 1.3.7), at scale analysis and clinical adoption has been hindered by challenges in data acquisition, requiring either invasive catheterisation (427) or manual segmentation and data extraction from non-invasive tests. Recent developments in quantitative cardiovascular magnetic resonance (CMR) perfusion permit
automated estimation of PTT inline as part of routine perfusion mapping without the need for additional acquisitions or processing, enabling large data analyses and potentially facilitating clinical adoption.

In this study, a fully automated, machine learning approach for identification of RV and LV arterial input functions during first pass rest perfusion imaging was deployed allowing in-line estimation of PTT and subsequent calculation of PBV. Details regarding the development of the technique are provided in Section 3.5 of this thesis. Following the incorporation of the method within the Gadgetron framework, we investigated the potential clinical utility of PTT and PBV by assessing correlations with other parameters and any independent prognostic significance.

7.2 Methods

7.2.1 Patients and study design:

This was a retrospective cohort study of patients referred to 2 centers (Barts Heart Centre and the Royal Free Hospital, London, United Kingdom), between March 2016 and August 2018. This cohort has been used to explore the prognostic effect of myocardial blood flow (MBF) and perfusion reserve (MPR), and has been previously described (80). In brief, consecutive adult patients referred for a myocardial perfusion scan were included. Patients with congenital heart disease, known intra-cardiac shunts (known to affect methods based on the indicator dilution principles (206)), and patients with inherited or infiltrative cardiomyopathies (hypertrophic cardiomyopathy and cardiac amyloid) were excluded.
The primary outcome was the incidence of major adverse non-fatal cardiovascular events (defined as myocardial infarction, stroke, heart failure admission and ventricular tachycardia or appropriate ICD treatment (including ICD shock and/or anti-tachycardia pacing). Secondary outcome was all-cause mortality. Clinical data including outcome events were retrieved from the electronic patient record and all-cause mortality outcomes were obtained from the National Health Service Spine portal, with follow-up starting from the date of the perfusion CMR examination. Comorbidities recorded included history of hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, stroke or transient ischemic attack, smoking, history of previous myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG), and cancer (all based on medical records).

The study was approved by the National Health Service Research Ethics Committee and Health Research Authority (Barts BioResource - REC ID 14/EE/0007, Royal Free Hospital - REC ID 07/H0715/101). The study conformed to the principles of the Helsinki Declaration and all patients provided written, informed consent.

7.2.2 Cardiovascular Magnetic Resonance

CMR studies were carried out on one of four 1.5T (Aera) or 3T scanners (Prisma, Siemens Healthineers, Erlangen, Germany). A standard clinical protocol including cine imaging, stress and rest perfusion followed by late gadolinium enhancement was used for all studies. Stress and rest first pass myocardial perfusion was performed, using adenosine as pharmacological stressor
according to guidelines (344). The myocardial perfusion sequence is a single-bolus, dual sequence described previously (100). Basal, mid-ventricular, and apical short-axis perfusion images were acquired at both stress and rest. Image acquisition was performed over 60-90 heartbeats and a bolus of 0.05 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Paris, France) was administered at 4 ml/s during both maximal hyperemia and subsequently at rest (for estimation of stress and rest myocardial blood flow (MBF) respectively. Myocardial perfusion reserve was defined as the ratio of stress MBF over rest MBF \[ MPR = \frac{MBF_{\text{stress}}}{MBF_{\text{rest}}} \]. PTT data was calculated only from rest perfusion imaging and PBV was estimated utilizing resting cardiac output measurement from cardiac volumes obtained from short-axis stack cine images.

7.2.3 Imaging analysis

Image analysis for cardiac volume parameters, presence and distribution of late gadolinium parameters was performed using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). The perfusion sequence deployed (100) involves the simultaneous acquisition of separately optimised sequences for myocardium and blood pool signals. Motion corrected low resolution dynamic images from a basal short axis view are used to extract the arterial input function (AIF) of the RV and LV. The quantitative mapping utilizes a convolutional neural network (CNN) approach to automatically segment the LV and RV cavities thereby allowing the estimation of arterial input function (signal intensity over time) for both ventricles during first pass of contrast. Details of the blood pool detection process were described previously (300,301). The resulting signal intensity curves are then converted to Gd concentration (mmol/L)
based on automatically generated look-up tables for the magnetization Bloch simulation (100). Automatic reconstruction and post processing is executed within the Gadgetron software framework (303), allowing in-line estimation of the time interval between the RV and LV curve AIF curves.

7.2.4 Pulmonary Transit Time and Pulmonary Blood Volume estimation

Background and information on the development of the method for PTT estimation deployed in this study was discussed in the main Methods Chapter (Section 3.5). Non-invasive methods of volume estimation are based on the indicator dilution principle and have been previously validated against invasive thermodilution methods (434). The PTT was estimated as the time between the centers of gravity (centroids) of the RV and LV arterial input function curves, after exclusion of the re-circulation component (Figure 7-1). The use of centroids of the AIF curves was previously shown to be superior to peak-to-peak methods for PBV estimation (213). Pulmonary transit time normalised for heart rate (PTTn) was estimated by dividing PTT with the duration of the cardiac cycle (R-R interval, seconds) as performed in previous studies (209,214)

\[
PTTn = \frac{PTT}{R-R \text{ interval (s)}} \quad (eq.1)
\]

Pulmonary blood volume was estimated as the product of PTT and cardiac output as originally described from indicator dilution methods (435):

\[
PBV = PTT \times \text{Cardiac output} \quad (eq. 2)
\]

This was indexed to body surface area (BSA), allowing calculation of Pulmonary blood volume index (PBVi),

\[
PBVi = \frac{PTT \times \text{Cardiac output}}{\text{BSA}} \quad (eq. 3).
\]
The LV stroke volume (SV) was estimated using steady state free precession (SSFP) cine images from manual planimetry of a full short axis stack in end-diastole and end-systole and the patient’s heart rate (HR) at rest was used to derive cardiac output (CO = SV x HR).

Figure 7-1 Automated, inline method of pulmonary transit estimation

A: Dynamic first pass perfusion imaging of a basal short axis slice showing the RV and LV cavities (here high resolution images).

B: Schematic gadolinium time-concentration curves in the RV and LV cavities with the recirculation component.
removed for clarity. The dashed lines indicate the location of the centroid in each cavity and the difference (i.e. the pulmonary transit time) between each centroid is indicated by the arrow. **C, D:** Examples of PTT estimation in study patients. (C) 59 year-old male, LVEF 72%, PTT = 5.3s, PBVi 374ml/m², (D) 57 year-old male, LVEF 19%, PTT = 19.1s, PBVi 596ml/m²

7.2.5 Statistical analysis

Continuous variables were reported as mean ± SD when normally distributed and as median (interquartile range (IQR)) when not. Normality was assessed by visual inspection of the frequency histograms and quantified using a Kolmogorov-Smirnov test. Categorical variables were summarised as frequencies and percentages. Comparisons between MACE and non-MACE groups were performed for continuous variables using a two-tailed unpaired Student’s t-test or a Mann-Whitney U test depending on normality, and categorical variables were compared with a χ² test. Correlations were assessed using Spearman’s rank correlation coefficient. Predictors of PTT were evaluated using a multivariate regression analysis, the model of which included parameters either known to correlate with PTT as shown in previous studies (214), or that would have a physiological basis for interacting with PTT. PTT was log-transformed in the regression model to meet the model assumptions. Unstandardised beta coefficients were obtained allowing predictors to be expressed in their original units. To identify independent prognosticators of MACE and all-cause mortality, separate Cox proportional hazard regression analyses were performed with adjustment for covariates including age, sex, left ventricular ejection fraction (LVEF), presence of late gadolinium enhancement (LGE), myocardial perfusion reserve (MPR), LA area index, diabetes mellitus, dyslipidemia, hypertension and previous history of myocardial infarction/ PCI/ CABG). The proportional hazards
assumption was checked using Schoenfeld residuals. A sensitivity analysis was also performed to obtain Firth’s bias-adjusted estimates to ensure there was no bias in the estimated coefficients due to the relatively low event rates. Results were similar to the original models. Survival curves were constructed according to the Kaplan-Meier method to estimate cumulative survival and compared using log-rank tests. The cut off values for PTT and PBVi were based on the mean values within the study population (8.05 seconds and 414ml/m² respectively). A \( p \)-value\(<0.05 \) was considered significant. Analysis was performed using SPSS software package (IBM SPSS Statistics, version 26.0).
7.3 Results:

7.3.1 Cohort description and baseline characteristics

A total 1049 patients with CMR myocardial perfusion imaging data were available for inclusion as previously described (80). Of these, 4 (0.4%) had confirmed intra-cardiac shunts and were therefore excluded, in addition to 60 (5.7%) patients with incomplete or erroneous rest perfusion data (including incorrect automated blood pool identification, incorrect timing of contrast administration, poor AIF signal of either the RV or LV). A total of 985 patients with available PTT data were therefore included in the final analysis.

Median age of the patients was 62 (52-71) years and 660 (67%) were male. There were 281 (28.6%) patients with diabetes mellitus and 306 (31%) patients had a prior history of either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). The median LVEF across the cohort was 62% (54-69). Baseline characteristics, including additional details of CMR parameters are summarized in Table 7-1.
Table 7-1 Baseline demographics and CMR parameters (n=985)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62 (52-71)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>660 (67%)</td>
</tr>
<tr>
<td>Body surface area, kg/m²</td>
<td>1.90 (1.8-2.1)</td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>281 (28.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>590 (60)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>479 (48.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>129 (13.1)</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>58 (5.9)</td>
</tr>
<tr>
<td>Previous MI/PCI/CABG</td>
<td>306 (31)</td>
</tr>
<tr>
<td>Smoking history (current or previous)</td>
<td>337 (34.2)</td>
</tr>
<tr>
<td>Cancer (active or previous diagnosis)</td>
<td>100 (10.2)</td>
</tr>
<tr>
<td><strong>Cardiovascular magnetic resonance parameters</strong></td>
<td></td>
</tr>
<tr>
<td>LVEDVi, ml/m²</td>
<td>75 (64-91)</td>
</tr>
<tr>
<td>LVSVi, ml/m²,</td>
<td>46 (40-53)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62 (54-69)</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>57 (48-68)</td>
</tr>
<tr>
<td>LA area index, cm²/m²</td>
<td>11.8 (10.1-13.9)</td>
</tr>
<tr>
<td>Presence of LGE, n %</td>
<td>416 (42%)</td>
</tr>
<tr>
<td>Stress MBF ml/g/min,</td>
<td>1.98 (1.6-2.5)</td>
</tr>
<tr>
<td>Rest MBF, ml/g/min,</td>
<td>0.89 (0.8-1.1)</td>
</tr>
<tr>
<td>MPR</td>
<td>2.39 (1.9-3.0)</td>
</tr>
<tr>
<td>Resting heart rate* (beats/minute)</td>
<td>68 (61-77)</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.97 (5.1-7.2)</td>
</tr>
</tbody>
</table>

Results presented as medians (IQR) unless otherwise stated; * at the time of rest perfusion acquisition. TIA – Transient Ischemic Attack; MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft surgery; LVEDVi - Left ventricular end-diastolic volume index; LVSVi - Left ventricular stroke volume index; LVEF - Left ventricular ejection fraction; LVMi - Left ventricular mass index; LA – left atrium; LGE – late gadolinium enhancement; MBF – myocardial blood flow; MPR – myocardial perfusion reserve;
7.3.2 Analysis of associations of PTT

Median pulmonary transit time was 7.7 seconds, (interquartile range (IQR), 6.4, 9.2). The median pulmonary blood volume index was 400 ml/m$^2$, (IQR 335, 475 ml/m$^2$). PTT was correlated with left ventricular end-diastolic volume index ($r = 0.37$), left atrial area index ($r = 0.33$) and inversely correlated with LVEF ($r = -0.39$), heart rate ($r = -0.51$) and myocardial blood flow at rest ($r = -0.43$) (Figure 7-2). In a multivariable regression analysis LVEF ($\beta = -0.007$, 95% CI -0.008, -0.006, $p < 0.001$), heart rate measured during rest perfusion ($\beta = -0.008$, 95% CI -0.010, -0.007, $p < 0.001$), age ($\beta = 0.003$, 95% CI 0.002, 0.004; $p < 0.001$), LA area index ($\beta = 0.019$, 95% CI 0.015, 0.023, $p < 0.001$), atrial fibrillation ($\beta = 0.118$, 95% CI 0.083, 0.154, $p < 0.001$), male sex ($\beta = 0.052$, 95% CI 0.026, 0.078, $p < 0.001$), diabetes ($\beta = -0.060$, 95% CI -0.087, -0.034, $p < 0.001$), hypertension ($\beta = -0.038$, 95% CI -0.064, -0.013, $p = 0.003$), and rest myocardial blood flow ($\beta = -0.098$, 95% CI -0.146, -0.050, $p = 0.006$) were independently associated with log$_e$ PTT (Table 7-2). These predictors explained 57.0% of the variance in PTT.
Figure 7-2 Associations of pulmonary transit time with cardiac parameters

Spearman’s (rho) correlation of pulmonary transit time (PTT) with heart rate, cardiac volume parameters, left ventricular ejection fraction, left atrial area and rest myocardial blood flow.
### Table 7-2 Multivariate regression analysis of parameters predicting loge
PTT

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β (unstandardized)</th>
<th>95% CI of β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA area index (ml/m²)</td>
<td>0.019</td>
<td>0.015 to 0.023</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>-0.008</td>
<td>-0.010 to -0.007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.003</td>
<td>0.002 to 0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.118</td>
<td>0.083 to 0.154</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>-0.007</td>
<td>-0.008 to -0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.060</td>
<td>-0.087 to -0.034</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.038</td>
<td>-0.064 to -0.013</td>
<td>0.003</td>
</tr>
<tr>
<td>Rest myocardial blood flow (ml/g/min)</td>
<td>-0.098</td>
<td>-0.146 to -0.050</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.052</td>
<td>0.026 to 0.078</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

β = unstandardized beta. LA – left atrium; LVEF – left ventricular ejection fraction

#### 7.3.3 Association of PTT and with outcomes

Data on MACE was available over a median period of 28.6 (IQR, 22.6 35.7) months during which period there were 71 (7.2%) MACEs in 61 (6.2%) patients. These included 29 (2.9%) myocardial infarctions, 10 strokes (1%), 23 (2.3%) hospitalizations for heart failure and 9 cases of ventricular tachycardia or appropriate ICD treatment (0.9%). Patients with MACE had longer PTT (8.4 seconds, IQR 7.1, 10.5 versus 7.6 seconds, IQR 6.3, 9.1; p=0.005) and larger PBVi (430ml/m², IQR 360, 542; versus 398ml/m², IQR 333,472; p=0.009). A similar difference was observed with PTT normalised for heart rate (PTTn; 8.5seconds, IQR 7.6,9.8 versus 9.2, IQR 8.0,10.8; p=0.003). Patients with MACE were also older, and more frequently had a history of diabetes, hypertension, previous revascularization and history of stroke (Table 7-3).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No MACE (n=924)</th>
<th>MACE (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean±SD</td>
<td>62 (52-70)</td>
<td>65 (59-74)</td>
<td>0.008</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>624 (67)</td>
<td>46 (75)</td>
<td>0.149</td>
</tr>
<tr>
<td>BSA, kg/m²</td>
<td>1.9 (1.9-2.1)</td>
<td>1.9 (1.75-2.0)</td>
<td>0.356</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>253 (27)</td>
<td>28 (46)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>543 (59)</td>
<td>47 (77)</td>
<td>0.005</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>446 (48)</td>
<td>33 (54)</td>
<td>0.378</td>
</tr>
<tr>
<td>Previous PCI/CABG</td>
<td>277 (24)</td>
<td>29 (48)</td>
<td>0.004</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>118 (12)</td>
<td>11 (18)</td>
<td>0.238</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>50 (5)</td>
<td>8 (13)</td>
<td>0.013</td>
</tr>
<tr>
<td>Cancer</td>
<td>95 (10)</td>
<td>5 (8)</td>
<td>0.602</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>50 (5)</td>
<td>8 (13)</td>
<td>0.013</td>
</tr>
<tr>
<td>Smoking history</td>
<td>312 (34)</td>
<td>25 (42)</td>
<td>0.250</td>
</tr>
<tr>
<td><strong>Cardiovascular magnetic resonance parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDVi, ml/m²</td>
<td>75 (64-90)</td>
<td>85 (66-116)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVSVi, ml/m²</td>
<td>45 (39-52)</td>
<td>44 (39-52)</td>
<td>0.439</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>63 (55-69)</td>
<td>58 (39-65)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>56 (47-67)</td>
<td>64 (53-77)</td>
<td>0.002</td>
</tr>
<tr>
<td>LA area index, cm²/m²</td>
<td>11.7 (10-13.7)</td>
<td>13.1 (11.6-16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any late gadolinium enhancement, n %</td>
<td>371 (40)</td>
<td>45 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>68 (60-77)</td>
<td>67 (60-75)</td>
<td>0.537</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.99 (5.07-7.22)</td>
<td>5.83 (4.75-6.95)</td>
<td>0.275</td>
</tr>
</tbody>
</table>
All-cause mortality data was available over a median of 31.4 (IQR 26.7, 38.3) months, and during this period 53 (5.4%) patients died. There was no statistically significant difference in PTT (7.7 seconds, IQR 6.5, 9.1 versus 7.6 seconds, IQR 5.9, 10.7; \(p=0.851\)), PTTn (8.4, IQR 7.64, 9.81 versus 8.84, IQR 7.22, 11.1; \(p=0.347\)) and PBVi (402 ml/m\(^2\), IQR 337, 474; versus 393 ml/m\(^2\), IQR 287, 512; \(p=0.526\)) between patients that survived and those that died during the follow up period. Univariate associations between imaging and clinical parameters and MACE are shown in Table 7-4.
Table 7-4 Univariate Cox Regression analysis of associations with MACE

<table>
<thead>
<tr>
<th>Predictors</th>
<th>P Value</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI for HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT (seconds)</td>
<td>&lt;0.001</td>
<td>1.213</td>
<td>1.120 - 1.313</td>
</tr>
<tr>
<td>PTTn</td>
<td>&lt;0.001</td>
<td>1.162</td>
<td>1.091 - 1.238</td>
</tr>
<tr>
<td>PBVi (ml/m²)</td>
<td>&lt;0.001</td>
<td>1.003</td>
<td>1.001 - 1.005</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>0.359</td>
<td>1.000</td>
<td>1.000 - 1.000</td>
</tr>
<tr>
<td>Cardiac index (CO/BSA)</td>
<td>0.513</td>
<td>1.000</td>
<td>1.000 - 1.000</td>
</tr>
<tr>
<td>Heart Rate (beats per minute)</td>
<td>0.609</td>
<td>0.995</td>
<td>0.975 - 1.015</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>&lt;0.001</td>
<td>0.966</td>
<td>0.951 - 0.982</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.002</td>
<td>1.035</td>
<td>1.012 - 1.059</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.003</td>
<td>2.146</td>
<td>1.297 - 3.511</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.008</td>
<td>2.249</td>
<td>1.238 - 4.086</td>
</tr>
</tbody>
</table>

In a multivariable-adjusted Cox regression analysis, both PTT and PBVI were independent predictors of MACE (Table 7-5). The model was adjusted for age, sex, diabetes, hypertension as well as prognostic imaging parameters (LVEF, presence of late gadolinium enhancement). The adjusted hazard ratio (HR) for 1 x standard deviation (2.39 seconds) increase in PTT for MACE was 1.43 (95% CI 1.10-1.85, p=0.007). The adjusted HR for 1 x standard deviation (118 ml/m²) increase in PBVi was 1.42 (95% CI 1.13-1.78, p=0.002).
Table 7-5 Cox Proportional Hazard Models for PTT and PBVi as predictors of MACE and all-cause mortality

<table>
<thead>
<tr>
<th>Predictors</th>
<th>MACE</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary transit time (PTT; seconds)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) per 1x SD increase</td>
<td>1.59 (1.31-1.92)</td>
<td>1.14 (0.90-1.46)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.283</td>
</tr>
<tr>
<td>Adjusted*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI) per 1x SD increase</td>
<td>1.43 (1.10-1.85)</td>
<td>0.85 (0.62-1.16)</td>
</tr>
<tr>
<td>P value</td>
<td>0.007</td>
<td>0.313</td>
</tr>
<tr>
<td>Model Chi-square value</td>
<td>53.79</td>
<td>79.14</td>
</tr>
</tbody>
</table>

| **Pulmonary blood volume index (ml/m²)** |                   |                     |
| Unadjusted                        |                   |                     |
| Hazard ratio (95% CI) per 1x SD increase | 1.46 (1.19-1.80) | 0.98 (0.74-1.29) |
| P value                           | <0.001            | 0.872               |
| Adjusted                          |                   |                     |
| Hazard ratio (95% CI) per 1x SD increase | 1.42 (1.13-1.78) | 0.95 (0.73-1.24) |
| P value                           | 0.002             | 0.698               |
| Model Chi-square value            | 56.61             | 78.20               |

*MACE - defined as myocardial infarction, stroke, heart failure admission and ventricular tachycardia or appropriate ICD treatment (including ICD shock and/or anti-tachycardia pacing); SD = standard deviation; (SD for PTT = 2.39s; SD for PBVi = 118ml/m²). Model for MACE was adjusted for age, sex, left ventricular ejection fraction (LVEF), diabetes, hypertension and presence of LGE. Model for all-cause mortality was adjusted for age, LVEF, Diabetes, Hypertension, presence of LGE and history of cancer. Both PTT and PBVi are independently associated with major adverse cardiovascular events but not all-cause mortality.*
Figure 7-3 Kaplan-Meier event-free survival curves for PTT and PBVi
Event-free survival curves for major adverse cardiovascular events (Heart failure hospitalization, myocardial infarction, stroke and ventricular tachycardia/ICD treatment) according to mean PTT (8.05 seconds, top panel) and mean PBVi (414ml/m$^2$, bottom panel). Longer PTT and higher PBVi were associated with higher rates of MACE events (log-rank $p=0.043$ and $p=0.021$ respectively).
A sensitivity analysis across various models was performed, with inclusion of variables in the multivariable models limited to prevent overfitting (supplemental data). Both PTT and PBVi remained predictive of MACE in additional models which included a number of different variables, including myocardial perfusion reserve (MPR), left atrial area index, history of dyslipidemia and history of previous myocardial infarction/PCI/CABG (supplemental data; Table 7-6 and Table 7-7). Following normalisation of PTT with heart rate (PTTn) the association with MACE and mortality remained unchanged (for MACE the adjusted HR for 1x standard deviation (2.58) increase in PTTn was 1.38 (95% CI 1.08-1.77, p=0.009), whereas for all-cause mortality the adjusted HR was 0.77 (95% CI 0.55-1.10, p=0.121) for the same variables included in Table 7-5. Additional sensitivity analysis of PTTn is shown in Table 7-8 of the Data supplement.

![Figure 7-4 Event-free survival curves (MACE) based on mean PTTn](image)

*Event-free survival curves for major adverse cardiovascular events (Heart failure hospitalization, myocardial infarction, stroke and ventricular tachycardia/ICD*)
(treatment) according to mean PTT normalised for heart rate (Mean PTTn=9.12).
Log-rank p=0.003

7.4 Discussion

This study investigated the prognostic power of pulmonary transit time and pulmonary blood volume measured using automated algorithms from routine quantitative myocardial perfusion CMR images. It demonstrated that PTT and PBVi are independently associated with adverse cardiovascular events in patients clinically referred for perfusion CMR, with a prognostic power incremental to established clinical risk factors and imaging biomarkers.

7.4.1 PTT and PBV as prognostic imaging biomarkers

Pulmonary transit time (PTT) represents the average time it takes for a bolus of intravenous contrast to pass from the right to the left side of the heart (80). The potential clinical utility of PTT and the derived PBV has been the focus of extensive research for several decades (435). Invasive evaluation of PTT-derived PBV from right and left heart catheterisation was shown to correlate with symptoms and New York Heart Association (NYHA) functional classification in patients with mitral stenosis (436) as well as in different models of heart failure and pulmonary hypertension (437).

Recently, a number of non-invasive imaging modalities including echocardiography (211,216,438), computed tomography (CT) (214) and CMR (209,210,217,218,432,439) have been deployed to measure PTT through first pass perfusion techniques, but clinical adoption and at scale evaluation was hindered by the need for manual segmentation and data extraction. Kinetic
analysis of the arterial input function curves derived from first pass perfusion reflects a combination of structural and haemodynamic parameters of the cardio-pulmonary axis, which provides a biological explanation for the association of PTT with adverse outcomes. Very few studies previously investigated the association of PTT parameters and outcomes, and these studies were focused on specific disease entities. During a median follow up of 26 months (n=112), Ricci et al, showed that increased PBVi (>492ml/m²), was independently associated with adverse outcomes in heart failure outpatients (210). Similarly, Swift et al, showed that PTT was an independent predictor of mortality among 85 patients with pulmonary arterial hypertension, over a 6-month follow up (218). In our study, both PTT and PBVi were independently associated with MACE, but not all-cause mortality. Data on the cause of death was not available for all patients, but the possibility of an association between cardiovascular mortality warrants further evaluation.

Data from previous CMR studies have shown PTT and PBVi to be increased in patients with impaired systolic LV function (209,210,428), and to be associated with markers of diastolic function in patients with hypertrophic cardiomyopathy (217). Using Computed Tomography data in patients with pulmonary hypertension, Colin et al (214) recently demonstrated that PTT positively correlated with worsening degree of mitral regurgitation and increasing pulmonary artery capillary wedge pressure estimates from right heart catheterisation. In our study, PTT only moderately correlated with LVEF, and LVEDVi. This is not surprising as PTT is not simply a surrogate marker of cardiac volumes and ejection fraction, but is likely reflective of a range of pathology
including diastolic dysfunction and pulmonary hypertension. Indeed, compared to previous studies, the larger sample size and the broadly unselected patient population of patients with known or suspected coronary disease, including patients with variable pathologies (including valve disease, diastolic and systolic dysfunction and lung disease) might explain the slightly weaker correlation of PTT with cardiac parameters observed in our data.

A number of studies investigating the relation between PTT and cardiac volumes or biomarkers used a normalised PTT by adjusting for heart rate. The method of correction of PTT varied between studies (216,217), but given the association between heart rate and PTT shown also in our data (Table 7-2, Figure 7-2) we performed a further analysis using PTT normalised for heart rate (PTTn). PTTn was associated with a similar predictive power in terms of MACE, and similarly to PTT and PBVi, was not predictive of all-cause mortality (Table 7-8). As the estimation of PBVi incorporates the use of cardiac output at rest, the impact of resting heart rate is incorporated in this metric. From a physiological perspective, PBVi would perhaps be expected to have greater prognostic value, and this was in fact seen in previous studies (210). In our cohort, cardiac output (and cardiac index) were not associated with prognosis (Table 7-4), therefore it is not surprising that PBVi performed similarly to PTT. It is however possible that the predictive power of these indices may vary in different populations, particularly in cohorts where cardiac output may be a more relevant parameter, itself encoding additional prognostic information.
Figure 7-5 Four-quadrant plot for PTT and PBVi and MACE

Four-quadrant plot showing the distribution of cardiac events in 4 subgroups, separated by the cohort’s mean values. Each dot represents a patient with MACE (PTT= 8.05 seconds [horizontal line y-axis] and PBVi = 414ml/m² [vertical line x-axis]).

The association between pulmonary transit time parameters and diabetes mellitus and hypertension is of interest. Despite the known association between diabetes and hypertension with MACE (also reflected in our outcome data), both of these conditions were associated with a shorter PTT and reduced PBVi. Although diabetes and hypertension are known to be associated with models of diastolic dysfunction, which can theoretically result in prolongation/increase of PTT metrics, both conditions are also known to be associated with reduced intravascular volume (440–443). Although characterisation of PTT and PBVi within patient subgroups was beyond the scope of our analysis, understanding the impact of specific disease models and the effects of physiological adaptations to exercise on these metrics may warrant further evaluation. Similarly, the physiological mechanisms dictating how PTT and PBVi change under conditions
of stress remain unclear. Whether evaluation of these indices during exercise or vasodilator stress encodes additional prognostic information remains to be determined.

The present study exploits recent technical developments in perfusion CMR, allowing a fully automated process of analysis, making its adoption feasible within the clinical workflow setting. The measurement and reporting of PTT is done as part of a rest perfusion scan, and does not require additional sequences to be run. Despite a small number of events, PTT and PBVi were shown to independently predict major adverse cardiovascular outcomes, with a predictive power incremental to well established imaging biomarkers including LVEF and LGE, as well as more contemporary markers such as MPR (80). The data presented highlight the need for systematic evaluation of PTT metrics in different disease models, including whether and to what extent these can be altered with treatment.

7.5 Limitations

Despite adjusting for a number of clinical and CMR parameters, our analysis was not adjusted for indices of diastolic dysfunction or valve disease (data for these were only available in some cases), both of which are known to affect PTT. Stroke volume was calculated from planimetry of short axis stack cine images rather than phase contrast velocity measurement, as the latter was not available. Although this may introduce a degree of error, particularly in the context of valve disease, this is not believed to alter the conclusion, as the PTT and PBVi varied over a much larger dynamic range than the stroke volume and the cardiac output. Furthermore, the study was designed primarily to assess the prognostic value of
biomarkers (PTT and PBVi) that could be automatically derived from CMR sequences obtained as part of routine clinical imaging protocols.

Although all first pass perfusion studies rely on the indicator dilution principles, there are important variations between different methods of PTT estimation. Different sampling locations for calculation of PTT have been described in the literature, including the pulmonary trunk to left atrium (213), the RV to the left atrium, as well as the RV to LV consistent with our study (209,211,214,216). Evidently, the estimation of PTT and PBVi will vary depending on the anatomical landmarks selected. In this study, the right and left ventricular cavities were used for sampling as these can easily be sampled during the perfusion sequence, eliminating the need for additional planning, image acquisition and off-line analysis.

Patients had been clinically referred for myocardial perfusion CMR, and therefore the cohort predominantly included patients with known or suspected coronary artery disease, as reflected by the high percentage of comorbidity described within the cohort. This may have introduced bias in terms of the association of PTT metrics. However, our analysis was adjusted for a number of cardiovascular risk factors as well as myocardial perfusion reserve (Supplemental data; Tables Table 7-6 and Table 7-7), previously shown to independently predict adverse events within this patient cohort (80).
7.6 Conclusions

Pulmonary transit time and pulmonary blood volume, measures of the cardiopulmonary system can now be derived automatically without user input from latest generation CMR perfusion mapping studies. Here we show these are independently associated with adverse cardiovascular events over and above conventional factors, potentially providing clinically feasible imaging biomarkers of cardio-pulmonary physiology.
### Table 7-6 Additional multivariable Cox Regression models of association between PTT and MACE

<table>
<thead>
<tr>
<th>Predictors</th>
<th>95% CI for HR</th>
<th>P Value</th>
<th>Hazard Ratio (HR)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong> Chi-square value -45.38</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PTT (seconds)</td>
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<td>1.174</td>
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<td></td>
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<tr>
<td>Age (years)</td>
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<td>0.217</td>
<td>1.016</td>
<td></td>
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<tr>
<td>LVEF (%)</td>
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<td>0.985</td>
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<td></td>
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<td>PTT (seconds)</td>
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<td>LVEF (%)</td>
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<td>0.510</td>
<td>0.993</td>
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<td>LGE</td>
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<td>Diabetes</td>
<td>1.204-3.491</td>
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<td>2.051</td>
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<td>History of MI, PCI and/or CABG</td>
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<td>0.731</td>
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<td>PTT (seconds)</td>
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<tr>
<td>LVEF (%)</td>
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<td>0.993</td>
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<td>Myocardial perfusion reserve</td>
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<td>LA area index (cm²/m²)</td>
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<td>0.041</td>
<td>1.101</td>
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<td><strong>Model 5</strong> Chi-square value -65.06</td>
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<tr>
<td>P Value</td>
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</tr>
<tr>
<td>Hazard Ratio (HR)</td>
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<td>Upper</td>
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<td>Model 4 Chi-square value -64.20</td>
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</tr>
<tr>
<td></td>
<td>$P$ Value</td>
<td>Hazard Ratio (HR)</td>
<td>Lower</td>
<td>Upper</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>PTT (seconds)</td>
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<td>LVEF (%)</td>
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<td>0.980</td>
<td>1.030</td>
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<td>1.039</td>
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<td>Myocardial perfusion reserve</td>
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<td>0.355</td>
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<td>LGE</td>
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<td>2.162</td>
<td>1.141</td>
<td>4.096</td>
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PTT = pulmonary transit time; PBVi = pulmonary blood volume index; LGE = Late gadolinium enhancement (incorporates both infarct and non-infarct pattern); LVEF = left ventricular ejection fraction; LA = left atrium; MPR = myocardial perfusion reserve

Table 7-7 Additional Multivariable Cox Regression models of association between PBVi and MACE

PTT (seconds) 0.004 1.163 1.049 1.290
Age (years) 0.481 1.009 0.985 1.033
LVEF (%) 0.709 1.005 0.980 1.030
Diabetes 0.036 1.785 1.039 3.066
Myocardial perfusion reserve 0.003 0.535 0.355 0.805
LGE 0.018 2.162 1.141 4.096

PTT = pulmonary transit time; PBVi = pulmonary blood volume index; LGE = Late gadolinium enhancement (incorporates both infarct and non-infarct pattern); LVEF = left ventricular ejection fraction; LA = left atrium; MPR = myocardial perfusion reserve
<table>
<thead>
<tr>
<th>Predictors</th>
<th>95% CI for HR</th>
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</thead>
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</tr>
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<td>PTTn</td>
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<tr>
<td>LVEF (%)</td>
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<td>Presence of LGE</td>
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<table>
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<td>Age (years)</td>
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<td>LVEF (%)</td>
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<td>Diabetes</td>
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<td>Myocardial perfusion reserve</td>
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<td>LGE</td>
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Chapter 8 Discussion and Conclusions

8.1 Overview of the thesis

The main hypothesis of this work was that novel CMR methods, particularly the use of quantitative parametric techniques can better characterise the pathophysiological processes that determine outcomes in patients with ischaemic cardiomyopathy. Given the central role of coronary artery revascularisation in the management of these patients, this thesis is centred around the use of coronary artery bypass graft surgery and explored the impact of this treatment on myocardial and coronary physiology.

I first deployed a combination of advanced imaging with CT coronary angiography and CMR to evaluate the impact of coronary artery bypass surgery by assessing patients before and after surgery in patients. Although the work described in Chapter 4 is primarily hypothesis generating, it highlights the following points:

1. I found that in the cohort examined, there was a significant improvement in functional status (assessed using a 6-minute walk test and patient-reported health status questionnaires) 6-months after CABG. Although this finding may be due to chance in view of the sample size, or a reflection of bias in completing the follow up assessment, it suggests that the improvement in functional status is not clearly related to the augmentation of MBF following surgical revascularisation.

2. Surgical revascularisation in patients with impaired LV function resulted in only partial revascularisation of the myocardium. At 6 months post CABG, about a third of myocardial territories were not considered revascularised. The reason for
this was multifactorial and included graft failure, the extent of revascularisation performed intra-operatively and progression of native vessel disease distal to the graft anastomosis).

3. Successful revascularisation using coronary grafts conduits resulted in improvement of segmental stress myocardial blood flow and perfusion reserve. However, at a patient level, the factors described in point “2” resulted in a blunted global improvement in stress myocardial blood flow and perfusion reserve.

In Chapter 4 I found that in patients with multi-vessel disease, surgical revascularisation did not result in an obvious increase in global perfusion indices during paired assessments. I therefore aimed to assess the performance of quantitative first pass perfusion imaging in patients post CABG. Specifically, whether results were confounded by a delay in contrast arrival through long coronary grafts resulting in artefactually lower stress and rest MBF. Given the variety of factors that can affect MBF estimation using adenosine stress (eg. extent of scar, LVEF, epicardial coronary disease, venous or arterial graft), I selected a consecutive cohort of patients with angiographically confirmed patent LIMA grafts to the LAD (thereby minimising variability in the correlation of anatomy and myocardial perfusion distribution), without evidence of any scar (defined by the absence of LGE) and assessed the predictors of MBF in this territory. The key findings of this work were the following:

1. In a selected cohort of patients with patent LIMA to LAD grafts and no scar in the myocardial territories examined, 71% of patients had evidence of inducible
perfusion defect on visual assessment. This also corresponded to a reduced MBF in this region.

2. Arterial delay of contrast through LIMA grafts likely causes a small underestimation of absolute MBF during stress. The degree of systematic underestimation is low, almost always <5% of the absolute MBF (in ml/g/min) and does not justify the degree of reduction in MBF observed in these patients. Although gadolinium kinetics (eg. dispersion) in the presence of grafts warrant further investigation, these results suggest that these defects are genuine and not likely to be caused by technical limitation.

3. The extent of native vessel disease is a key determinant of myocardial blood flow irrespective of graft patency. The presence of total occlusion of the native vessel leads to a reduction in stress MBF particularly in proximal myocardial segments, whilst its impact becomes less apparent towards the apex.

Taken together, the findings of both Chapter 4 and 5 would suggest that myocardial blood flow remains low post CABG and that the values obtained with perfusion mapping using CMR do not seem to be significantly affected by an artefact in the methodology caused by delayed arrival of contrast through the grafts. These chapters also suggested that multiple mechanisms are likely to involved in maintaining a low stress MBF and MPR post-surgery. In fact, using the same quantitative perfusion mapping technique with CMR, the absolute stress MBF in post CABG patients was comparable to severe forms of myocardial pathology such as un-treated 3 vessel disease and hypertrophic cardiomyopathy.
Figure 8-1 Absolute stress MBF across spectrum of disease
The work performed in Chapter 6, naturally followed from the findings of the previous chapters. The key question that remained was whether the reduction in myocardial perfusion indices post CABG (even without establishing its mechanism) was associated with adverse clinical outcomes. Evaluation of this had never been performed in the context of patients with prior CABG surgery (across any imaging modality), presumably given the technical challenges in simultaneously adjusting for all the parameters that influence myocardial perfusion in these patients.

In view of this, I evaluated the prognostic impact of stress MBF and MPR in a cohort of patients with previous surgical revascularisation. Although this was a broadly unselected cohort of patients who underwent perfusion imaging based on a clinical indication, the impact of quantitative perfusion on outcomes was adjusted for the amount of scar (using quantitative LGE analysis), the presence of regional ischaemia on visual assessment, as well as a number of clinical and imaging parameters. This work offered significant insights into the importance of MBF in this population. The key findings were as follows:

1. Both stress MBF and MPR independently predicted all-cause mortality and major adverse cardiovascular events (defined as non-fatal myocardial infarction and late revascularisation). For 1 ml/g/min decrease in stress MBF the hazard ratio for death or MACE was 2.56 (95%CI, 1.45-4.35) and for 1 unit decrease in MPR the adjusted HR was 1.61 (95%CI, 1.08-2.38).
2. Importantly, this association remained after adjusting for the presence of regional ischaemia on visual assessment and the presence/extent of scar expressed as a percentage of global LGE. In fact, this observation raises questions about the importance of differentiating non-invasive detection of ischaemia and reduced myocardial blood flow, both on myocardial physiology but more importantly on their different impact on clinical outcomes.

A common theme throughout this thesis, was that patients with ischaemic cardiomyopathy represent a very heterogeneous group, with significant variability in their cardiac anatomy and myocardial physiology. This complicates not only their clinical evaluation but also identifying (and treating) the factors that determine their clinical outcomes. It is clear that no single imaging biomarker, including quantitative myocardial perfusion or tissue characterisation can fully characterise their physiology in its entirety. Given the central role of quantitative perfusion mapping with CMR in the work presented in this thesis, I identified an opportunity to obtain information on cardiopulmonary physiology using the arterial input function acquired during routine perfusion imaging. For this, I focused on the extraction of two historical (but recently re-visited) parameters: *pulmonary transit time* and *blood volume*. Through close collaboration with Dr Peter Kellman from NIH, we developed and implemented an entirely automated method of PTT estimation within the existing Gadgetron framework. I evaluated the prognostic role of PTT and PBV in an unselected cohort of patients with known or suspected coronary artery disease. The following are therefore the key findings of Chapter 7:
1. This was the first study deploying a fully automated in-line method of extracting PTT, and confirmed that PTT and PBV may act as surrogate biomarkers that incorporate a number of parameters affecting cardio-pulmonary haemodynamics.

2. I found that PTT is affected by patient characteristics, comorbidities, and parameters of cardiac structure and function. Increasing age, male sex, the presence of LV cavity dilatation and impairment all increase PTT and PBV. In contrast, diseases associated with reduced intravascular volume such as diabetes were shown to be associated with reduced PTT and PBV.

3. Finally, I found that PTT and PBV predicted patient outcomes, independent of established imaging biomarkers and clinical factors, including the presence of LGE, LVEF, myocardial perfusion indices and a number of prognostically important clinical parameters such as age diabetes.
8.2 Future work

The field of cardiac imaging has undergone significant developments in recent years, not only enabling enhanced diagnostic accuracy but providing tools for re-evaluating normal physiology and pathophysiological processes. Advances in scanner performance, image reconstruction and wider availability of machine learning methods for data analysis have made it possible to introduce quantitative methods of analysis both into clinical research and the clinical workflow. Capacity for fast, automated, large scale imaging analysis has expanded and will inevitably continue to do so. At the same time, artificial intelligence methods of imaging analysis already offer enhanced precision and diagnostic accuracy (335,337).

Quantitative indices of myocardial blood flow can be acquired in a highly automated fashion and offer incremental diagnostic value in patients with chronic coronary syndrome, particularly those with advanced complex disease. Despite this, both clinical decision-making and the way we evaluate the impact of revascularisation continues to be based on qualitative assessment of ischaemia, potentially missing useful clinical information. Indeed, recent studies, such as the ORBITA (42) and ISCHEMIA (33) studies have challenged our traditional ideas of myocardial ischaemia and its impact on patient symptoms and outcomes. However, as methodologies evolve, our perspectives towards these concepts should also change. This work suggests that quantitative evaluation of myocardial blood flow may be a useful and perhaps more appropriate method of assessing the treatment effects of revascularisation and that it may provide novel insights into the factors that determine outcomes in a range of patient populations. Throughout this work, quantitative perfusion appears to offer
incremental value to qualitative ischaemia evaluation, which is beyond merely an enhancement of diagnostic accuracy. Estimation of myocardial blood flow appears to provide insights into the impact of revascularisation (a quantitative measure of treatment effect) and to be an independent predictor of prognosis. At the same setting, simultaneous volume, function and tissue characterisation offer a comprehensive assessment of myocardial physiology. From a clinical perspective, there is a need to explore the use of quantitative methods of assessment in prospective studies evaluating the impact of both revascularisation and medical therapy. For example, paired imaging using quantitative evaluation of MBF before and after treatment may be used for assessing the impact of different revascularisation strategies, enhancing our understanding of the link between revascularisation, cardiac physiology, symptoms and outcomes. Revascularisation with percutaneous coronary intervention in patients with ischaemic cardiomyopathy was not shown to improve patient outcomes in the recently published REVIVED study (24). Future mechanistic studies using similar methodology described in this thesis focusing on perfusion indices can potentially provide explanations and insights into these results, helping to understand the role of revascularisation in this setting.

In the context of coronary artery bypass surgery perfusion indices may alter the way define complete revascularisation and our understanding of its impact on prognosis. Furthermore, correlation of myocardial perfusion and coronary anatomy can provide insights into the mechanisms determining global myocardial blood flow in this population (native disease progression, graft failure, microvascular disease), potentially offering new therapeutic targets and more personalised clinical decision-making.
Similarly, part of this work focused on the development of two quantitative non-invasive biomarkers – pulmonary transit time and pulmonary blood volume. This is the first report of a method that allows acquisition of these parameters in a fully automated manner, which allowed them to be evaluated at scale. The notion that the curve characteristics (shape, symmetry, degree of dispersion) of the arterial input function encode physiological information was established more than a century ago, but only now technical advances have made this information accessible non-invasively and at this scale. For example, the impact of valve disease on the shape of AIF is part of ongoing work.

However, clinical interpretation of these biomarkers requires additional validation work. Better understanding of normal ranges and how these overlap with different disease or extreme phenotypes is essential. We have begun to explore this in specific disease cohorts as well as athletes. Preliminary (unpublished) data from our group suggests that PBV in athletes appears to significantly overlap with patients with impaired systolic function and previous work forms a biological basis for such observation. Montero et al (444) demonstrated that PBV increased in healthy volunteers following a 6-week supervised endurance training programme, which was associated with improvement in peak oxygen uptake (VO$_{2}^{\text{max}}$), an effect that was subsequently abolished by the removal of blood with venesection. Although an increase in PTT and PBV is undoubtably a pathophysiological response to various disease states, expansion of pulmonary blood volume seems to offer beneficial physiological effects in athletes and healthy individuals (431). We will do more work.
Similarly, differences across age groups and sex should be further explored. Beyond this, what is also unknown is how PTT and PBV may change with treatment and whether these can serve as early markers of decompensation. Certainly, there is a potential for these indices to provide a tool for evaluating cardiovascular disease models where current imaging biomarkers are known to underperform. For example, PTT and PBV may have a role in the evaluation of disease models where dual pathology may be present (eg. LV diastolic impairment and co-existing valve disease) offering a quantitative measure of the combined impact of disease on cardiopulmonary physiology.
8.3 Limitations

The work presented in this thesis demonstrates an attempt to deploy a combination of quantitative CMR tools to better characterise and differentiate the impact of specific pathophysiological aspects of ischaemic cardiomyopathy. The work is entirely observational and although provides novel insights into our understanding of this complex disease model, it does not provide definitive answers with regards to the clinical utility of MBF and MPR, or indeed that of PTT and PBV. Clinical adoption of these indices remains a challenge, and despite a rapidly expanding body of evidence on their diagnostic and prognostic role, primarily driven by advances in machine learning and improved accessibility to large clinical datasets, evidence that their clinical use can improve patient outcomes is lacking.

Beyond this, there are additional methodological limitations acknowledged within each chapter that focus around aspects of individual study designs. Most of this work described is retrospective, involving a single centre limiting its generalisability. Furthermore, there are differences between CMR sequences, vendors, field strengths, scanner availability and cost, that are likely to continue to limit the widespread clinical adoption of these tools in the immediate future. Translation of this work into clinical practice requires additional validation steps, primarily aiming to establish how these indices change across the spectrum of disease (Figure 8-1), how they change with treatment and how they predict and more importantly influence patient prognosis. Although more work is needed, this work has contributed to this effort.
Chapter 9  Academic Outputs

9.1  Awards during this studentship

- **Gerald M Pohost Award finalist**, SCMR 2022 - Award for the best JCMR manuscript 2021

- **Cardiology President’s Medal Runner-up**, Royal Society of Medicine, June 2021. Presented work on Pulmonary Transit Time.


9.2  Publications during the studentship (*joint-first author*)


9.2.1 Reviewer

- Journal of American College of Cardiology: Cardiovascular imaging (2020)
9.2.2 Presentations

Oral

- Cardiology President’s Medal Runner-up, Royal Society of Medicine, London, June 2021
- Prognostic value of Pulmonary Transit Time and Pulmonary Blood Volume estimation using myocardial perfusion CMR, Early career award finalist; SCMR 2021
- Use of quantitative myocardial perfusion mapping by CMR for characterisation of ischaemia in patients post coronary artery bypass graft surgery, EACVI 2020
- Integration of electro-anatomical and cardiac MRI imaging data in patients with Implantable Cardioverter-Defibrillators undergoing ventricular tachycardia ablation, SCMR 2020, Orlando
- Cardiac magnetic resonance detects early cardiac involvement in HIV patients: oedema and inflammation, which may be reversible with therapy; EuroCMR 2019, Venice
- The value of scar mapping by cardiac magnetic resonance imaging pre ablation for ventricular tachycardia: should an implantable cardioverter defibrillator put you off?; EuroCMR 2019, Venice
- General anaesthesia: a stress on the heart?; EuroCMR 2019, Venice

9.3 Teaching

- Cardiovascular Metabolic module – 2nd year MBBS students, 2018-2020
- MSc student essay marking, UCL, 2019
- Rapid CMR outreach team, SCMR, Havana, Cuba - November 2019. SCMR outreach team; Rapid Cardiac MRI project
- SCMR webinar series (Cardio-oncology session), June 2020

9.4 Professional development

- Level 3 accreditation in CMR – July 2021
- Adult Cardiac MRI (EACVI written exam) - November 2020
- Level 2 accreditation in CT Coronary angiography, March 2020
- Good Clinical Practice Course – September 2018, Recertification September 2020
• Introduction to regression analysis, Centre for applied statistics, January 2020
• Introduction to SPSS, Centre for applied statistics, January 2020
• Royal Papworth Congenital CMR course, October 2020
• Advanced life support re-certification, March 2021
Chapter 10  References


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