Intracoronary hemodynamics in stable coronary artery disease

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Declaration of Originality

I hereby declare that the work presented in this thesis is my own.

Dr. Christopher M Cook
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Abstract

Invasive physiological stenosis assessment is recommended to identify myocardial ischemia and guide percutaneous coronary intervention (PCI) in patients with stable coronary artery disease (CAD). The therapeutic aims of PCI in stable CAD are to relieve ischemia, resolve angina symptoms and improve exercise capacity. However, the relationship between physiological stenosis severity (i.e. the diagnostic test) and angina-limited exercise capacity (i.e. the therapeutic target) is poorly understood. Accordingly, this represents an important gap in knowledge relevant to the contemporary management of stable CAD.

This gap in knowledge persists because of the lack of physical exercise as an available stressor in the coronary catheter laboratory. However, by use of a catheter laboratory table-mounted supine ergometer, in the series of studies that constitute this thesis, I have been able to invasively characterise systemic, coronary and microcirculatory hemodynamic responses at rest, during pharmacological hyperemia and during maximal physical exercise.

The findings of my thesis are as follows. In Chapter 3 I compare invasive hemodynamic responses to adenosine versus physical exercise stress in patients with stable angina and coronary stenosis. My findings demonstrate that despite the prominent role of adenosine in myocardial ischemia testing, the stress response produced by adenosine is markedly different from physical exercise stress in systemic, coronary and microvascular circulations.

In Chapter 4 I assess the immediate impact of PCI on exercise hemodynamics in patients with stable coronary artery disease. My findings comprehensively characterise the pathophysiology of effort angina. Specifically, I demonstrate that in the presence of a physiologically significant epicardial coronary stenosis, there is failure of augmentation of coronary flow to meet the increasing myocardial oxygen demands of exercise.

Mechanistically, this is explained by premature exhaustion of microvascular dilatation with
incremental exercise. Conversely, following PCI, by alleviation of stenosis resistance in the epicardial circulation, normal vasodilator capacity of the microcirculation (and thus augmentation of coronary flow) is restored to match increasing myocardial workloads.

In Chapter 5 I demonstrate that an association does indeed exist between physiological stenosis severity and angina-limited exercise time in patients with stable angina. Importantly, I further demonstrate the lack of association between anatomical stenosis severity and angina-limited exercise time. This combination of findings further emphasises the rationale for physiology-guided revascularisation in the contemporary management of stable CAD.

Lastly, from mechanistic insights gained during conduct of this thesis, in Chapter 6, I determine the physiological mechanism of FFR/iFR discordance in stable coronary artery disease – a frequent diagnostic dilemma for the physician. My findings demonstrate that disagreement in ischemia detection between FFR and iFR is explained by differences in hyperemic coronary flow velocity. Specifically, coronary stenoses classified as FFR+/iFR- demonstrate similar coronary flow characteristics to both FFR-/iFR- and angiographically unobstructed vessels.
Dedication

This thesis is dedicated to my wife Megan; you are a constant source of love, support and encouragement. Thank you for always being by my side, you truly are my better half.

To my daughter Emily; you are my greatest achievement in life. Your passage into this world was difficult, but your strength and resilience in overcoming adversity has been staggering. You have taught me how much there is to life; you are my world.

To my mum and dad, you sacrificed so much to provide me all of the opportunities in life to succeed – from the bottom of my heart, thank you.
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I am extremely grateful to the Medical Research Council for the financial support required for this thesis. It is a true privilege to have had the opportunity to receive funding to undertake my PhD.

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1. Introduction

Parts of this Chapter have been published as:

The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve

Cook CM, Göteborg M, Sen S, Nijjer S, Escaned J, Davies JE.

1.1 Overview

In this Introduction section I will summarise the contemporary management of patients presenting with chest pain and stable coronary artery disease. In particular, I will focus on the role of physiological stenosis assessment in the identification of myocardial ischemia to guide revascularisation decision-making. I will describe the various physiological indices available, with particular emphasis on the two most commonly used indices in clinical practice - the Fractional Flow Reserve (FFR) and the instantaneous wave-Free Ratio (iFR).

Lastly, I will highlight that despite the majority of revascularisations for stable coronary artery disease being performed for symptomatic (and not prognostic) benefit, there is currently a lack of understanding regarding the relationship between physiological stenosis severity and angina-limited exercise capacity.

1.2 Coronary artery disease

Coronary artery disease (CAD) is a major cause of death and disability in the United Kingdom (UK) and worldwide (1). CAD is characterised by the progressive buildup of cholesterol plaques within the wall of coronary arteries – a disease process referred to as atherosclerosis. Unstable coronary artery disease (or acute coronary syndrome) is characterised by the acute rupture or erosion of one or more of these atherosclerotic plaques. The release of thrombogenic material from within the ruptured plaque forms a nidus for clot formation that can occlude blood flow within the coronary vessel. Unless patency of the coronary artery is urgently restored, most commonly by emergency percutaneous coronary intervention (PCI), irreversible myocardial injury will ensue with an associated high morbidity and mortality (2, 3).

Conversely, in stable coronary artery disease, atherosclerotic plaques increase in size stably over time. This can form narrowings within the coronary artery (stenoses) that progressively encroach on the vessel lumen, reducing its patency. If sufficiently severe, stenoses can
restrict coronary blood flow, leading to the development of myocardial ischemia and symptoms of angina.

Unlike the treatment of unstable coronary artery disease, where the prerequisite therapy is clearly defined as the urgent need to restore coronary blood flow in order to improve prognosis (4–6), the treatment of stable coronary artery disease involves a graduated and multi-modal approach. Within the following section I will summarise the contemporary management of patients presenting with chest pain and stable coronary artery disease.

1.3 The contemporary management of stable CAD

1.3.1 Diagnosis and investigation

Risk factor modification, pharmacological treatment and ischemia-driven revascularisation of coronary stenoses are the central tenets of the contemporary management of stable CAD are (7). However, before such therapy can be initiated and appropriately tailored, the diagnosis of stable CAD must first be made. Recently published National Institute for Health and Care Excellence (NICE) guidelines place paramount importance on confirming the presence of the typical symptoms of angina prior to consideration of any further cardiac investigation (8). This reflects the primary goal of revascularisation in stable CAD being directed at the relief of symptoms, rather than improving prognosis (7, 9).

Typical angina refers to chest pain that occurs predictably and reproducibly with exertion or emotional stress that is reliably relieved by rest or nitroglycerin (8). Following confirmation of these symptoms, a variety of non-invasive tests are available to determine the presence of CAD, either anatomically or on the basis of inducible ischemia during functional testing.
Within the UK, NICE now recommend a first-line anatomical approach, advocating the use of computer tomography coronary angiography (CTCA) to quantify the severity of CAD and guide the need for invasive coronary angiography (ICA) (8). However, considerable variation in practice exists regarding the non-invasive investigation of stable angina, often reflecting local centre expertise and the availability of test equipment. Accordingly, many centres still use one or a combination of functional non-invasive ischemia tests such as stress echocardiography, nuclear medicine scans or stress cardiac magnetic resonance (CMR) as investigations to determine the presence of CAD.

Stress agents recommended by NICE include exercise, adenosine, dipyridamole or dobutamine. Adenosine stress is frequently used because it is considered to induce a condition believed to be similar to the vasodilation caused by physical activity (10).

1.3.2 Optimal medical therapy

The initial management of stable angina is optimal medical therapy (OMT). This encompasses the use of first-line anti-anginal medications such as beta blockers or calcium channel blockers, in addition to short acting nitrates, lifestyle measures and secondary prevention medications for cardiovascular disease.

The provision of OMT relies on monitoring the treatment response to increasing levels of anti-anginal therapy. If monotherapy fails to control angina symptoms, then the addition of a second drug is advocated. Rarely a third drug (e.g. Ranolazine) can be added in an attempt to achieve symptom control, however, frequently the failure of two anti-anginal medications prompts referral for ICA and consideration of revascularisation.
1.3.3 Ischemia-driven revascularisation

Prior to discussion regarding invasive coronary angiography and the selection of coronary stenoses to undergo revascularisation, I will first outline the rationale for ischemia-driven revascularisation as a fundamental concept in the management of stable CAD.

Appreciation of the importance of ischemia-driven revascularisation comes from large observational datasets that have consistently demonstrated a strong association between the presence of ischemia and poor prognosis. Iskander et al performed a meta-analysis of studies comparing the clinical outcomes of over 12,000 patients with coronary artery disease and ischemia quantified by myocardial perfusion imaging (11). The results indicated that for patients with coronary stenoses of equivalent angiographic severity, the long term (5-year) rate of death or myocardial infarction was markedly higher in the presence of ischemia compared to the absence of ischemia (7.4% vs 0.6%).

These results were subsequently combined with those from other large non-invasive ischemia imaging datasets (12–15) to further investigate the relationship between ischemia and clinical outcomes. This combined analysis of over 20,000 patients demonstrated that in known or suspected CAD, the extent and severity of ischemia was a powerful predictor of adverse cardiovascular outcome (16). More specifically, the data also indicated that in the absence of ischemia, adverse event rates remained low (Figure 1.01).

1.3.4 Invasive coronary angiography and visual stenosis assessment

Invasive coronary angiography and visual assessment of the severity of CAD has traditionally been considered the gold-standard investigation for the diagnosis of coronary artery disease (and determination of subsequent revascularisation strategy). In certain clear-cut instances, this approach remains broadly true. For example, the angiographic
identification of triple vessel disease with left main stem involvement remains a class 1 indication for revascularisation by coronary artery bypass surgery (7). Indeed, the landmark SYNTAX study (17), which compared clinical outcomes of revascularisation by CABG versus multivessel PCI, validated the use of the SYNTAX score – an angiographic risk assessment tool useful for the overall prognostication and determination of revascularisation strategy in patients with complex CAD.

However, because the coronary angiogram is only a two-dimensional representation of the internal lumen of a complex three-dimensional structure, the angiographic severity of an individual coronary stenosis is not a reliable assessment of its hemodynamic significance (18) and ischemic potential (Figure 1.02) (19). Furthermore, visual quantification of stenosis severity is highly subjective, with considerable inter and intra operator variability in the interpretation of percentage diameter narrowing (20); as well as a tendency for human interpretation to overestimate disease severity compared to quantitative coronary angiography (QCA) techniques (21).

Cognisant of these limitations of coronary angiography, as well as the clinical need to accurately identify ischemia to guide revascularisation, coronary physiology has emerged as a key diagnostic tool in the contemporary management of stable CAD. In the following sections of this Introduction I will discuss the background, validation and clinical trial data supporting the use of the two most commonly used coronary physiology indices – the fractional flow reserve (FFR) and the instantaneous wave-Free Ratio (iFR). I will also summarise lesser used physiology indices of relevance to the studies performed in this thesis.

1.4 Coronary physiology for the invasive identification of ischemia

1.4.1 Background
Since the introduction of FFR over 20 years ago (22), physiology guided revascularisation has become an established practice in the modern, evidence-based management of patients with coronary artery disease. The central premise of coronary physiology is that it permits identification of myocardial ischemia on a per-vessel basis, measurable at the time of revascularisation decision-making.

1.4.2 The pre FFR era

The purpose-built pressure wires currently used to make coronary physiology measurements are the result of years of development and miniaturization of pressure sensor technology. However, in the pioneering procedures of Andreas Grüntzig in the late 1970s, such high-fidelity equipment was not available. Nevertheless, the importance of quantifying the hemodynamic impact of a coronary stenosis (and the resultant response to balloon angioplasty) lead Grüntzig to measure and report the trans-stenotic pressure gradient through the fluid filled guiding catheter (23). However, owing to the significant impediment to antegrade flow imposed by the catheters themselves, trans-stenotic pressure recordings failed to gain acceptance after it was demonstrated that the measurement was not always reliable (24).

In the early 1990s, as intracoronary pressure and flow velocity sensor-tipped guidewires became sufficiently miniaturised, a host of additional coronary physiology measurements were proposed (25) (Table 1.01). Furthermore, the notion of performing measurements during pharmacological hyperemia emerged. In the early days of coronary physiology, efforts to quantify the hemodynamic impact of a stenosis focused mainly upon the measurement of coronary flow rather than pressure. Instead the pressure component of combined coronary pressure and flow indices were considered merely supportive of why flow may not increase (or increase abnormally) in response to an impaired distal hyperemic response (25).
1.4.3 FFR – introduction

In 1993 Pijls et al published work on the Fractional Flow Reserve (22). Unlike preceding approaches to coronary physiological assessment, FFR specifically sought to determine coronary flow assessment by using pressure only based assessments during hyperemia. By expanding upon the earlier work of Gould et al (26), who had described the coronary circulation as an electrical circuit of variable serial resistances with the stenosis of the epicardial artery being one component, Pijls applied Ohm’s Law (V=IR) to rationalise that when coronary resistance was stable and minimal (as occurred during maximal arterial dilatation) (27, 28), a direct relation between coronary pressure and flow could be presumed.

FFR is defined as the ratio of the pressure distal to a stenosis (Pd) relative to the pressure proximal to the stenosis (Pa) during hyperemia induced by a vasodilating agent. Accordingly, an FFR value of 0.80 represents a 20% pressure loss across the stenosis. This theory was tested experimentally in five anaesthetised dogs in whom pressure derived FFR was compared with Doppler derived fractional coronary artery flow reserve in surgically dissected, balloon ligated proximal circumflex arteries during intracoronary administration of papaverine (22). Despite the inherent differences between human and animal models, in these early experiments Pijls demonstrated that FFR could theoretically be used under idealised experimental conditions to determine the flow-limiting potential of a coronary stenosis.

Nowadays only a simplified version of FFR is used, whereby the right atrial pressure measurement is omitted. However, the description of FFR to individually quantify myocardial (FFRmyo), coronary (FFRcor), and collateral (FFRcoll) components of the coronary circulation (Table 1.02) helped validate the concept and engender continued research in humans.
1.4.4 FFR – validation

Early studies of FFR in the human model focused on establishing FFR cut off values for the detection of inducible ischemia defined by a variety of non-invasive tests. The first of these studies used exercise treadmill testing (ETT) pre and post percutaneous transluminal coronary angioplasty (PCTA) in a total of 60 patients with single-vessel disease and normal left ventricular function (29).

The key findings of this first-in-man study demonstrated a cut off value of FFRmyo <0.75 accurately discriminated between lesions associated with inducible ischemia and those not, as defined by ETT. Moreover, the hypothesis that FFRmyo of angiographically normal stenoses should equal ~1.0 was supported by the subgroup of 5 patients (18 unobstructed vessels) in whom the mean FFRmyo value was 0.98±0.03.

Multiple comparisons have since been made between FFR and a range of non-invasive ischemia tests spanning a variety of clinical settings using a spectrum of pharmacological vasodilator agents. Important findings across this more disparate dataset transpired. Firstly, the so called FFR grey zone emerged as a concept following the observation that the specificity of FFR for the identification of ischemia compared to non-invasive testing decreased in the FFR 0.76 to 0.80 range. Secondly, the overall diagnostic accuracy of FFR (i.e. classification agreement between FFR and non-invasive test) for the detection of ischemia was approximately 80%. This fair but imperfect level of agreement between FFR and other ischemic indices reflects the lack of a true gold standard test for ischemia, with the limitations of each modality effectively ever preventing a perfect test for ischemia detection.

1.4.5 FFR - clinical outcome studies

The early FFR ischemia detection studies provided the important foundations for the design
of subsequent FFR patient outcome studies. Of particular importance were the
establishment of a single FFR ‘ischemic’ cut off value and the observation that deferral of
revascularisation according to the FFR >0.75 cut off value appeared to be safe.

1.4.6 DEFER

To help define the potential role of FFR as a generalisable tool for clinical decision-making,
the prospective, randomised Deferral Versus Performance of PTCA (percutaneous
transluminal coronary angioplasty) in Patients Without Documented Ischemia (DEFER)
study was conducted (30). In this study, a total of 325 patients with stable coronary disease
and intermediate lesions referred for PTCA underwent FFR and subsequent randomization
to one of three groups. If the FFR was >0.75, patients were randomly assigned to deferral
(deferral group; n=91) or performance (performance group; n=90) of PTCA. If the FFR was
<0.75, PTCA was performed as planned (reference group; n=144). The primary end point
was absence of adverse cardiac events during 24 months of follow-up. Subsequent to this
originally reported end point, longer term follow up of the DEFER cohort is now available at 5
years (31) and 15 years (32). Across this broad time span, the core messages that in
patients with stable coronary disease, deferral of stenoses with FFR >0.75 is comparatively
safe and that revascularisation of stenoses with FFR >0.75 confers no additional therapeutic
benefit has remained.

1.4.7 FAME

With data from DEFER supporting that medical therapy alone was likely as effective as
revascularisation in non-ischemic coronary stenoses, the Fractional Flow Reserve versus
Angiography for Multi vessel Evaluation (FAME) study was performed to assess the clinical
effectiveness of an FFR-guided versus angiography guided approach to revascularisation in
patients with multi-vessel coronary artery disease (33). In this prospective, multicentre trial,
1005 patients with at least 50% of the vessel diameter in at least two of the three major epicardial coronary arteries were randomly assigned to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements. A notable difference to any of the previous FFR studies (22, 34, 35) was the upward adjustment of the FFR cut off for hemodynamic significance from <0.75 (referred to as the ischemic cutpoint) to ≤0.80 (referred to as the clinical cut off value). The rationale for this was that FFR >0.80 had been demonstrated to exclude ischemia in 90% of cases (36), and that by accepting the upper limit of the gray zone, the potential number of ischemic lesions left untreated was decreased (33).

The primary end point for the FAME study was the rate of death, nonfatal myocardial infarction (MI) and repeat revascularisation at 1 year. If randomised to angiography guidance, the protocol mandated that all visually estimated >50% stenoses underwent PCI at the operator’s discretion versus only stenoses with FFR ≤0.80 if randomised to FFR. The headline result of the FAME study was a significant reduction in major adverse cardiac events at 1 year in the FFR versus angiography alone group (13.2% versus 18.3% [RR 0.72, CI 0.54–0.96, respectively; p=0.02).

1.4.8 FAME 2

Both DEFER and FAME supported the strategy of revascularisation of ischemic lesions and medical treatment of non-ischemic lesions. Having already highlighted the inadequacies of coronary angiography alone to guide revascularisation, the 2009 Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease (FAME 2) study tested the hypothesis that FFR-guided percutaneous coronary intervention (PCI) plus optimal medical therapy would be superior to optimal medical therapy alone (37). The study population consisted of patients with multi-vessel coronary artery disease already on optimal medical therapy and in whom PCI was being considered. FFR was first performed in all indicated
stenoses. If at least one stenosis was FFR ≤0.80, patients were randomly assigned to receive either PCI in addition to OMT or OMT alone. If all stenoses were FFR >0.80, patients continued on OMT. The primary end point was a composite of death, myocardial infarction, or urgent revascularisation.

The study was halted prematurely (mean follow-up 7 months) after a significant reduction in the composite primary endpoint emerged in the PCI versus OMT group (HR 0.32, 95% CI 0.19 to 0.53, p<0.001). However, this composite endpoint was driven by significantly fewer urgent revascularisations in the PCI arm (HR 0.13, 95% CI 0.06 to 0.30, p<0.001), rather than any signal for decreased mortality or myocardial infarction.

The premature termination of the study in this fashion obliged the FAME 2 investigators to limit their conclusions to FFR-guided PCI plus optimal medical therapy led to a decreased need for urgent revascularisation, as compared with optimal medical therapy alone (37). Additionally, the study received criticism about the absence of blinding of patients and investigators. Nevertheless, in 2013, FFR received level 1A recommendation by the European Society of Cardiology (ESC) to guide revascularisation in stable angina patients with intermediate coronary stenosis and no prior ischemia test.

1.5 iFR – introduction

Since the early work of Gould et al in the canine model (38), it has long been appreciated that resting coronary flow remains stable across a wide range of stenosis severities (until near occlusion). In contrast, hyperemic flow declines significantly beyond approximately 50% reduction in lumen diameter (Figure 1.03) (38). The stable flow conditions that exist in the resting state provide an ideal environment for the application of a pressure-based index of stenosis severity. However, the confounding influences of myocardial contraction and relaxation on flow initially proved insurmountable for early attempts at applying resting
pressure based indices (39). In order to understand why iFR is now capable of determining physiological stenosis severity in the resting state, a basic understanding of the mechanisms of cardiac mechanics is required. Using wave intensity analysis (WIA), it is possible to perform quantifiable measurements in humans to elucidate such mechanisms.

Derived from combined coronary pressure and flow data, WIA permits the separation of waves (a disturbance that spreads directionally with time) according to their origin and direction of travel. This makes WIA a useful tool to interrogate the coronary circulation, given that both proximal and distal vascular beds (aortic and microcirculatory-originating) of the coronary artery contribute energy to the system. By classifying waves by their origin (proximal or distal) and influence on blood flow (expansion or compression), a total of six waves can be identified in the human coronary circulation (40). The wave-free period (WFP) occurs in diastole where it was observed that the generation of new waves is absent, and competing waves that affect coronary blood flow are quiescent (41) (Figure 1.04). The defining features of the wave-free period of diastole are i) flow velocity is approximately 30% higher than whole cycle resting flow velocity, ii) intra-coronary pressure and flow decline together in a linear fashion, and iii) microvascular resistance is significantly more stable and lower than that over the rest of the cardiac cycle (41). From a physiological standpoint, these features make the WFP a suitable window within the cardiac cycle during which a pressure-only assessment of the hemodynamic significance of coronary stenoses can be made, without the need for maximal pharmacological vasodilatation. Furthermore, because the wave-free period exists as a proportion of diastole changing with alterations of the R-R interval, iFR can also be calculated dynamically on a beat-by-beat basis without requiring several beats to be averaged at a time. (41).

1.5.1 iFR - what does it measure?
Although the WFP provided the theoretical framework for iFR, it did not sufficiently explain exactly ‘what’ iFR was measuring. Unlike FFR, which was defined from first principles as the maximum achievable myocardial blood flow in the presence of a coronary artery stenosis as a percentage of the maximum blood flow in the hypothetical case of a completely normal artery (22), the definition of iFR was initially less clear, opting instead for a technical description of the ratio of distal coronary to aortic pressure during the wave-free period of diastole (41).

Subsequent study of the coronary pressure–flow relationship in humans with and without angiographic evidence of obstructive atherosclerosis under resting and hyperemic conditions provided the necessary insight to determine physiologically what iFR actually measures. By replicating the earlier animal studies in humans, the IDEAL study (42) demonstrated that trans-stenotic pressure gradients at rest were predominantly determined by compensatory vasodilator changes in microvascular resistance (Figure 1.05, top panel). Therefore, according to the homeostatic principles of coronary autoregulation, for a stenosis to have a meaningful physiological impact upon the flow of blood to the myocardium it should have a gradient that is detectible at rest (42). In simpler terms, by means of the distal pressure value obtained during the wave-free period of diastole, iFR measures the physiological impact of a coronary stenosis on the distal coronary bed (Figure 1.05, bottom panel).

### 1.5.2 iFR validation

The path of iFR into contemporary clinical guidelines (43) paralleled that of FFR. Following the initial description of the iFR concept, a series of comparative studies with other tests of myocardial ischemia were performed. The ADVISE and ADVSE-Registry studies were the first to assess the diagnostic accuracy of iFR against FFR as the ischemic reference standard. Following these initial comparisons of iFR to FFR, a series of further comparison studies between iFR, FFR and third party arbiters of ischemia were conducted.
The CLARIFY study compared iFR and FFR to the hyperemic stenosis resistance (HSR) index (44). The HSR is a combined pressure and flow-velocity index that essentially calculates the gradient of the pressure-flow curve (45), as originally described by Gould (39). In CLARIFY, iFR, FFR and iFRa (iFR with adenosine) had equal diagnostic efficiency to match an ischemic classification with HSR (both 92%, with no significant difference between the 2 tests and no diagnostic advantage demonstrate with the administration of adenosine) (44). A second, larger study similarly assessed iFR and FFR against HSR in 120 stenoses. In that study, iFR was found to have a significantly higher classification match than FFR (89% versus 82%, p<0.01) (10). A third study assessed iFR and FFR against a comprehensive combined ischemic reference of myocardial perfusion scintigraphy (MPS) and HSR (46). No significant difference was found between each index (46), and the results were consistent with other non-selective cohorts using MPS (47). A fourth study compared iFR and FFR against positron emission tomography (PET), which is recognized as the gold standard for quantifying myocardial blood flow (MBF) (48). De Waard et al performed (H215O) PET imaging in 34 patients with 49 intermediate coronary stenoses followed by invasive pressure-wire assessment. Both iFR and FFR had a 76% classification agreement with PET, and both had similar AUC for ROC analysis (0.85 for FFR and 0.86 for iFR, p=0.71) (48). Notably, both iFR and FFR had an identical pattern of agreement and disagreement with PET MBF. A second, larger (13H3) PET study has more recently been performed and demonstrated similar classification agreement between iFR and FFR compared to PET derived CFR (74% for iFR and 70% for FFR, p=0.36) across 115 LAD stenoses (49). Finally, iFR and FFR have been compared with invasive coronary flow reserve (CFR) (50). When iFR, FFR and CFR were measured in 216 stenoses, iFR had closer agreement with CFR than FFR did, with a statistically significant higher AUC (iFR 0.82 versus FFR 0.72, p<0.001) (50). Even when constrained to the physiological range of 0.60–0.90, iFR maintained a stronger association with CFR than FFR (AUC 0.78 versus
0.59, P<0.001) (50). Importantly, the findings of this study suggest iFR has a closer association than FFR with both hyperemic flow velocity and CFR.

1.5.3 iFR – clinical outcome data

The recently reported DEFINE-FLAIR (51) and iFR-SWEDEHEART (52) trials addressed whether an iFR-only guided approach using a single cut off to guide to revascularisation was a safe and feasible alternative to FFR. The rationale for such studies was clear; namely, that an iFR-only approach would permit the avoidance of adenosine, a potential improvement in procedural time and costs and a reduction in adverse patient side effects. Although the primary study objectives were to establish noninferiority of iFR to FFR for the invasive assessment of stenoses of ambiguous hemodynamic severity, the ultimate goal was to provide further catalyst to the generally low adoption of coronary physiology techniques in clinical decision-making.

DEFINE FLAIR was a conventional prospective, multicentre international, double-blinded patient strategy study design (51). In contrast, iFR-SWEDEHEART adopted an open-label registry based randomised clinical trial design (RRCT) using the Swedish Coronary Angiography and Angioplasty Registry (SCAR) for enrollment (52). In both trials, patients with intermediate severity coronary artery disease were randomly allocated in a 1:1 ratio to undergo either iFR-guided or FFR-guided coronary revascularisation. Both stable patients and those with acute coronary syndrome (ACS) and non-culprit vessels with intermediate disease were included. The primary end point across both trials was harmonised as the 1-year risk of major adverse cardiac events, as a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularisation.

1.5.4 DEFINE FLAIR
The DEFINE FLAIR trial demonstrated that coronary revascularisation guided by iFR was noninferior to revascularisation guided by FFR with respect to the risk of major adverse cardiac events at 1 year. Among a total study population of 2492 patients, the primary end point occurred in 78 of 1148 patients (6.8%) in the iFR group and in 83 of 1182 patients (7.0%) in the FFR group (difference in risk, −0.2 percentage points; 95% CI −2.3 to 1.8; p<0.001 for noninferiority; HR=0.95; 95% CI, 0.68 to 1.33; p=0.78).

Important secondary findings that favored iFR over FFR were also elucidated. The number of patients who had adverse procedural symptoms and clinical signs was significantly lower in the iFR group than in the FFR group (39 patients [3.1%] versus 385 patients [30.8%], P<0.001), and the median procedural time was significantly shorter (40.5 minutes versus 45.0 minutes, p=0.001).

1.5.5  iFR SWEDEHEART

The results of the iFR SWEDEHEART trial were concordant with that of DEFINE FLAIR. Namely, that among patients with stable angina or an acute coronary syndrome, an iFR-guided revascularisation strategy was noninferior to an FFR-guided revascularisation strategy with respect to the rate of major adverse cardiac events at 1 year. Among 2037 patients randomised to undergo revascularisation guided by either iFR or FFR, the primary end point event occurred in 68 of 1012 patients (6.7%) in the iFR group and in 61 of 1007 (6.1%) in the FFR group (difference in event rates, 0.7 percentage points; 95% CI −1.5 to 2.8%; p=0.007 for noninferiority; HR=1.12; 95% CI 0.79 to 1.58; p=0.53). Similar findings regarding adverse procedural symptoms related to FFR measurement were also reported, with chest discomfort during the procedure reported by 3.0% of the patients in the iFR group and by 68.3% of the patients in the FFR group (P<0.001).
In 2017, iFR-guided revascularisation was incorporated into the Appropriate Use Criteria for myocardial revascularisation. In 2018, iFR received a class 1A recommendation for use from the European Society of Cardiology as a physiological index to guide revascularisation in stable CAD patients.

1.6 Coronary flow-based indices of hemodynamic stenosis severity

During the preceding sections, I focused detailed attention on coronary pressure-based FFR and iFR. This is because they are the two most frequently used indices in clinical practice, and the only indices to have patient outcome data and guideline recommendations to support their use. However, it is important to note that in the determination of the hemodynamic severity of a coronary stenosis, coronary pressure measurements are only used as a surrogate measure for coronary flow.

Despite the ischemic potential of a stenosis being best identified by direct quantification of flow-limitation, coronary flow-based indices of physiological stenosis severity are rarely used in clinical practice. The primary reason for this is the relative difficulty associated with performing coronary flow measurements. Specifically, Doppler flow signals require constant optimisation to ensure the capture of high-quality coronary flow velocity data. This can be particularly demanding in tortuous, diffusely diseased or small calibre vessels. Additionally, the flow sensor-tipped coronary wire is significantly less manoeuvrable than the more modern coronary pressure wires, thereby making optimisation of flow signals procedurally more difficult. These factors combine to reduce the reproducibility of invasively acquired coronary flow measurements – an important factor limiting its more widespread use in routine clinical practice.
Conversely, coronary pressure measurements are highly reproducible and do not require any significant optimisation in order to obtain high-quality measurements. Therefore, although conceptually less physiologically informative than coronary flow, pressure-based FFR and iFR remain the most commonly used physiological indices in clinical practice.

1.6.1 Coronary flow reserve

Notwithstanding the aforementioned practical limitations associated with measuring flow, the coronary flow reserve (CFR) was one of the first indexes conceived to determine physiological stenosis severity and has since been demonstrated to be a strongly prognostic index (53). As determined by the landmark study of Gould et al, as diameter stenosis severity increases, hyperemic flow decreases (Figure 1.03) (39). This observation forms the basis of the CFR measurement, which is defined as the ratio of hyperemic to baseline flow velocity within a coronary artery (54).

Because CFR is dependent on the microcirculatory response to vasodilatation, it is considered to be a combined measurement of both epicardial stenosis and microcirculatory resistance. Therefore, if CFR is measured and it is normal (conventionally considered > 2.0), then both epicardial and microcirculatory resistances are low and thus free of significant disease (54). Accordingly, in such circumstances, a normal CFR can be used to demonstrate the non-flow limiting nature of a coronary stenosis. However, the converse is less true, because an abnormal CFR (i.e. CFR <2.0) may be the result of either high stenotic or high microcirculatory resistance, with an inability to differentiate between the two.

Interestingly, although FFR is also inherently dependent on the microcirculatory response to vasodilatation, unlike CFR, it is still considered to be a stenosis specific measure of hemodynamic stenosis severity (22).
1.6.2 Hyperemic stenosis resistance

The hyperemic stenosis resistance (HSR) is a combined coronary pressure and flow index, calculated by dividing the trans-stenotic pressure gradient by the distal flow velocity during hyperemia. Because HSR indexes the pressure drop across a stenosis against the change in flow, it provides a more specific measure of epicardial stenosis resistance. This circumvents the aforementioned limitations of CFR by providing a means of isolating stenosis resistance from that of the microcirculation.

HSR has been demonstrated to be a better predictor of inducible ischemia when compared to SPECT, CFR and FFR (45). However, despite its theoretical and apparent physiological superiority for ischemia detection, it remains minimally adopted in clinical practice owing to the aforementioned challenges associated with measuring coronary flow velocity.

1.7 Revascularisation in stable CAD – to improve symptoms or prognosis?

In the preceding sections I have explained both the rationale for ischemia-guided revascularisation and the role of coronary physiology to identify ischemia during invasive coronary angiography. Accordingly, coronary physiology plays an integral role in facilitating ischemia-guided revascularisation, and its use in stable CAD is recommended. However, despite an adherence to the principles of ischemia-driven PCI, there remains little clinical data to support a prognostic role for PCI in stable CAD.

The most high-profile trials that failed to demonstrate a reduction in the risk of cardiovascular events from ischemia-guided PCI in stable CAD are the Clinical Outcomes Utilising Revascularisation and Aggressive drug Evaluation (COURAGE) (55) and the Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) (56) trials.
COURAGE was a randomised controlled trial of 2287 patients with stable angina, significant coronary stenosis (defined as at least >70% angiographic stenosis in at least one proximal epicardial coronary artery) and objective evidence of ischemia (determined either clinically or via functional ischemia stress testing). Patients were randomly assigned to PCI (plus OMT) or OMT alone. At a median follow-up time of 4.6 years (interquartile range 3.3 to 5.7 years), the primary endpoint of a composite of all cause death and non-fatal MI was similar between PCI and OMT groups (19.0% vs 18.5%, p=0.62).

In the BARI 2D trial, 2368 patients with type 2 diabetes and angiographic CAD (defined as ≥50% stenosis of a major epicardial coronary artery associated with a positive stress test or ≥70% stenosis of a major epicardial coronary artery and classic angina) were randomised to a 'prompt' revascularisation strategy with PCI/CABG in combination with OMT versus a conventional OMT approach. The primary endpoints were all cause death and a composite endpoint of death, non-fatal MI or stroke. At 5 years of follow-up, survival was similar between prompt revascularisation and OMT groups (88.3% vs 87.8%, p=0.89). Similarly, freedom from the composite major adverse cardiovascular events did not differ between prompt revascularisation and OMT groups (77.2% vs 75.9%, p=0.13).

Thus, in over 5,000 patients, rates of all-cause mortality and MI have been demonstrated to be similar in patients who received an initial treatment strategy of PCI (plus OMT) as compared to those who were treated with OMT alone.

Critiques of the COURAGE and BARI 2D trials exist (57). Of most relevance to this thesis, although ischemia-driven revascularisation was intended, neither trial adopted a physiology-guided PCI approach. This raises the question of whether all of the lesions revascularised were indeed truly ischemic. Providing some insight into this, the aforementioned FAME 2 trial assessed FFR-guided revascularisation (plus OMT) versus OMT alone. As outlined
earlier on in this Chapter, FAME 2 demonstrated a reduction in MACE in the group randomised to revascularisation with FFR ≤0.80 compared to the group treated with OMT alone. However, unlike COURAGE and BARI 2D, the primary composite endpoint for FAME 2 also included urgent revascularisation (which proved to be the overwhelming driving factor for the overall reduction in MACE). However, in an open-label trial design, urgent revascularisation may pose a significant bias in favour of revascularisation (58).

Based on further critiques of COURAGE and BARI 2D (principally that both trials enrolled patients only after invasive coronary angiography and thus selection bias may have occurred), The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial aims to determine the optimal treatment strategy of patients with stable angina with evidence of ischemia with regards to an initial invasive versus conservative approach (59). Specifically, within ISCHEMIA, 5179 participants were recruited following clinically indicated stress imaging testing, but before cardiac catheterisation. Patients were then randomised in a 1:1 fashion to invasive management (where if during ICA significant coronary artery disease is present, coronary revascularisation will be performed) or conservative management (where OMT alone is received with a possibility for revascularisation if medical therapy fails to control symptoms). The trial is powered to detect a difference in a composite endpoint of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalisation for unstable angina or heart failure. The highly anticipated results of the ISCHEMIA trial are due to be reported in December 2019.

In summary, based on current evidence from multiple randomised controlled trials, the results of which have also been combined in meta-analyses (60, 61); PCI primarily remains a treatment for reducing angina symptoms and improving functional exercise capacity in patients with chest pain and stable CAD (7, 9).
1.8 Aims of this thesis

Whilst international treatment guidelines recommend the use of coronary physiology to guide revascularisation in stable CAD, the relationship between physiological stenosis severity (i.e. the diagnostic test) and angina-limited functional capacity (i.e. the therapeutic target) remains poorly understood. Accordingly, this represents an important gap in knowledge relevant to the contemporary management of stable CAD.

To bridge this knowledge gap, I will conduct a series of studies designed to investigate the relationship between physiological stenosis severity and angina-limited exercise capacity. In order to achieve this, I will maximally exercise patients with stable coronary artery disease during cardiac catheterisation. By using a catheter-table-mounted supine ergometer, I will invasively assess coronary, microcirculatory and systemic hemodynamics at rest, maximal pharmacological hyperemia and maximal physical exercise; before and immediately after PCI (Figure 1.06).

Using this supine ergometer experimental model, I will first aim to assess the physiological differences between exercise hyperemia and adenosine hyperemia. Specifically I will investigate if conditions of maximal pharmacological stress are indeed representative of vasodilation caused by physical activity in patients with coronary stenosis (10).

Secondly, I aim to assess the impact of PCI on exercise hemodynamics in patients with stable coronary artery disease. This study will provide the mechanistic understanding required to determine the invasive pathophysiology of exertional angina as well as characterise the exercise hemodynamic changes that occur immediately post revascularisation with coronary stenting.
Thirdly, I aim to determine the relationship between clinically used coronary physiology indices of stenosis severity and angina-limited exercise capacity. I further aim to determine if baseline physiological stenosis severity is capable of predicting the change in functional capacity that occurs immediately following PCI.

Lastly, from insight gained during the conduct of this thesis, I provide an additional results Chapter where I aim to determine the physiological mechanism explaining disagreement between hyperemic (FFR) and non-hyperemic (iFR) indices of stenosis severity. To achieve this, I will use data from the largest collection of combined coronary pressure and flow data available (42).
Figure 1.01: Prediction of cardiac death and non-fatal myocardial infarction by assessment of ischaemia in seven large studies comprising more than 20 000 patients.

In patients without ischaemia, outcome is excellent. (Reproduced, with permission, from Schwitter et al, doi:10.1093/eurheartj/ehq481).
Figure 1.02: Correlation between diameter stenosis (DS) vs. fractional flow reserve (FFR) in the overall population (A) and specifically in the left main stem (B) and the three major branches (C–E).
The x-axes indicate the functional metric (FFR), and the y-axes indicate the angiographic metrics (DS). Reproduced, with permission, from Toth et al doi: 10.1093/eurheartj/ehu094)
Figure 1.03: Experimental Versus Clinical Stenosis Severity
(A) Coronary flow reserve versus arteriographic percent diameter stenosis in canine experimental model. (Adapted, with permission, from Gould et al. DOI: 10.1016/j.jcmg.2009.06.004)
Figure 1.04: Schematic Diagram Illustrating the Wave-Free Period of Diastole and Associated Hemodynamic Characteristics

(A) The green shading highlights the wave-free period of diastole where the multiple different waves propagating from the proximal and distal ends of the vessel are quiescent. Coronary pressure (orange) and flow (blue) are linearly related during the wave-free period. (B) Flow velocity (top trace), proximal (light blue), and distal (purple) pressure traces and instantaneous resistance (bottom trace) demonstrate the stability of the wave-free period beat to beat. Reprinted, with permission, from Nijjer et al doi: 10.1253/circj.CJ-15-0044
Figure 1.05: Coronary autoregulation as a means of quantifying physiological stenosis severity under resting conditions
Panel A: With increasing stenosis severity, resting coronary flow velocity (dotted line) is maintained at a stable level by progressive compensatory reduction of microvascular resistance (dashed line). Panel B: Schematic representation of the behavior of resting coronary physiology in the face of increasing stenosis severity. The physiological impact of a coronary stenosis on the distal coronary bed can be quantified by a falling distal coronary pressure (Pd) in the resting state.
Figure 1.06: Study flow chart

Coloured boxes indicate Chapters within this thesis and their relation to the study protocol.
Table 1.01: Pre FFR-era coronary physiology indices

<table>
<thead>
<tr>
<th>Index</th>
<th>Physiological parameter</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-stenotic gradient at rest</td>
<td>Pressure</td>
<td>Provides a quantifiable measure of the acute hemodynamic change after coronary intervention Hyperemia not required</td>
<td>Systematic overestimation of physiological severity due to partial obstruction of antegrade flow by measuring catheter (25)</td>
</tr>
<tr>
<td>Trans-stenotic gradient during hyperemia</td>
<td>Pressure</td>
<td>Provides a quantifiable measure of the acute hemodynamic change after coronary intervention Hyperemia magnifies the pressure gradient signal, facilitating easier quantification</td>
<td>Absence of a significant hyperemic trans-stenotic pressure gradient physiologically ambiguous - values can be related to the absence of a flow-limiting stenosis or to the presence an impaired distal vasodilator response to hyperemia Hyperemia required</td>
</tr>
<tr>
<td>Coronary flow reserve (CFR)</td>
<td>Flow</td>
<td>Well validated for the detection of a lesion of increasing severity Measurement of flow (rather than pressure) is physiologically more intuitive for the identification of ischemia</td>
<td>Lack of a definitive normal value CFR values can be influenced by hemodynamics, loading conditions and contractility (62) An abnormal CFR does not delineate between epicardial and microvascular disease Similar CFR values may be obtained at different levels of resting and hyperemic flow Hyperemia required</td>
</tr>
<tr>
<td>Maximal hyperemic coronary flow velocity</td>
<td>Flow</td>
<td>Indicative of the increase in coronary conductance achieved with balloon angioplasty.</td>
<td>Abnormal maximal hyperemic coronary flow velocity does not delineate between epicardial and microvascular disease Hyperemia required</td>
</tr>
<tr>
<td>Slope of the relation between mean gradient and coronary flow</td>
<td>Pressure and flow</td>
<td>The slope of this relation is inversely correlated with the resistance of the stenotic lesion.</td>
<td>Use of mean gradient and flow velocities at baseline and maximal hyperemia oversimplifies coronary pressure/flow relationships (25)</td>
</tr>
<tr>
<td>Slope of the instantaneous hyperemic flow velocity/pressure relation</td>
<td>Pressure and flow</td>
<td>Provides a more comprehensive interpretation of the fluid dynamics across the stenotic lesion, as well as of the myocardial capillary circulation</td>
<td>Offline calculation limits clinical applicability and prevents use in unselected patients</td>
</tr>
</tbody>
</table>

Hyperemia required
Table 1.02: Calculations of myocardial, coronary and collateral FFR

<table>
<thead>
<tr>
<th>Component of coronary circulation</th>
<th>FFR derivative</th>
<th>Equation</th>
<th>Considerations</th>
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</thead>
</table>
| Myocardium                       | Myocardial FFR (FFRmyo) | $P_d - P_v$ | $P_a - P_v$ | Requires measurement of mean right atrial pressure.  
Is dependent on the health of the microcirculation. |
| Epicardial coronary artery       | Coronary FFR (FFRcor) | $P_d - P_w$ | $P_a - P_w$ | Requires measurement of mean coronary wedge pressure or distal coronary pressure during balloon inflation.  
Is dependent on the health of the microcirculation. |
| Collateral supply                | Collateral FFR (FFRcoll) | FFRmyo-FFRcor | Requires measurement of mean coronary wedge pressure or distal coronary pressure during balloon inflation.  
Is dependent on the health of the microcirculation. |
2. Materials and Methods
2.1 Patient recruitment and ethical approval

2.1.1 Participating centres

Participants for this study were recruited from two UK-based specialist cardiology centres: The Hammersmith Hospital (Imperial College Healthcare NHS Trust) and The Essex Cardiothoracic Centre (Basildon and Thurrock University Hospitals NHS Foundation Trust).

Initially I envisaged only a single-centre approach at the Hammersmith Hospital for the conduct of this study. However, following an interim analysis of recruitment performance at 3 months, a slower than anticipated recruitment rate was identified. Accordingly, I applied for a minor amendment to the ethics committee and added The Essex Cardiothoracic Centre as an additional recruiting centre. I obtained honorary contract status for undertaking clinical research in the Basildon and Thurrock University Hospitals NHS Foundation Trust and procured duplicate equipment to ensure the availability of identical apparatus at each site.

2.1.2 Ethical approval and patient consent

Ethical approval for the study protocol was awarded by the London-Central Research Ethics Committee (16/LO/1928) in November 2016. Following ethical approval, I identified patients from routine elective coronary angioplasty waiting lists at both participating centres. After review of previously acquired diagnostic coronary angiogram images to determine anatomical suitability, I approached patients in their scheduled pre-assessment clinic and offered them the opportunity to participate in the study. All patients were provided the approved patient information sheet (PIS) and the study protocol was fully explained. Specifically, patients were informed that participation in the research study would entail a longer than usual procedure time, that no clinical benefit from participation would be gained
and that refusal to participate would not in any way influence their ongoing clinical care. No follow up was required for this study.

2.1.3 Inclusion criteria

The inclusion criteria for this study were as follows:

- Exertional angina, scheduled for elective coronary angioplasty on clinical grounds
- Single-vessel coronary artery disease
- Right radial artery access
- Ability to exercise without exertion-limiting comorbidity or frailty

2.1.4 Exclusion criteria

The exclusion criteria for this study were as follows:

- Multi-vessel coronary artery disease
- Left main stem or ostial stenosis
- Left ventricular ejection fraction <50%
- Moderate/severe valvular disease
- Chronotropic incompetence with pacemaker
- Severe airways disease

2.2 Specialist equipment and cardiac catherisation laboratory set up

2.2.1 The ComboWire XT

In order to acquire combined coronary pressure and flow velocity data, a dual-sensor coronary guide wire was required. The ComboWire XT (herein referred to as Combowire) is
a 0.014” steerable guidewire with both a piezoresistive pressure sensor and Doppler sensor housed near the wire tip (Figure 2.01).

The pressure sensor contains multiple resistors embedded in a thin silicon diaphragm that changes conformation in response to alterations in blood pressure. During flexion of the silicon diaphragm, the changes in resistance are converted into a pressure signal by factory-calibrated electronic processing within the ComboMap console system (see next section).

The Doppler sensor utilises the same technology as is found in hand-held Doppler probes used for ultrasonography. Piezoelectric crystals housed within the sensor vibrate when an electrical current is applied to them and emit sound waves outwardly. When these sound waves are reflected back to the crystals they are converted into an electrical current. Using the pulse-wave Doppler method, the electronic signals are processed within the ComboMap console system to determine coronary blood flow velocity.

2.2.2 The ComboMap system (model 6800)

As described in the previous section, the Combowire relays coronary pressure and flow velocity data in the form of electrical signals which require processing in a dedicated console unit. For the purposes of this study, the ComboMap system (herein referred to as Combomap) was used and processed the following data: 1) distal coronary pressure (Pd) and coronary flow velocity measured from the Combowire in the trans-stenotic position; 2) the aortic pressure measured from the guiding catheter tip; and 3) the electrocardiogram (ECG) measured from the patient.

The Combomap is a standalone unit with a touch screen display and remote control unit for real-time optimisation of data signals (Figure 2.02). All data is acquired prospectively but is
archived on the Combomap hard drive for export and post-hoc analysis after completion of hemodynamic data recording.

All recordings were time-stamped, beginning at time zero. Accordingly, detailed contemporaneous notes were made in order to accurately match up the various timings of each stage of the research protocol to the time-stamped hemodynamic recordings.

2.2.3 Lode Angio Bicycle Ergometer

For this study, patients were required to maximally exercise during invasive coronary catheterisation. This was achieved using a catheter-table-mounted bicycle ergometer, optimised for supine ergometry use (Figure 2.03). The Lode Angio Bicycle Ergometer series (herein referred to as ergometer) operates independent of pedaling speed in the range of 7 - 1000 watt, permitting a consistent load to be delivered to patients, independent of pedaling speed or background fitness.

The ergometer was programmed by a dedicated software programme (Lode Ergometer Manager, V 10.5.1, Lode, Groningen) and operated from a laptop computer that was connected to the ergometer via a USB connection. All exercise performance data was recorded in LEM and was exported for post-hoc analysis by a dedicated export programme (Lode Export Manager 10, V 10.5.1, Lode, Groningen)

2.3 Cardiac Catherisation laboratory set up

Prior to arrival of the patient in the coronary catheterisation laboratory, all specialist research apparatus was assembled and tested for functionality. All conventional angioplasty equipment was also prepared in the usual manner by clinical members of the catheter laboratory team.
The ergometer was attached to the catheter table and secured using custom built fixation clamps. The ergometer was positioned centrally to prevent any rotational movements during pedaling. Modifications to the catheter laboratory table were required in order to create additional working space to support the angioplasty equipment. This was necessary as movement during pedaling precluded the use of the usual working space located between the patient’s legs. To modify the working space, an additional radial board was positioned as displayed in Figure 2.04.

With the patient positioned on the catheter laboratory table, the ergometer position was further adjusted to the patient’s height to ensure a comfortable pedaling position. The patient’s right leg was fixed into the right pedal of the ergometer at the start of the case and a pillow positioned under the knee to support its partial flexion. Only at the time of exercise stress testing was the left foot positioned into the left pedal.

Surgical drapes were then placed over the patient and ergometer, ensuring adequate coverage of the additional working space. During exercise the drapes at the foot end of the catheter table were lifted and affixed to a drip stand to create a tent-like structure that permitted unimpeded pedaling. The Combomap was positioned on a separate mobile table and placed to the right-hand side of the second operator. The table surface was further draped with a surgical gown to provide an additional sterile working space for storage of the Combowire between hemodynamic recordings during the coronary angioplasty stage of the procedure (Figure 2.05).

2.4 Cardiac catheterisation and coronary angioplasty
Cardiac catheterisation was performed according to standard clinical practice. All procedures were performed by Consultant interventional cardiologists via right radial artery access and a 6-French system.

2.4.1 Catheters

All coronary angiography and physiological measurements were performed using standard guiding catheters. For the left coronary system, a Judkins left 3.5 or Extra Back Up (EBU) 3.5 guide catheter was used. For the right coronary system, a Judkins right 4.0 was used.

2.4.2 Medication

Prior to their scheduled angioplasty procedure, all patients were pre-treated with dual antiplatelet therapy prescribed by their usual care physician (aspirin 300mg loading dose, followed by 75mg once daily thereafter; clopidogrel 300mg/600mg followed by 75mg once daily thereafter thereafter). As per routine clinical practice, patients were continued on their usual medications.

During cardiac catheterisation, intracoronary nitroglycerin (300mcg) was administered prior to the acquisition of all coronary angiography images and was repeated prior to all coronary physiology measurements. This ensured stabilisation of epicardial vessel resistance and prevented epicardial coronary artery spasm that may lead to inaccurate measurements of physiological stenosis severity. Furthermore, intracoronary nitrate administration additionally aided in accurate vessel sizing in preparation for stent selection and angioplasty.

Weight-adjusted intracoronary heparin (70-100U/kg) was administered prior to instrumentation of the coronary system with either standard coronary guidewires or the
Further boluses of intracoronary unfractionated heparin were given throughout the duration of a case to ensure an activated clotting time of >250 seconds.

2.4.3 Induction of pharmacological hyperemia

Pharmacological hyperemia was induced by a 2-minute intravenous infusion of adenosine at a dose of 140mcg/kg/min via the left ante cubital fossa vein. Femoral venous access was precluded owing to the need for supine exercise.

The intravenous rather than intracoronary route was chosen for two reasons. First, the temporal changes in systemic, coronary and microcirculatory hemodynamics over a standardised length adenosine infusion (rather than intracoronary bolus) permitted a comparative analysis between the invasive hemodynamics of pharmacological versus physical exercise stress (as described in Chapter 3). Second, an intravenous infusion of adenosine permitted ample time to obtain an optimal coronary flow velocity trace. Conversely, owing to the short duration of hyperemia with intracoronary adenosine bolus, coronary flow velocity trace optimisation may not have always been achieved.

2.4.4 Coronary angioplasty

Coronary angioplasty was performed according to standard clinical practice. Specifically, the research protocol did not mandate any choice of coronary guidewire, balloon or stent. Similarly, the use of adjunctive intracoronary imaging and/or stent optimisation was left to the operator’s discretion.
2.4.5 Exercise protocol

A stepwise exercise protocol starting at 40 W and increasing by 20 W every minute was used for all patients (Figure 2.06). As mentioned previously, the ergometer was independent of pedaling speed in the range of 7 - 1000 W, ensuring consistent load delivery to all patients. The stepwise protocol was chosen after review of existing ergometry study designs (63–65).

2.5 Data acquisition and optimisation

2.5.1 Anatomical lesion data

Quantitative coronary angiography (QCA; McKesson, San Francisco) was used to measure coronary stenoses length, mean percentage diameter stenosis and mean percentage stenosis area. QCA was performed in two orthogonal angiographic views using the contrast-filled catheter diameter for calibration. Values were then averaged between the two orthogonal views.

2.5.2 ECG data

The ECG trace was optimised using the Combomap user-interface to ensure appropriate gain and identification of the R-wave. It was critical that the R-wave was the largest peak on the ECG trace as it was used to determine the cardiac cycle length in post-hoc analysis. Optimisation of the ECG trace was further essential owing to a degree of movement artefact encountered during exercise.

2.5.3 Aortic pressure measurement and optimisation

Aortic pressure was measured through the lumen of the guiding catheter. Fluctuations in pressure were transmitted from the tip of the guiding catheter through the thin column of
incompressible fluid to an external pressure transducer mounted to the catheter table. At the start of every case, the fluid-filled catheter was positioned at the height of the right atrium and zeroed against atmospheric pressure. The external pressure transducer was also adjusted to each individual patient and fixed to a location approximately at the level of the aortic root (typically 5cm below the sternum).

Once the fluid filled guiding catheter was connected to the pressure transducer, aortic pressure waveforms were continuously displayed on both a monitor in front of the operator and also on the Combomap console. To ensure high-quality aortic pressure signals, the fluid filled catheter was regularly flushed with heparinised saline to remove micro-bubbles, blood and contrast media from the lumen that could otherwise have damped the aortic pressure trace. Furthermore, prior to all recordings of aortic pressure for analysis purposes, the introducer needle was removed from the O-ring and the Y-connector was firmly closed. This prevented any small leak of fluid from the guiding catheter that could otherwise artefactually lower the aortic pressure leading to inaccurate coronary physiology measurements.

It was essential to continuously monitor the aortic pressure trace for artefacts. One of the most common artefacts encountered in clinical practice is damping of the aortic pressure trace (heralded by a loss of normal dichrotic notch morphology, Figure 2.07). This artefact is caused when the guide catheter tip wedges in the coronary artery ostium, effectively causing a degree of ostial stenosis. This can potentially cause trauma to the vessel either directly or during contrast media injection. Furthermore, damping of the aortic pressure signal can lead to an artefactual lessening of the trans-stenotic pressure gradient (or ratio), and thus must be avoided.

Within the present study, damping of the aortic pressure trace was not encountered because the guide catheter was intentionally backed out into the aortic root during all physiological measurements and supine exercise. This was particularly crucial during exercise in order to
prevent trauma to the vessel ostium during exercise. Furthermore, disengagement of the guiding catheter also ensured high-fidelity aortic pressure waveforms suitable for post-hoc pulse wave analysis (as described in Chapter 4). Lastly, for safety reasons specific to this study, patients with an ostial stenosis were excluded from participation.

2.5.4 Coronary pressure measurement and optimisation

Before inserting the Combowire into the body of the patient, a number of preparatory steps were performed. Firstly, the wire was flushed with room temperature heparinised saline whilst remaining within its housing. This was performed with the wire resting on the table. Once flushed, and without handling of the wire housing, the two connectors on the distal portion of the Combowire were attached to the pimmette (RJ45 type for pressure and multi-pin for flow velocity) in order for the console system to activate and calibrate the wire.

The tip of the Combowire did not come pre-shaped. In order for the wire to be safely passed into the coronary vessel without potentially causing harm to the vessel wall (i.e. dissection), the wire tip was manually shaped. This was performed away from the actual tip of the wire, where the delicate flow sensor was located.

Once inserted into the guiding catheter and advanced to the ostium of the coronary blood vessel, the Combowire pressure signal was aligned in both phase and value to that of the aortic pressure signal (transduced simultaneously from the guiding catheter tip). This process is termed ‘normalisation’ and was performed at the start of every acquisition of coronary physiology data. Following normalisation and administration of intracoronary nitroglycerin (300mcg), the Combowire was advanced down the coronary vessel and across the stenosis. The tip of the Combowire was advanced a minimum of three vessel diameters distal to the stenosis, in a location suitable for making intracoronary pressure and flow measurements. Owing to the need to repeat coronary pressure and flow measurements
following coronary angioplasty, the Combowire tip position was acquired fluoroscopically to provide a reference location.

Optimisation of the distal coronary pressure trace was rarely required, owing to the highly reproducible and robust nature of pressure waveform data. The only distal coronary pressure artefact I encountered was ‘wire whipping’ – an artefact caused by the pressure sensor striking the vessel wall and causing large positive deflections in the pressure trace. This was easily overcome by minor adjustment of the Combowire to remove the sensor from contact with the vessel wall.

Following completion of all trans-stenotic pressure measurements, the Combowire was withdrawn from the coronary vessel and pulled back into the guiding catheter. At the tip of the catheter a check for pressure wire drift was performed. Pressure wire drift is a phenomenon common to all piezoresistor pressure sensor technologies. It occurs because there is a gradual degradation of signal output from the piezoresistive sensor over time. This can occasionally result in pressure readings becoming offset from the original calibrated state, determined during the normalisation process. Small amounts of pressure wire drift (±0.02 units) are clinically acceptable. Accordingly, the study protocol mandated that all coronary pressure measurements be repeated (following repeat normalisation) if pressure wire drift greater than ±0.02 was detected. However, this was not required for any of the physiological measurements within this study as no occurrences of pressure wire drift greater than ±0.02 were encountered.

2.5.5 Coronary flow velocity measurement and optimisation

The piezoelectric crystals located at the tip of the Combowire emit a pulsed Doppler beam with a sampling angle of 45 degrees. In order to align the Doppler beam to optimally sample the highest flow velocity, fine rotational adjustments of the Combowire were required.
Manipulations to wire position were performed whilst reviewing the quality of the spectral flow traces on the Combomap screen. The aim of this optimisation process was to achieve the highest velocity trace possible with the densest spectral envelope possible (Figure 2.08).

Acquiring high-quality coronary flow velocity data was occasionally challenging. Throughout each research case multiple, small manipulations of the Combowire were required; particularly when hemodynamic conditions changed (as occurred during adenosine hyperemia and during exercise). Detailed contemporaneous notes were made to document the periods of highest-quality flow data most suitable for post-hoc analysis.

Although the Combomap displayed the spectral traces of instantaneous coronary flow velocity, these data were not archived to the console hard drive (as per the factory settings of the Combomap). Instead, only the digital tracking line was recorded and available for subsequent export and analysis of the instantaneous peak velocity (Figure 2.09). Therefore, in addition to the optimisation of the Doppler coronary flow velocity signal as already described, it was essential to ensure accurate tracking of the digital line to the spectral envelope. This was achieved by continuously altering the velocity scale (to ensure the spectral trace was appropriately scaled to the display panel) and by adjusting the thresholding settings until the spectral envelopes were accurately traced.

2.6 Post-acquisition analysis of hemodynamic data

2.6.1 Export of Combomap data

Data were exported from the Combomap via USB. The data was outputted in .SDY file format, written at a sampling frequency of 200Hz. Each .SDY file contained data from the three Combomap inputs: 1) the aortic pressure trace (Pa); 2) the coronary pressure and coronary flow velocity traces from the Combowire; and 3) the ECG trace.
2.6.2 Software packages

A combination of four software packages were used to process and analyse the combined coronary pressure and flow data exported from the Combomap.

2.6.3 Study Manager

The raw data contained within the .SDY file was first opened using the proprietary Study Manager software programme (Version 2.2.11.16, Academic Medical Centre, The Netherlands). Study Manager allowed for graphical review of the combined coronary pressure and flow data, indexed against time (Figure 2.10). In conjunction with the timing notes made during each live recording, it was possible to select out (snip) portions of the recording with the highest quality flow recordings for subsequent analysis. A minimum of 5 consecutive beats was used in all studies. Appropriately snipped data files were then exported from Study Manager in a .csv file format for analysis in one of the three following software environments.

2.6.4 R Studio

A bespoke R studio programme (Version 1.0.153) written by me was used for the post-acquisition calculation of all coronary physiological indices other than iFR. This programme manipulated the raw .csv data using the ‘dplyr’ package and plotted the raw data using the ‘ggplot2’ package.

2.6.5 Matlab

A bespoke Matlab programme (Mathworks, Inc., Version 6.0.0.88) written by previous researchers from within the group was used for the post-acquisition calculation of iFR. This
programme identified the diastolic iFR window (41) using fully automated algorithms acting over the ECG-gated, time-aligned pressure traces (Figure 2.11)

2.6.6 Python

A bespoke Python programme (PyCharm Community Edition, Version 2017.2.4) written in conjunction with a collaborating researcher from within the research group was used to perform pulse wave analysis of aortic pressure data. This programme ensemble averaged cardiac cycles through ECG-gating and semi-automatically identified the upstroke and peak of the aortic pressure tracing and the trough of the dichrotic notch (Figure 2.12)

2.7 Post-acquisition analysis of exercise data

2.7.1 Export of ergometer data

Lode Ergometry Manager (LEM) was used to control the ergometer and record test subject exercise performance data via a personal laptop computer. Based on the study participant’s height and weight, LEM automatically calculated total energy expenditure in kilojoules (KJ), peak metabolic equivalents (METs) and peak workload (Watts). The LEM expansion module Export (LEM-E) was subsequently used to export this test subject exercise performance raw data in a textfile format for further manipulation in R Studio.

2.8 Safety and feasibility testing

Prior to determining the final design of the study, a series of safety and feasibility assessments were first performed. During these tests, healthy volunteers maximally exercised on the coronary catheter laboratory table without invasive physiological
assessments. These initial tests helped determine the optimal catheter laboratory set up and identified the need to modify the sterile working space.

2.8.1 Safety considerations regarding exercise during cardiac catheterisation

Following discussion and feedback from the Consultant operators, a series of safety measures were also implemented into the study protocol. First, it was mandated that the target-vessel be secured with a standard coronary guidewire prior to insertion of the Combowire. Operators expressed concern that if at any point vessel patency were to be compromised, especially during exercise, a Combowire-only approach would be insufficient to ensure a safe and immediate restoration of flow by emergency angioplasty. With patient safety of paramount importance, a dual wire approach (i.e. a standard workhorse guidewire to secure the target vessel and a Combowire for physiological measurements) was adopted for all cases. The necessary presence of a second coronary wire in the vessel did not appreciably degrade the fidelity of the coronary pressure and flow data recorded.

Second, it was mandated that the guiding catheter be withdrawn from the coronary ostium during exercise to prevent possible trauma to the coronary vessel ostium. The placement of both a standard coronary guidewire and a Combowire in the target vessel provided additional support for this manoeuvre. Furthermore, withdrawal of the guiding catheter facilitated acquisition of high-quality aortic pressure waveform without damping for pulse wave analysis purposes.

Third, a decision was made against performing physiological assessments in unobstructed reference vessels. Were this to have been performed, study participants would have been exposed to the risk of wiring a coronary vessel that would otherwise not be instrumented for clinical reasons. This risk was deemed too great. Furthermore, the assessment of invasive
coronary pressure and flow hemodynamics during supine exercise in unobstructed vessels has previously been reported (63).

Last, a decision was made against the inclusion of a sham control arm within the study protocol. The reason for not blinding study participants to whether they had received angioplasty or not were several-fold. Primarily, maintenance of effective patient blinding would not have been possible without the use of sedation. Sedation would have impaired subsequent exercise performance, making comparative assessment impossible. Furthermore, the inclusion of a sham control arm would have necessitated a third bout of maximal exercise which may not have been acceptable to study participants or the busy clinical coronary catheterisation laboratory settings in which the study was conducted.

2.9 Reproducibility

2.9.1 Reproducibility of hemodynamic measurements

The reproducibility of coronary hemodynamic measurements has been previously reported. The standard deviation of the difference between repeated 30-second recordings of blood pressure and coronary flow velocity were 5.2 mmHg for systolic blood pressure, 1.9 mmHg for diastolic blood pressure and 5.7 cm/s for peak coronary Doppler flow velocity (40).

2.9.2 Reproducibility of maximal supine exercise

Following review of the scientific literature, I discovered that the reproducibility of maximal supine ergometry had not previously been reported. As part of the safety and feasibility testing, ten healthy control subjects underwent paired, maximal supine exercise assessment on the coronary catheter laboratory table. Maximal exertions were performed 30 minutes apart with the participants blinded to their initial exercise time. This pilot phase suggested
satisfactory reproducibility of maximal supine exercise on the coronary catheter table, with a mean difference of just -6.9 seconds and a standard deviation of difference (SDD) of 32 seconds (Figure 2.13).
Figure 2.01: ComboWire XT
Figure 2.02: Combomap
Figure 2.03: Lode Angio Ergometer
Pictured with specially designed fixation clamps to mount to the coronary catheter laboratory table.
Figure 2.04: Coronary catheterisation laboratory set up I
(A) The ergometer was first mounted centrally on the coronary catheterisation table. (B) An additional radial board was then positioned as shown in the photograph in order to create additional working space.
Figure 2.05: Coronary catheterisation laboratory set up II
Photograph illustrating the full experimental apparatus set up, inclusive of Combomap console and sterile drapes.
Figure 2.06: Lode Ergometry Manager

Screenshot of Lode Ergometry Manager user interface demonstrating the stepwise exercise protocol and exercise performance data windows.
Figure 2.07: Aortic pressure damping artefact

Screenshot taken from a coronary pressure measurement during intravenous adenosine infusion. The aortic (red) pressure trace is damped, as demonstrated by the loss of the dichrotic notch.
Figure 2.08: Optimal coronary flow signal

Screenshot from Combomap illustrating ECG (top panel), aortic (red) and distal coronary (yellow) pressure signal (middle panel) and instantaneous coronary flow velocity spectra (bottom panel). The coronary flow signals demonstrate dense and well delineated spectra.
Figure 2.09: Thresholding error
Screenshot from Combomap illustrating thresholding error of the tracking line (blue) to coronary flow spectra.
Figure 2.10: Study Manager software programme

Data exported from the Combomap console viewed in the Study Manager software programme. ECG (top panel), coronary pressure (middle panel) and coronary flow velocity (bottom panel) can be reviewed and selected (snipped) for subsequent analysis. All data is time aligned (x axis).
Figure 2.11: Matlab software programme
Data exported from the Combomap console viewed in a bespoke Matlab software programme. This was used to retrospectively calculate iFR values (third panel) from the Combowire data.
Figure 2.12: Python software programme
Data exported from the Combomap console viewed in a bespoke Python software programme. This was used for aortic pressure pulse wave analysis.
Figure 2.13: Reproducibility of supine ergometer maximal exercise time in healthy controls
(A) Scatter plot. (B) Bland-Altman plot.
3. Comparing invasive hemodynamic responses to adenosine versus physical exercise stress in patients with stable angina and coronary stenosis
3.1 Abstract:

3.1.1 Background

Adenosine stress is commonly used as a pharmacological alternative to exercise stress in the investigation of patients with stable coronary artery disease and suspected myocardial ischemia. However, despite its widespread use as a stress agent, it is not known how invasive hemodynamic responses compare between adenosine and exercise stress in patients with stable angina and coronary stenosis.

3.1.2 Methods

Twenty-three patients (21 male; age, 60.6 ± 8.1 years) with single-vessel coronary stenosis underwent cardiac catheterisation. Continuous trans-stenotic coronary pressure-flow measurements were performed during: i) maximal adenosine hyperemia, and ii) maximal physical exercise using a catheter-table-mounted supine ergometer. The order of adenosine and exercise was randomly assigned. Systemic, coronary and microcirculatory hemodynamic responses were compared between adenosine and exercise stresses.

3.1.3 Results

Mean stenosis diameter was 74.6% ± 10.4. Median (interquartile range) FFR was 0.54 (0.44 to 0.72). At maximal adenosine versus maximal exercise stress, mean aortic pressure (Pa, 91 ± 16 mmHg vs 99 ± 15 mmHg, p<0.0001), distal coronary pressure (Pd, 58 ± 21 mmHg vs 69 ± 24 mmHg, p<0.0001), trans-stenotic pressure ratio (Pd/Pa, 0.63 ± 0.18 vs 0.69 ± 0.19, p<0.0001), microvascular resistance (MR, 2.9 ± 2.2 mmHg.cm-1.sec-1 vs 4.2 ± 1.7 mmHg.cm-1.sec-1, p=0.001), heart rate (HR, 80 ± 15 bpm vs 85 ± 21 bpm, p=0.02) and rate-pressure product (RPP, 7522 ± 2335 vs 9077 ± 3200, p=0.0001) were all lower.
Conversely, coronary flow velocity (APV, 23.7 ± 9.5 cm/s vs 18.5 ± 6.8 cm/s, p=0.02) was higher. Additionally, temporal changes in Pa, Pd, Pd/Pa, MR, HR, RPP and APV during adenosine versus exercise stress were all significantly different (p<0.05 for all).

3.1.4 Conclusions

In patients with stable angina and coronary stenosis, invasive systemic, coronary and microcirculatory hemodynamics are markedly different between adenosine and exercise stress.
3.2 Introduction

Adenosine is a naturally occurring vasodilator with an essential role in the autoregulation of coronary blood flow (68). Administration of adenosine induces maximal vasodilatation of the coronary microcirculation leading to stabilisation (and minimisation) of microvascular resistance and a resultant increase in coronary blood flow (69, 70) - a process termed adenosine hyperemia.

As explained in the Introduction section of this thesis, under conditions of stable microvascular resistance, the flow-limiting potential of a coronary stenosis can be estimated using coronary pressure measurements to calculate the fractional flow reserve (FFR). In addition to this practical role, adenosine hyperemia is also considered to be physiologically representative of the vasodilation caused by physical exercise (10). Because of the presumed similarity between adenosine hyperemia and physical exercise, it is commonly considered that hyperemic FFR measurements are physiologically more informative about exercise induced-ischemia than resting coronary pressure measurements (71).

However, it is not known how invasive physiological responses to adenosine stress compare to physical exercise stress in patients with stable angina and coronary stenosis. In this Chapter I will compare invasive systemic, coronary and microcirculatory hemodynamic responses during both adenosine and exercise stress in patients with stable angina and coronary stenosis.
3.3 Methods

3.3.1 Study population

Patients were recruited from elective coronary angioplasty waiting lists at both the Hammersmith Hospital and the Essex Cardiothoracic Centre. Inclusion criteria were single-vessel coronary artery disease and exercise capacity limited by angina (confirmed during the exercise stage of the study protocol). Exclusion criteria were multi-vessel coronary artery disease, left main stem or ostial stenosis, left ventricular ejection fraction <50%, moderate/severe valvular disease, chronotropic incompetence with pacemaker, severe airways disease, physical inability to exercise or exercise capacity not limited by angina. Patients continued all their usual medications and were loaded with dual antiplatelets as per routine practice of the recruiting centre. All subjects gave written consent in accordance with the protocol approved by the regional ethics committee (16/LO/1928).

3.3.2 Catheterisation protocol

The patient was positioned on the catheterisation laboratory table and secured to a premounted supine cycle ergometer (Lode Angio, Lode, Groningen). The ergometer was connected to a laptop computer with software (Lode Export Manager 10, V 10.5.1, Lode, Groningen) to initiate the exercise protocol and acquire performance data. The target-vessel was intubated with a standard 6F guide catheter from the right radial artery. Intra-arterial unfractionated heparin (70-100 U/kg) and intracoronary nitroglycerin (300mcg) were given prior to coronary angiography and physiological measurements.

The optimal working view was determined, and a standard coronary guidewire was advanced distally to secure the target vessel – a safety feature of the experiment design as detailed in the preceding Methodology Chapter. A dual pressure and velocity sensor 0.014"
intracoronary wire (Combowire XT, Volcano Corp, California) was then advanced to the tip of the guiding catheter and the pressure signals normalised. The Combowire tip-mounted sensor was advanced distal to the stenosis by a minimum of 15mm and its position recorded cineographically. An optimal Doppler velocity trace was obtained by rotational manipulation of the Combowire. Continuous pressure-flow measurements were performed under resting conditions, during a 2-minute intravenous infusion of adenosine and during an incremental exercise protocol. The order of adenosine and exercise was randomly assigned. A return to baseline hemodynamic conditions was mandated between each stage of the experimental protocol. Prior to removal from the patient, the Combowire was returned to the catheter tip to assess for pressure drift.

3.3.3 Exercise protocol

An incremental exercise protocol starting at 40 Watts and increasing by 20 Watts every minute was used for all patients. The guiding catheter was disengaged from the coronary ostium for the duration of exercise to prevent vessel trauma and to permit central aortic pressure waveform recording without damping. Exercise was continued until the development of rate-limiting angina symptoms or physical exhaustion.

3.3.4 Data analysis

The electrocardiogram, pressure waveforms and coronary flow velocity signals were directly extracted from the digital archive of the device console (ComboMap, V 1.9, Volcano Corporation) for offline analysis. Exercise data were exported from the ergometer software package using a dedicated export manager (Lode Export Manager 10, V 10.5.1, Lode, Groningen). Functional parameters quantified were exercise time (seconds), maximum workload (Watts), energy expenditure (KJ) and peak metabolic equivalent (MET).
3.3.5 Statistical analysis

Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were expressed as mean (± standard deviation unless otherwise specified). Categorical variables were expressed as numbers and percentages. Continuous variables were compared with paired t-tests. Repeated measures ANOVA was used to evaluate trends across the stages of adenosine versus exercise stress. Applicable tests were 2 tailed and p < 0.05 was considered statistically significant. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).
3.4 Results

3.4.1 Study population

Twenty-three patients (21 male; age, 60.6 ± 8.1 years) completed the study protocol. The baseline characteristics of the study population are summarised in Table 3.01. The majority of patients were in Canadian Cardiovascular Society (CCS) class 2 or 3 at enrolment. The mean number of prescribed antianginal medications per patient was 1.4 ± 0.7.

3.4.2 Stenosis and procedural characteristics

All stenoses were focal and predominantly proximal (57% [13/23]). The most frequently assessed vessel was the left anterior descending (LAD) artery (52% [12/23]). Stenoses were anatomically and physiologically severe. Mean stenosis diameter by quantitative coronary angiography was 74.6% ± 10.4. Median (interquartile range) FFR was 0.54 (0.44 to 0.72). Full anatomical and physiological stenosis characteristics are shown in Table 3.02.

3.4.3 Adenosine and exercise stress characteristics

Steady-state adenosine hyperemia was achieved in all patients within two minutes of intravenous adenosine infusion. Mean exercise time, peak METs, peak Watts and total energy expenditure were 144 ± 77 seconds, 4.3 ± 1.2 METs, 85 ± 30 Watts and 7.8 ± 7.0 KJ, respectively.

3.4.4 Systemic hemodynamic responses

Systemic hemodynamic responses at maximal adenosine versus maximal exercise stress are displayed in Figure 3.01A. Mean aortic pressure (91 ± 16 mmHg vs 99 ± 15 mmHg,
Temporal changes in systemic hemodynamics during adenosine and exercise are displayed in Figure 3.01B. The most marked difference was observed in the mean aortic blood pressure response to adenosine versus exercise (p<0.0001). During adenosine infusion there was a progressive decline in Pa pressure towards maximal adenosine stress. Conversely, during exercise, there was an initial increase in mean aortic blood pressure followed by a subsequent decline at maximal exercise stress. Heart rate and rate-pressure product increased during both stresses, however, the patterns of increase were significantly different during adenosine versus exercise (p<0.001 for HR and p<0.0001 for RPP).

3.4.5 Coronary hemodynamic responses

Coronary hemodynamic responses at maximal adenosine versus maximal exercise stress are displayed in Figure 3.02A. Coronary flow velocity (APV, 24 ± 10 vs 19 ± 7 cm/s, p=0.02) and the trans-stenotic pressure drop (ΔP, 33 ± 15 vs 29 ± 18 mmHg, p=0.01) were significantly higher at maximal adenosine versus maximal exercise stress. Conversely, distal coronary pressure (Pd, 58 ± 21 vs 69 ± 24 mmHg, p<0.0001) and trans-stenotic pressure ratio (Pd/Pa, 0.63 ± 0.18 vs 0.69 ± 0.19, p<0.0001) were significantly lower at maximal adenosine versus maximal exercise stress. Only stenosis resistance was similar between maximal adenosine and maximal exercise stress (SR, 1.8 ± 1.6 vs 1.9 ± 2.1 mmHg.cm⁻¹.sec⁻¹, p=0.81).

Temporal changes in coronary hemodynamics during adenosine and exercise stress are displayed in Figure 3.02B. During adenosine infusion there was a progressive increase in coronary flow velocity towards maximal adenosine stress. During exercise stress, coronary
flow velocity increased differently, plateauing earlier and at a lower value than during adenosine stress (p=0.03).

Consequent to the larger rise in coronary flow velocity with adenosine, the trans-stenotic pressure drop was greater (p=0.002) and the distal coronary pressure (p<0.0001) and trans-stenotic ratio lower (p<0.0001) throughout adenosine compared to exercise stress. Stenosis resistance remained similarly constant throughout both adenosine and exercise stress (p=0.34).

3.4.6 Microvascular hemodynamic responses

Microvascular hemodynamics at maximal adenosine versus maximal exercise stress are displayed in Figure 3.03. Microvascular resistance (MR, 2.9 ± 2.2 vs 4.2 ± 1.7 mmHg.cm⁻¹.sec⁻¹, p=0.001) was significantly lower at maximal adenosine versus maximal exercise stress. The pattern of decline in microvascular resistance with adenosine and exercise was also markedly different (Figure 3.03B, p<0.0001). During adenosine infusion, microvascular resistance decreased profoundly and early. In contrast, during exercise, microvascular resistance decreased gradually, reaching a higher nadir value at peak exercise stress. Full numerical comparison of systemic, coronary and microvascular hemodynamic responses to adenosine versus exercise stress are displayed in Table 3.03.
3.5 Discussion

This Chapter sought to compare invasive hemodynamic responses between adenosine and physical exercise stress in patients with stable angina and coronary stenosis. The main findings were as follows.

First, systemic hemodynamic responses were different between pharmacological and physical stress. Specifically, mean aortic blood pressure (Pa), heart rate (HR) and myocardial workload (RPP) were lower at maximal adenosine versus maximal exercise stress.

Second, coronary hemodynamic responses were different between pharmacological and physical stress. Specifically, $\Delta P$, distal coronary pressure (Pd) and the trans-stenotic pressure ratio (Pd/Pa) were lower, and coronary flow velocity (APV) higher, at maximal adenosine versus maximal exercise stress.

Last, systemic hemodynamic responses were different between pharmacological and physical stress. Specifically, microvascular resistance (MR) was lower at maximal adenosine versus exercise.

In summary, compared to physical exercise, in patients with stable angina and coronary stenosis, adenosine stress elicited a markedly different hemodynamic response in coronary, microvascular and systemic circulations (Figure 3.04).

3.5.1 The exogenous administration of adenosine

Adenosine is a naturally occurring nucleoside base of both adenosine triphosphate (ATP) and the signaling molecule cyclic adenosine monophosphate (cAMP) (72). The effects of
adenosine are mediated by two distinct receptors (73). Within the coronary circulation, adenosine primarily exerts its pharmacologic effect on the A2A receptor (74). Activation of this receptor produces vasodilatation of the coronary microcirculation, leading to a fall in microvascular resistance and a resultant increase in coronary blood flow (69, 70). Although these effects are broadly consistent across the majority patients, in total, seven distinct patterns of coronary hemodynamic response to intravenous adenosine infusion have been demonstrated (75). Due to a variety adenosine receptor subtypes expressed across multiple human organ systems, exogenous administration of adenosine is also associated with a range of systemic effects. These include flushing, dyspnea, chest pain, gastrointestinal discomfort, headache, atrio-ventricular conduction block, arrhythmias and bronchospasm (76).

3.5.2 Adenosine versus exercise stress

Within the present study, microvascular resistance was observed to be significantly lower, and coronary flow velocity significantly higher, during maximal adenosine versus maximal exercise stress. This was noted in combination with a lower mean aortic blood pressure during adenosine stress. The exact mechanism(s) to explain these findings is not clear. However, it may simply be that endogenous adenosine production during maximal physical exercise is lower than the amount of adenosine administered exogenously during FFR assessment (140mcg/kg/min).

The present study is the first to assess invasive hemodynamic responses during adenosine versus exercise stress in patients with stable angina symptoms and coronary stenosis. However, the changes in exercise coronary blood flow and cardiac-coronary coupling have previously been described in healthy subjects (63). Within the study by Lumley et al, in patients without angina or coronary stenosis, adenosine hyperemia similarly produced a larger augmentation in coronary blood flow associated with a greater reduction in
microvascular resistance than exercise (63). Therefore, the hemodynamic differences between adenosine and exercise stress appear independent of the presence of either coronary stenoses or angina symptoms.

3.5.3 Clinical implications

In non-invasive ischemia testing with adenosine (e.g. positron emission tomography or cardiac magnetic resonance), pharmacological hyperemia is used to induce regional differences in myocardial perfusion. This provides non-invasive flow-based measures of ischemia such as resting flow rate, hyperemic flow rate and CFR. However, in invasive ischemia testing with adenosine, because coronary flow is not routinely measured, pharmacological hyperemia is primarily used to minimise myocardial resistance - a prerequisite physiological state for FFR measurement. The findings of the present Chapter indicate that beyond this practical role facilitating FFR assessment, adenosine hyperemia does not accurately simulate physical exercise stress conditions.

3.6 Limitations

Within the present study, only patients with severe, single vessel coronary stenosis who were physically capable of exercising during their invasive coronary catheterisation procedure were recruited. Accordingly, this reflects a selected patient population with a relatively low mean age (60.6 ± 8.1 years) and an almost complete absence of diabetes mellitus. Young age (77) and freedom from diabetes (78) are associated with a more profound hyperemic flow responses to adenosine. Accordingly, the adenosine responses observed in the present study may not be fully representative of the broader spectrum of patients with coronary artery disease and angina encountered in real world clinical practice.
Within this study protocol, administration of intracoronary nitroglycerine was mandated prior to performing all angiography and physiology measurements. This was required to stabilise epicardial resistance in order to prevent vessel spasm. However, it is well recognised that in a proportion of patients with atherosclerosis, endothelial dysfunction (i.e. paradoxical coronary vasoconstriction) can be a significant contributor to exercise-induced angina symptoms (79). However, owing to the administration of intracoronary nitroglycerine, any such endothelial dysfunction would have been masked (and thus unmeasured) within the current study. Accordingly, the exercise capacity and coronary hemodynamic response of our study population may be an overestimation of that experienced under real-world exercise conditions.

Lastly, although a return to baseline heart rate and systolic blood pressure was mandated between adenosine and exercise stress runs, it is conceivable that a warm-up (75) or preconditioning effect (80, 81) may have occurred between the two stressor stimuli. To mitigate this potential (and unmeasured) confounding influence, the order of exercise and adenosine stress was randomised for each patient.
3.7 Conclusions

Adenosine stress elicited a markedly different physiological response to physical exercise stress in patients with stable angina and coronary stenosis. These differences were seen in coronary, microcirculatory and systemic hemodynamics.

3.8 Chapter Synthesis

In this Chapter I compared invasive hemodynamic responses between adenosine and exercise stress in patients with stable angina and coronary stenosis. My findings demonstrated that the hemodynamic responses to adenosine versus exercise stress were markedly different. These findings indicate that beyond its role in minimising microvascular resistance (required for FFR measurement), adenosine hyperemia does not accurately reproduce physical stress conditions.

These findings are of relevance when considering the ability of FFR to predict angina-limited exercise capacity versus non-hyperemic physiological indices of stenosis severity; as will be assessed in Chapter 5 of this thesis.
### Baseline Characteristics

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<tr>
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<td>Hypertension</td>
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<td>Statin</td>
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<td>ACE-I/ARB</td>
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<td>Nitrates</td>
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<td>9 (39%)</td>
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</table>

PCI indicates percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society; bpm, beats per minute; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.
### Demographics

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PCI indicates percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society; bpm, beats per minute; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.
Table 3.02: Anatomical and physiological stenosis characteristics

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<th>Target vessel (LAD/Cx/RCA)</th>
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<tr>
<td>Stenosis location (proximal/mid/distal)</td>
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<td>Diameter stenosis by QCA</td>
<td>74.46% (10.4)</td>
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<td>Stenosis length (mm)</td>
<td>10.7 (3.9)</td>
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<tr>
<td>FFR</td>
<td>0.56 (0.18)</td>
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<tr>
<td>iFR</td>
<td>0.59 (0.27)</td>
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<tr>
<td>Whole-cycle Pd/Pa</td>
<td>0.70 (0.22)</td>
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LAD indicates left anterior descending; Cx, circumflex; RCA, right coronary artery; QCA, quantitative coronary angiography; mm, millimetre; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; whole-cycle Pd/Pa, baseline distal-to-aortic pressure ratio.
Table 3.03: Hemodynamic responses to adenosine versus exercise stress

<table>
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<tr>
<th>Variable</th>
<th>Baseline</th>
<th>1 minute</th>
<th>Half maximum stress</th>
<th>Maximum stress</th>
<th>Baseline</th>
<th>1 minute</th>
<th>Half maximum stress</th>
<th>Maximum stress</th>
<th>p-value (ANOVA)</th>
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<tr>
<td>Pa</td>
<td>97.1 (11.5)</td>
<td>91.8 (13.2)</td>
<td>91.8 (13.2)</td>
<td>90.7 (15.7)</td>
<td>98.7 (12.1)</td>
<td>105.5 (14.3)</td>
<td>107.1 (14.6)</td>
<td>99.3 (15.1)</td>
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<td>HR</td>
<td>68.7 (13.0)</td>
<td>76.2 (18.1)</td>
<td>76.2 (18.1)</td>
<td>80.3 (14.6)</td>
<td>72.1 (14.7)</td>
<td>85.2 (13.1)</td>
<td>85.1 (15.9)</td>
<td>84.7 (21.2)</td>
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<tr>
<td>RPP</td>
<td>6913 (1826)</td>
<td>7288 (2370)</td>
<td>7288 (2370)</td>
<td>7522 (2335)</td>
<td>7552 (2153)</td>
<td>8927 (3206)</td>
<td>9250 (3608)</td>
<td>9077 (3201)</td>
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<tr>
<td>APV</td>
<td>16.24 (5.7)</td>
<td>22.6 (9.5)</td>
<td>22.6 (9.5)</td>
<td>23.7 (9.5)</td>
<td>15.3 (4.9)</td>
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<td>19.0 (7.2)</td>
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<tr>
<td>ΔP</td>
<td>23.3 (19.8)</td>
<td>32.2 (15.8)</td>
<td>32.2 (15.8)</td>
<td>32.9 (15.4)</td>
<td>25.3 (21.5)</td>
<td>24.0 (18.2)</td>
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<tr>
<td>Pd</td>
<td>73.7 (21.9)</td>
<td>59.8 (17.9)</td>
<td>59.8 (17.9)</td>
<td>57.8 (21.1)</td>
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<td>Pd/Pa</td>
<td>0.76 (0.20)</td>
<td>0.65 (0.17)</td>
<td>0.65 (0.17)</td>
<td>0.63 (0.18)</td>
<td>0.74 (0.21)</td>
<td>0.77 (0.16)</td>
<td>0.74 (0.18)</td>
<td>0.69 (0.19)</td>
<td>&lt;0.0001</td>
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<tr>
<td>SR</td>
<td>1.7 (1.8)</td>
<td>1.9 (1.8)</td>
<td>1.9 (1.8)</td>
<td>1.8 (1.6)</td>
<td>2.1 (2.7)</td>
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<td>1.9 (2.1)</td>
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<tr>
<td>MR</td>
<td>5.0 (2.1)</td>
<td>3.0 (1.5)</td>
<td>3.0 (1.5)</td>
<td>2.5 (1.0)</td>
<td>5.1 (1.9)</td>
<td>4.7 (1.7)</td>
<td>4.5 (1.7)</td>
<td>4.2 (1.7)</td>
<td>&lt;0.0001</td>
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Values are mean ± SD. Pa indicates mean aortic pressure; HR, heart rate; RPP, rate-pressure product; APV, average peak coronary flow velocity; ΔP, trans-stenotic pressure drop; Pd, distal coronary pressure; PP, pulse pressure; PdPa, trans-stenotic pressure ratio; SR, stenosis resistance; MR, microvascular resistance.
Figure 3.01: Systemic hemodynamic responses to adenosine versus exercise stress
(A) Boxplots of systemic hemodynamic responses during maximal adenosine (red) versus maximal exercise (blue) stress. The horizontal black line indicates the mean value. The box indicates the standard deviation and the whiskers indicate the range of values. (B) Temporal trends in systemic hemodynamic responses during adenosine (red) versus exercise (blue) stress. The error bars indicate the standard error. *Significant difference between adenosine versus exercise hemodynamic response, p<0.05. Pa indicates mean aortic pressure; HR, heart rate; RPP, rate-pressure product.
Figure 3.02: Coronary hemodynamic responses to adenosine versus exercise stress
(A) Boxplots of coronary hemodynamic responses during maximal adenosine (red) versus maximal exercise (blue) stress. (B) Temporal trends in coronary hemodynamic responses during adenosine (red) versus exercise (blue) stress. *Significant difference between adenosine versus exercise hemodynamic response, p<0.05. APV indicates average peak coronary flow velocity; ΔP, trans-stenotic pressure drop; Pd, distal coronary pressure; Pd/Pa, trans-stenotic pressure ratio; SR, stenosis resistance.
Figure 3.03: Microcirculatory hemodynamic response to adenosine versus exercise stress

(A) Boxplots of the microcirculatory hemodynamic response during maximal adenosine (red) versus maximal exercise (blue) stress. (B) Temporal trends in the microcirculatory hemodynamic response during adenosine (red) versus exercise (blue) stress. *Significant difference between adenosine versus exercise hemodynamic response, p<0.05. MR indicates microvascular resistance.
Figure 3.04: Invasive hemodynamic responses to adenosine versus physical exercise stress
Schematic illustration of the comparison between invasive hemodynamic responses to adenosine versus physical exercise stress in patients with angina and coronary stenosis. All abbreviations as per previous Figures.
4. The hemodynamic impact of percutaneous coronary intervention in stable coronary disease assessed during exercise

This Chapter is part of the following publication:

Impact of Percutaneous Revascularization on Exercise Hemodynamics in Patients With Stable Coronary Disease

Christopher M Cook* MBBS BSc, Yousif Ahmad* BMBS, James P Howard* MB BChir., Matthew J Shun-Shin* BM BCh., Amarjit Sethi* MBBS Ph.D., Gerald J Clesham* MB BChir., Ph.D., Kare H Tang* MBBS., Sukhjinder S Nijjer* MB ChB., Ph.D, Paul A Kelly* MB ChB, MD, John R Davies** MBBS, Pd.D, Iqbal S Malik* MBBS, Ph.D., Rafi Kaprielian* MBBS, M.D., Ghada Mikhail* MBBS, M.D., Ricardo Petraco* M.D., Ph.D., Firas Al-Janabi** MBBS, Grigoris V Karamasis* M.D., Shah Mohdnazri** M.D., Reto Gamma* M.D., Rasha Al-Lamee* MBBS, Thomas R Keeble** MBBS, M.D., Jamil Mayet* MB ChB, M.D., MBA, Sayan Sen* MBBS, Ph.D., Darrel P Francis* MB BChir., MA, M.D. and Justin E Davies* M.D., Ph.D.

J Am Coll Cardiol. 2018 Aug 28;72(9):970-983. doi: 10.1016/j.jacc.2018.06.033
4.1 Abstract

4.1.1 Background

In patients with stable coronary artery disease (SCD), the primary treatment goal of percutaneous coronary intervention (PCI) is the relief of angina and improvement in functional exercise capacity. However, the impact of PCI on exercise hemodynamics in patients with stable coronary disease is not known.

4.1.2 Objectives

To examine the impact of PCI on exercise responses in the coronary circulation, the microcirculation and systemic hemodynamics in patients with stable coronary artery disease.

4.1.3 Methods

Twenty-one patients (mean age, 60.3 ±8.4 years) with SCD and single-vessel coronary stenosis underwent cardiac catheterisation. Pre-PCI, patients exercised on a supine ergometer until rate-limiting angina or exhaustion. Simultaneous trans-stenotic coronary pressure-flow measurements were made throughout exercise. Post-PCI, this process was repeated. Physiological parameters, rate-limiting symptoms and exercise performance were compared between pre-PCI and post-PCI exercise cycles.

4.1.4 Results

PCI reduced ischemia as documented by FFR value (pre-PCI: 0.59 ±0.18 to post-PCI: 0.91 ±0.07), iFR value (pre-PCI: 0.61 ±0.27 to post-PCI: 0.96 ±0.05) and CFR value (pre-PCI: 1.7 ±0.7 to post-PCI: 3.1 ±1.0, p<0.001 for all). PCI increased peak-exercise average peak
coronary flow velocity (p<0.0001), coronary perfusion pressure (distal coronary pressure, p<0.0001), systolic blood pressure (p=0.01) and myocardial workload (rate-pressure product, p<0.01). These changes observed immediately following PCI resulted from the abolition of stenosis resistance (p<0.0001). PCI was also associated with an immediate improvement in exercise time (+67 seconds, 95% CI 31-102 seconds, p<0.0001) and a reduction in rate-limiting angina symptoms (81% reduction in rate-limiting angina symptoms post-PCI, p<0.001).

4.1.5 Conclusions

In patients with stable coronary artery disease and severe single-vessel stenosis, objective physiological responses to exercise immediately normalize following PCI. This is seen in the coronary circulation, the microcirculation and systemic hemodynamics.
4.2 Introduction

As outlined in the Introduction section of this thesis, in patients with stable coronary artery disease (SCD), the primary treatment goal of percutaneous coronary intervention (PCI) is the relief of angina and improvement in functional capacity (7, 9). However, the therapeutic mechanisms of PCI in stable coronary artery disease have never been invasively assessed during physical exercise.

Supine ergometer experiment protocols have recently been applied to the study of a variety of anginal conditions. These include the physiological mechanisms underlying the warm-up angina phenomenon (64), the mechanisms of angina in severe aortic stenosis (63), and the alleviation of angina on exertion by sublingual nitroglycerin (65).

In this Chapter I will utilise my supine ergometer experimental model to maximally exercise patients during cardiac catheterisation, immediately before and after PCI. Specifically, I will compare invasive systemic, coronary and microcirculatory hemodynamic responses before and after PCI to determine the impact of PCI on exercise hemodynamics in patients with stable coronary disease.
4.3 Methods

Because the supine ergometer experimental model is a central methodology to this thesis, to avoid duplication, I will focus only on the additional methods employed to acquire the post-PCI hemodynamic measurements and detail methods that are unique to this Chapter.

4.3.1 Catheterisation protocol (including PCI)

In addition to the pre-PCI combined coronary pressure and flow measurements as described in Chapter 3, PCI was then performed according to standard clinical practice. Stent optimisation was performed at the operator’s discretion. Following PCI, the Combowire was reintroduced, advanced to the guiding catheter tip and renormalised as before. The Combowire was advanced to the same intracoronary position as previous, with cross-reference to the cine-acquired roadmap image for confirmation. Continuous pressure-flow measurements were performed under resting conditions, during a 2-minute intravenous infusion of adenosine and during an incremental exercise protocol. The order of adenosine and exercise was randomly assigned. As with the pre-PCI measurements, a return to baseline hemodynamic conditions was mandated between each stage of the experimental protocol following PCI.

4.3.2 Exercise protocol

As per the pre-PCI stage of the protocol, an incremental exercise protocol starting at 40 Watts and increasing by 20 Watts every minute was used for all patients. The guiding catheter was disengaged from the coronary ostium for the duration of exercise to prevent vessel trauma and to permit central aortic pressure waveform recording without damping.
Exercise was continued until the development of rate-limiting angina symptoms or physical exhaustion. Specific to this Chapter, systemic serum lactate levels were also measured from arterial blood drawn from the guiding catheter immediately prior to, and at peak-exercise in order to quantify the rise in serum lactate during exercise.

4.3.3 Pulse Wave Analysis of Central Aortic Pressure

Central arterial pressure waveforms were obtained from the fluid-filled guiding catheter in the aortic root. A custom-made software package (PyCharm CE, V 2017.2.4) was used to analyse a minimum of 5 consecutive ensembled cardiac cycles through ECG-gating. Semi-automatic identification of the upstroke and peak of the arterial tracing and the trough of the dichrotic notch permitted calculation of the tension-time index (TTI – relating to myocardial oxygen demand (66)), diastolic time index (DTI – relating to coronary perfusion (67)), diastolic time fraction (DTF) and pulse pressure (PP). The rate-pressure product (RPP) is a surrogate marker of myocardial oxygen consumption and myocardial workload (82), and was calculated as the product of central systolic blood pressure and heart rate.

4.3.4 Statistical analysis

Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were expressed as mean (± standard deviation or standard error). Categorical variables were expressed as numbers and percentages. Continuous variables were compared with paired t-tests or paired Wilcoxon signed rank tests, as appropriate. Categorical variables were compared with chi-square or Fisher exact tests, as appropriate. Repeated measures ANOVA was used to evaluate trends across the stages of exercise pre and post-PCI. If significant, differences in separate exercise stages were evaluated with paired t-tests. Applicable tests were 2 tailed and p < 0.05 was considered statistically significant. All
analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).
4.4 Results

4.4.1 Study population

Twenty-one patients (19 male; age, 60.3 ± 8.4 years) completed the full study protocol comprising both pre and post-PCI components. The baseline characteristics of the study population are summarised in Table 4.01. The majority of patients were in Canadian Cardiovascular Society (CCS) class 2 or 3 at enrolment. The mean number of prescribed antianginal medications per patient was 1.4 ±0.7.

4.4.2 Stenosis and procedural characteristics

Stenosis characteristics are shown in Table 4.02 and in Figure 4.01. The stenoses were angiographically and physiologically severe. Mean stenosis diameter by quantitative coronary angiography was 75.7% ±10.3. FFR averaged 0.59 ±0.18, iFR 0.61 ±0.27, coronary flow reserve (CFR) 1.7 ±0.7 and hyperemic stenosis resistance (HSR) 2.3 ±2.3.

All stenoses were focal and were predominantly proximal (62% [13/21]), most frequently in the left anterior descending (LAD) artery (52% [11/21]). All PCI was performed successfully with drug eluting stents. The mean number of stents implanted per patient was 1.0 ± 0.2, the mean length of stent was 23 ± 8.3mm and the mean diameter of stent was 3.3 ± 0.4mm. Post-dilatation was performed in 18 (82%) of 22 stents. Post-PCI, FFR rose to 0.91 ±0.07, iFR to 0.96 ±0.05, CFR to 3.1 ±1.0 and HSR fell to 0.2 ±0.2 (p<0.0001 for all).

4.4.3 Symptom and exercise responses

Before PCI, 95% of patients stopped exercising because of chest pain or breathlessness (Figure 4.02). In contrast, after PCI, only 10% did so, with the remainder stopping because
of physical exhaustion without chest pain or breathlessness. Before PCI, baseline serum lactate was 1.0 ± 0.41 mmol/L and this increased to 2.4 ± 1.1 mmol/L at peak-exercise (+240%). After PCI, baseline serum lactate was 1.3 ± 0.51 mmol/L and this increased to 4.1 ± 1.8 mmol/L at peak-exercise (+315%, p<0.001 for the difference in increment of serum lactate during exercise). Exercise time increased by 67 seconds (95% CI 31-102 seconds, p<0.001, Figure 4.03) after PCI. Full exercise performance data are shown in Table 4.03.

4.4.4 Systemic hemodynamic responses

Before PCI, blood pressure initially rose progressively with exercise but then fell at peak-exercise when symptoms developed (peak-exercise 7.7 mmHg below the preceding time-point, p=0.01, Figure 4.04). After PCI, blood pressure rose initially again, however, at peak-exercise blood pressure plateaued and did not decline. Corresponding to peak-exercise in the pre-PCI state, at the equivalent exercise time-point in the post-PCI state, blood pressure was significantly higher (delta 14.0 mmHg, p=0.01). Because patients could exercise for longer following PCI, an extra time-point at an even higher workload was recorded, and again this was significantly higher than peak-exercise during the pre-PCI state (delta 12.0 mmHg, p=0.02). The same pattern was seen for rate-pressure product.

Analysis of central arterial pressure waveforms during exercise are summarized in Figure 4.05. Pulse pressure increased with exercise (p<0.001) both before and after PCI. Because both heart rate and systolic blood pressure increased together, TTI did not increase significantly during exercise (p=0.51). In line with the overall increase in heart rate (and thus shortening of diastole), DTI and diastolic time fraction both decreased significantly with exercise (p <0.0001). Changes in PP, TTI, DTI and DTF during exercise were similar both before and after PCI (p>0.05 for all). Full systemic hemodynamic responses are shown in Table 4.04.
Coronary and microcirculatory hemodynamic responses

Coronary circulation and microvascular responses to exercise are summarized in Figure 4.06. Resting coronary flow velocity was similar both before and after PCI (p=0.19). Flow significantly increased during both pre and post-PCI exertions (p=0.03) but displayed markedly different patterns of rise (p<0.01). Before PCI, coronary flow velocity increased minimally with exercise and plateaued early. Conversely, after PCI, coronary flow velocity increased in a near-linear fashion with exercise and was significantly higher for all time-matched stages of exercise (p<0.0001). At peak-exercise, coronary flow velocity was 65% higher after PCI than before (18.2 cm/s ±7.7 versus 30.1 ± 8.6 cm/s, p<0.00001).

Distal coronary pressure (Pd), trans-stenotic pressure gradient, trans-stenotic pressure ratio (Pd/Pa) and stenosis resistance were all markedly improved at all stages of exercise following PCI (p<0.0001 for all, Table 4). Diastolic microvascular resistance (DMR), the portion of the cardiac cycle where myocardial compressive forces are at their lowest (83), was significantly lower at rest (p=0.05) before PCI (p=0.04; Figure 4.06). Furthermore, the pattern of decline in DMR was different (p=0.01) before versus after PCI. Before PCI, diastolic microvascular resistance reached its minimum value earlier during exercise than in the post-PCI state. Full coronary and microcirculatory hemodynamic responses are shown in Table 4.04.
4.5 Discussion

This Chapter sought to determine the invasive pathophysiology of exercise-induced angina and quantify the impact of PCI on exercise hemodynamics in patients with stable coronary disease.

My findings first show that coronary flow and pressure cannot rise to meet the demands of physical exercise when there is a significant coronary stenosis. PCI immediately normalizes the ability of coronary flow and pressure to rise to match this myocardial demand.

Secondly, PCI improves coronary, microvascular and systemic hemodynamic responses to exercise. By abolishing stenosis resistance with instantaneous effect, PCI restores the coronary vessel to its primary role as a conduit and the capacity of the microcirculation to progressively vasodilate during exercise.

Thirdly, in patients with stable angina and physiologically significant single-vessel disease unblinded to the fact that they have received PCI, PCI immediately improves exercise capacity and reduces rate-limiting angina symptoms (Figure 4.07).

4.5.1 PCI and changes in the coronary circulation response to exercise

Because oxygen extraction is near maximal even at rest (84), the principal way myocardial oxygen demand on exercise can be met is through an increase in coronary blood flow (85). I found that coronary flow increased in very different ways before versus after PCI. Before PCI, coronary flow plateaued early during exercise. This can be explained by both mechanical limitation to flow from the stenosis, manifesting as high stenosis resistance, and premature maximal dilatation of the microcirculatory vascular bed.
Immediately after PCI, flow increased almost linearly with exercise and was significantly higher at all stages of exertion by comparison with the corresponding pre-PCI measurements. This was due to a large fall in stenosis resistance and a corresponding increase in microcirculatory resistance at rest. These physiological adaptations following PCI restored the coronary vessel to its primary role as a conduit (86) and also restored the capacity of the downstream microcirculatory bed to progressively vasodilate during exercise.

Exercise coronary pressures, too, showed a different pattern after PCI than before. Distal coronary pressure is effectively the pressure perfusing the coronary bed (85). Before PCI, distal coronary pressure was low at rest, rose slightly during early exercise but actually fell again at peak-exercise, culminating in hypoperfusion of the coronary bed. The fall in Pd pressure before PCI may have been the result of the concomitant fall in Pa driving pressure that was also observed. After PCI, distal coronary pressure started higher, rose slightly and then was maintained. This is consistent with normalization of the coronary perfusion response to exercise.

4.5.2 PCI and changes in the microcirculatory response to exercise

In health, the large increase in coronary flow necessary during physical exercise is achieved predominantly by a large fall in microvascular resistance (87). When there is a hemodynamically significant coronary stenosis, lowering distal coronary pressure, this process of vasodilatation is enacted even at rest. This homeostatic mechanism, termed coronary autoregulation (39, 42), allows perfusion to be adequate at rest despite a large stenosis resistance in the resting state. During exercise, however, because this microcirculatory vasodilatation has already been exhausted to maintain resting coronary
flow, there is little remaining capacity to vasodilate to accommodate the necessary increase in flow.

PCI eliminates the stenosis resistance and thereby eliminates the need for microcirculatory vasodilator capacity to be consumed at rest. As shown in Figure 6, the resting diastolic microcirculatory resistance is higher than before PCI. It decreases progressively with exercise and by peak-exercise it has fallen to the same level as pre-PCI peak-exercise. This suggests that the microcirculation is not inherently affected by PCI, but that PCI restores the conduit function of the epicardial artery so that the microcirculatory vasodilatory capacity can be reserved for use during exercise.

Whether the stimulus to increase coronary flow is pharmacological vasodilatation or the increased myocardial demand from physical exercise, if part of the microcirculatory vasodilatory capacity has already been used to maintain resting coronary flow, then less vasodilator capacity remains to further increase flow. This mechanism also explains the low CFR observed in our patients before PCI that was subsequently restored to normal following stenting.

4.5.3 Effect of PCI on systemic hemodynamic responses to exercise

During physical exercise, heart rate, systolic blood pressure and ventricular contractility normally increase (85). In my patients before PCI, at peak-exercise there was a reversal of this pattern with a fall in blood pressure and heart rate and therefore in the rate-pressure product. This may be a systemic manifestation of inability of myocardial perfusion to increase adequately in the territory subtended by the stenosed artery. In support of this interpretation, after PCI, at the identical level of exercise the blood pressure and rate-pressure product were significantly higher.
Pulse wave analysis of aortic pressure waveforms during exercise did not reveal any significant differences before versus after PCI. This is in contrast with the findings of previous catheter laboratory exercise studies investigating the warm-up angina phenomenon (64) and the physiological effect of sublingual nitroglycerin in patients with stable angina (65). Within those studies, in the absence of PCI, significant lowering of afterload, the tension time index and the Buckberg index were observed on repeat exercise. Such findings indicate that with a stenosis remaining in situ, the primary adaptive measures to reduce ischemia during repeat exercise are the enhancement of subendocardial perfusion and the downregulation of myocardial oxygen demand (64). Conversely, in the present study, where PCI was performed, restoration of normal coronary blood flow during exercise was the overwhelming therapeutic hemodynamic alteration. Accordingly, within my study, transmural redistribution of perfusion was not observed on repeat exercise; and an increase rather than decrease in myocardial workload was demonstrated.

4.6 Limitations

To avoid duplication, I will highlight only the limitations that are specific to this Chapter.

This study addressed only single vessel disease and only cases with sufficiently focal lesions that there was good expectation of full resolution by stenting. Accordingly, this represents a highly selected group of patients. General clinical practice covers a much wider variety of disease anatomy. It is not known how multivessel disease or multivessel PCI might fair in such a study. The advantage of discrete single vessel disease is that the anatomy and physiology have a good chance of being normalised by the PCI.
I only enrolled patients who would be able to exercise on a supine bicycle. This meant that more frail individuals were not eligible. It also meant that if the operator needed to carry out femoral access, the patient could not conduct the protocol. Furthermore, owing to the potential for (unmeasured) myocardial stunning or hibernation immediately post-PCI, the improvement in functional capacity demonstrated in our study may be an underestimation of the longer-term therapeutic effect.

I did not measure reproducibility of supine exercise in our patients. This was in order to minimise the burden on patients participating in the study, as well as the significant time burden imposed on busy clinical catheter laboratory lists. My reason to believe that the supine exercise test might have satisfactory reproducibility is that before this study began we ran a pilot study of paired supine exercise tests 30 minutes apart with healthy controls who were blinded to time during exercise. This pilot phase, as outlined in the Methods and Materials section of this thesis, suggested satisfactory reproducibility, with mean difference of just -6.9 seconds and a standard deviation of difference (SDD) of 32 seconds.

This study did not blind patients to the presence of PCI and therefore I must bear in mind that any subjectively reported reduction in symptoms and objectively observed increase in exercise capacity is mediated by a combination of the physical and psychological effects of PCI, the latter of which may be particularly prone to bias. The reason that I did not blind patients in this study is that a blinding protocol would necessitate sedation for allocation concealment and this would have impaired exercise performance.
4.7 Conclusions

Examining solely objective physiological measures during physical exercise, PCI for single-vessel stable coronary artery disease shows clear evidence of immediately resolving clinical markers of myocardial ischemia during exercise. There is immediate normalisation of the pattern of exercise induced changes: in coronary pressure, flow and resistance; in systemic blood pressure, heart rate and rate-pressure product; and in the microcirculatory vasodilator reserve to physical exercise.

4.8 Chapter synthesis

In this Chapter I investigated the hemodynamic impact of PCI in stable coronary disease and its relationship with post-PCI changes in exercise capacity. My findings demonstrated that PCI immediately improved ischemia and objectively documented exercise responses in the coronary circulation, the microcirculation and systemic hemodynamics. Under unblinded conditions, these hemodynamic improvements were associated with a significant increase in exercise capacity and a marked reduction in angina symptoms following PCI. Lastly, this study demonstrated the apparent safety of performing maximal physical exercise immediately after coronary stenting.

In the following Chapter I will investigate the relationship between physiological stenosis severity and angina-limited exercise capacity. Furthermore, I will determine if coronary physiology measurements are capable of predicting the improvement in exercise time immediately following PCI.
Table 4.01: Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.3 (8.4)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (91)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Family history of ischemic heart disease</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>LVEF &lt; 40%</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CCS class</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>II</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>III</td>
<td>12 (57%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Statin</td>
<td>20 (95%)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>CCB</td>
<td>8 (38%)</td>
</tr>
</tbody>
</table>

Values are n, mean ± SD, or n (%). PCI indicates percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.
### Table 4.02: Procedural details

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel (LAD/Cx/RCA)</td>
<td>11/6/4</td>
</tr>
<tr>
<td>Stenosis location (proximal/mid/distal)</td>
<td>13/6/2</td>
</tr>
<tr>
<td>Area stenosis by QCA</td>
<td>93.1% (5.7)</td>
</tr>
<tr>
<td>Diameter stenosis by QCA</td>
<td>75.7% (10.3)</td>
</tr>
<tr>
<td>Stenosis length (mm)</td>
<td>11.0 (4.13)</td>
</tr>
<tr>
<td>FFR</td>
<td>0.59 (0.18)</td>
</tr>
<tr>
<td>iFR</td>
<td>0.61 (0.27)</td>
</tr>
<tr>
<td>CFR</td>
<td>1.7 (0.7)</td>
</tr>
<tr>
<td>HSR</td>
<td>2.3 (2.3)</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>23 (8.3)</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.3 (0.4)</td>
</tr>
<tr>
<td>Stent post-dilatation</td>
<td>82% (18/22)</td>
</tr>
<tr>
<td>FFR post-PCI</td>
<td>0.91 (0.07)*</td>
</tr>
<tr>
<td>iFR post-PCI</td>
<td>0.96 (0.05)*</td>
</tr>
<tr>
<td>CFR post-PCI</td>
<td>3.1 (1.0)*</td>
</tr>
<tr>
<td>HSR post-PCI</td>
<td>0.2 (0.2)*</td>
</tr>
</tbody>
</table>

Values are n, mean ± SD, or n (%). LAD indicates left anterior descending; Cx, circumflex; RCA, right coronary artery; QCA, quantitative coronary angiography; mm, millimetre; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; CFR, coronary flow reserve; HSR, hyperemic stenosis resistance; PCI, percutaneous coronary intervention. *Significant difference pre versus post-PCI, p<0.0001.
Table 4.03: Exercise performance data before and after PCI

<table>
<thead>
<tr>
<th></th>
<th>Pre-PCI</th>
<th>Post-PCI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time (Sec)</td>
<td>145 (80)</td>
<td>212 (74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distance covered (m)</td>
<td>529 (484)</td>
<td>854 (571)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Max workload (Watts)</td>
<td>83 (30)</td>
<td>103 (30)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Max intensity (MET)</td>
<td>4.3 (1.2)</td>
<td>5.2 (1.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total energy expenditure (KJ)</td>
<td>7.9 (7.3)</td>
<td>13.1 (8.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>12 515 (3697)</td>
<td>14 903 (3897)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values mean ± SD. PCI indicates percutaneous coronary intervention; Sec, seconds; m, metres; MET, metabolic equivalent; KJ, kilojoule.
Table 4.04: Systemic, coronary and microcirculatory hemodynamic responses to exercise before and after PCI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-PCI</th>
<th>Post-PCI</th>
<th>p-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 minute</td>
<td>t50 (Expro)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67 (13)</td>
<td>83 (18)</td>
<td>85 (22)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>142 (18)</td>
<td>152 (21)</td>
<td>160 (21)</td>
</tr>
<tr>
<td>RPP (2355)</td>
<td>13069</td>
<td>14122</td>
<td>12515</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>62 (11)</td>
<td>65 (10)</td>
<td>65 (13)</td>
</tr>
<tr>
<td>TTI (mmHg/sec)</td>
<td>44 (8)</td>
<td>44 (8)</td>
<td>45 (7)</td>
</tr>
<tr>
<td>DFI (mmHg/sec)</td>
<td>46 (12)</td>
<td>34 (7)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>DTF</td>
<td>0.57 (0.07)</td>
<td>0.51 (0.06)</td>
<td>0.49 (0.07)</td>
</tr>
<tr>
<td>APV (cm/s)</td>
<td>15 (5)</td>
<td>18 (7)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>SR (mmHg.cm^-1.sec^-1)</td>
<td>2.7 (3.1)</td>
<td>2.60 (3.2)</td>
<td>2.7 (3.1)</td>
</tr>
<tr>
<td>dP (mmHg)</td>
<td>28 (21)</td>
<td>30 (20)</td>
<td>31 (20)</td>
</tr>
<tr>
<td>PdPa</td>
<td>0.70 (0.22)</td>
<td>0.72 (0.19)</td>
<td>0.69 (0.16)</td>
</tr>
<tr>
<td>Pd (mmHg)</td>
<td>90 (23)</td>
<td>76 (24)</td>
<td>75 (25)</td>
</tr>
<tr>
<td>DMR (mmHg.cm^-1.sec^-1)</td>
<td>3.0 (1.4)</td>
<td>2.4 (1.1)</td>
<td>2.1 (1.0)</td>
</tr>
</tbody>
</table>

Values are mean ± SD. HR indicates heart rate; SBP, systemic blood pressure; RPP, rate-pressure product; PP, pulse pressure; TTI, tension-time index; DFI, diastolic time index; DTF, diastolic time fraction; APV, average peak coronary flow velocity; SR, stenosis resistance; dP, pressure-gradient; PdPa, pressure ratio; Pd, distal coronary pressure; DMR, diastolic microvascular resistance.
Figure 4.01: Coronary angiograms of the 21 included patients
The target lesion is marked with a red asterix.
Figure 4.02: Limiting symptoms on exercise before and after PCI
(A) Reasons for the termination of exercise before (red dot) and after (blue dot) PCI. (B) Exercise induced rise in arterial blood lactate before and after PCI. The horizontal black line indicates the mean value. The box indicates the standard deviation and the whiskers indicate the range of values.
Figure 4.03: Exercise time before and after PCI

(A) Mean exercise time of the study population, before (red bar) and after (blue bar) PCI. The error bars indicate the standard error. (B) Individual patient data.
Figure 4.04: Systemic hemodynamic responses to exercise
Heart rate, systolic blood pressure and rate-pressure product responses to exercise at baseline (Base), 1 minute of exercise (1 min), 50% of the pre-PCI time (t50Expre), peak-exercise time pre-PCI (PeakExpre) and peak-exercise time post-PCI (PeakExpost), before (red) and after (blue) PCI. The error bars indicate the standard error. *Significant difference between time-matched exercise stages pre versus post-PCI, p<0.05. †Significant difference between peak-exercise pre versus post-PCI, p<0.05.
Figure 4.05: Aortic pressure waveform responses to exercise
Pulse pressure, tension time index, diastolic time index and diastolic time fraction responses to exercise, before (red) and after (blue) PCI.
Figure 4.06: Coronary and microcirculatory hemodynamic responses to exercise

Coronary flow velocity, stenosis resistance, pressure gradient, pressure ratio (Pd/Pa), distal coronary pressure (Pd) and diastolic microvascular resistance (DMR) responses to exercise, before (red) and after (blue) PCI. *Significant difference between time-matched exercise stages pre versus post-PCI, p<0.05. †Significant difference between peak-exercise pre versus post-PCI.
**Figure 4.07:** The hemodynamic and functional impact of percutaneous coronary intervention in stable coronary disease

PCI indicates percutaneous coronary intervention; METS, metabolic equivalents; KJs, kilojoules; iFR, instantaneous wave-Free Ratio; FFR, fractional flow reserve; CFR, coronary flow reserve.
5. Predicting angina-limited exercise capacity using coronary physiology

This Chapter is part of the following oral presentation:

Predicting angina-limited exercise capacity using coronary physiology

September 21st, TCT 2018, San Diego, California
5.1 Abstract

5.1.1 Background

Coronary physiology is recommended to guide percutaneous coronary intervention (PCI) in patients with angina and stable coronary artery disease. PCI in such settings aims to relieve angina and improve exercise capacity. However, the relationship between physiological stenosis severity and angina-limited exercise capacity is poorly understood.

5.1.2 Methods

Fractional Flow Reserve (FFR), instantaneous wave-Free Ratio (iFR), coronary flow reserve (CFR) and hyperemic stenosis resistance (HSR) were measured in 23 patients (61 ± 8 years) with severe single-vessel coronary stenosis. Immediately following physiological assessment, patients maximally exercised on a catheter-table-mounted supine ergometer until they developed angina (ET:\text{angina}). Relationships between iFR, FFR, CFR, HSR and ET:\text{angina} were assessed using linear regression. Twenty-one patients (91%) underwent subsequent PCI and repeat maximal supine exercise. This permitted additional assessment of the relationships between the post-PCI increment in exercise time (\Delta ET) and both baseline FFR, iFR, CFR, HSR and \Delta FFR, \Delta iFR, \Delta CFR and \Delta HSR.

5.1.3 Results

Mean stenosis diameter was 74.6% ± 10.4. Median (interquartile range) FFR, iFR, CFR and HSR were 0.54 (0.44 - 0.72), 0.53 (0.38 - 0.83), 1.67 (0.84 - 3.16) and 1.35 (1.11 - 1.63), respectively. Mean ET:\text{angina} was 144 ± 77 seconds (4.3 ± 1.2 metabolic equivalents, METs). Neither patient characteristics nor anatomical stenosis characteristics were significant predictors of ET:\text{angina} (p>0.05 for all). Conversely, FFR (R=0.52, p<0.01), iFR (R=0.68, p<0.001), CFR (R=0.40, p=0.05) and HSR (R=-0.59, p<0.01) all predicted ET:\text{angina}. Post-PCI, median FFR rose to 0.91 (0.85 - 0.96), iFR to 0.98 (0.94 - 0.99), CFR to 2.73 (2.50 - 3.12)
and HSR fell to 0.16 (0.06 - 0.37, p<0.0001 for all). Post-PCI ΔET was further predicted by baseline iFR (R=-0.51, p=0.02) and ΔiFR (R=0.53, p=0.01).

5.1.4 Conclusions

In settings representative of routine clinical practice, physiological stenosis severity was predictive of angina-limited exercise capacity and the functional improvement following PCI. Conversely, no relationship was demonstrated between anatomical stenosis severity and functional exercise capacity.
5.2 Introduction

Coronary physiology is recommended to identify ischemia and guide percutaneous coronary intervention (PCI) in stable coronary artery disease (7, 9). The primary aims of PCI in such settings are to relieve angina and improve exercise capacity (88). However, as outlined as the central theme of this thesis, the relationship between physiological stenosis severity and angina-limited exercise capacity is poorly understood.

The most commonly used physiological indices are the Fractional Flow Reserve (FFR) and the instantaneous-wave Free Ratio (iFR). Both FFR and iFR evaluate the hemodynamic significance of a coronary stenosis by quantification of the trans-stenotic pressure ratio. FFR is measured across the entire cardiac cycle during maximal pharmacological hyperemia (22), whereas iFR is measured during the wave-free period of diastole, without hyperemia (83). Although lesser used, hyperemic stenosis resistance (HSR) and coronary flow reserve (CFR) have features that distinguish them from FFR and iFR. HSR is a combined measurement of coronary pressure and flow reported to have the highest predictive power to identify myocardial ischemia (45). CFR is a coronary flow-based measurement that incorporates physiological assessment of both the stenosis and the microcirculation, and is well-validated for prognostication in stable coronary artery disease (89).

In this Chapter I will use data collected as part of my supine ergometer experiment to investigate the relationships between FFR, iFR, HSR, CFR and angina-limited exercise time. Additionally, I will determine whether any of these indices are capable of predicting the change in maximal exercise time assessed immediately following PCI.
5.3 Methods

As before, to avoid duplication of reporting, I will describe only the additional methods performed relevant to this current Chapter.

5.3.1 Exercise protocol

For this Chapter I will include only those patients that exercised until the development of angina (defined as chest pain or rate-limiting shortness of breath). This includes data from 3 patients that were recruited to the study after the publication of findings reported in Chapter 4. As described previously, all patients exercised on an incremental exercise protocol starting at 40 Watts and increasing by 20 Watts every minute. The time from the start of exercise to the onset of angina ($ET_{angina}$) was recorded.

5.3.2 Calculation of physiologic indices

\[
\begin{align*}
\text{Pa} &= \text{Proximal (aortic) pressure (mmHg)} \\
\text{Pd} &= \text{Distal (coronary) pressure (mmHg)} \\
\text{FFR} &= \frac{\text{Pd}}{\text{Pa}} \text{ at whole-cycle during pharmacological hyperemia} \\
\text{iFR} &= \frac{\text{Pd}}{\text{Pa}} \text{ at baseline over iFR window} \\
\text{HSR} &= \frac{\text{Pa-Pd (mmHg)}}{\text{Whole - cycle hyperemic flow velocity (cm/s)}} \\
\text{CFR} &= \frac{\text{Whole-cycle hyperemic flow velocity}}{\text{Whole-cycle baseline flow velocity}}
\end{align*}
\]

5.3.3 Statistical analysis

Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were expressed as mean ($\pm$ standard deviation). Categorical variables were expressed as numbers and percentages. Continuous variables were compared with paired $t$-tests or
paired Wilcoxon signed rank tests, as appropriate. Linear regression analysis was used to investigate the relationship between $\text{ET}_{\text{angina}}$ and patient characteristics, anatomic stenosis characteristics and physiological stenosis characteristics (FFR, iFR, HSR and CFR). Tests for non-linearity were performed to validate this approach and exclude the need for modelling using restricted cubic splines (90). Multiple linear regression analysis was performed to identify predictors of $\text{ET}_{\text{angina}}$, in which significant variables ($p<0.05$) in univariate analysis were entered as independent variables. Absence of multicollinearity of independent variables was checked prior to multiple regression, and where present ($R > 0.8$), only the strongest-correlated variable on univariate analysis was included in the model. Lastly, univariate linear regression analysis was performed to identify predictors of the change in exercise time ($\Delta \text{ET}$) following PCI, in which baseline iFR, FFR, HSR and CFR and $\Delta$ iFR, $\Delta$ FFR, $\Delta$ HSR and $\Delta$ CFR were assessed. Applicable tests were 2 tailed and $p < 0.05$ was considered statistically significant. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).
5.4 Results

5.4.1 Study population
Twenty-three patients (21 male; age, 60.6 ± 8.1 years) completed the pre-PCI component of the study protocol. Twenty-one of these patients (19 male; age, 60.3 ± 8.4 years) competed the full study protocol comprising of PCI, post-PCI physiological assessment and post-PCI maximal exercise. Of the 2 patients that did not complete the post-PCI exercise phase, one had stenting that extended into their left main stem (an exclusion criterion) and one experienced persistent low-level chest discomfort following stenting, precluding them from repeat exercise.

The baseline characteristics of the pre-PCI study population are summarised in Table 5.01. The majority of patients were in Canadian Cardiovascular Society (CCS) class 2 or 3 at enrolment. The mean number of prescribed antianginal medications per patient was 1.4 ± 0.7.

5.4.2 Stenosis and procedural characteristics
Anatomical and physiological stenosis characteristics across the study population are shown in Table 5.02. All stenoses were focal and were predominantly proximal (57% [13/23]), most frequently in the left anterior descending (LAD) artery (52% [12/23]). Mean stenosis diameter by quantitative coronary angiography was 74.6% ± 10.4. Median (interquartile range) FFR, iFR, HSR and CFR were 0.54 (0.44 to 0.72), 0.53 (0.38 to 0.83), 1.35 (1.11 to 1.63) and 1.67 (0.84 to 3.16), respectively.

All PCI was performed successfully with drug eluting stents. The mean number of stents implanted per patient was 1.0 ± 0.2, the mean length of stent was 23 ± 8.3mm and the mean diameter of stent was 3.3 ± 0.5mm. Post-PCI, FFR rose to 0.91 (0.85 to 0.96), iFR to 0.98 (0.94 to 0.99), CFR to 2.73 (2.50 to 3.12) and HSR fell to 0.16 (0.06 to 0.37), (p<0.0001 for
all; Figure 5.01). Median improvement in physiological stenosis severity was $\Delta 0.34$ (0.21 – 0.42) for FRR, $\Delta 0.25$ (0.09 – 0.54) for iFR, $\Delta 1.28$ (0.74 – 1.50) for CFR and $\Delta -1.37$ (-2.38 - -2.08) for HSR. Vessel-specific anatomical and physiological stenosis characteristics are shown in Table 5.03.

5.4.3 Symptoms and exercise capacity

Before PCI, the majority of patients experienced chest pain at peak exertion (87% [20/23]). The remaining patients experienced rate-limiting dyspnoea (13% [3/23]). Mean exercise time before PCI was 144 ± 77 seconds (4.3 ± 1.2 metabolic equivalents, METs). Following PCI, exercise time increased to 219 ± 69 seconds (+ 75 seconds, 95% CI 31-120 seconds, p<0.001 for the difference in exercise time).

5.4.4 Predictors of angina-limited exercise time

The relationship between angina-limited exercise time ($E_{\text{angina}}$), patient characteristics and anatomical stenosis characteristics are displayed in Table 5.04. Patient characteristics were not significant predictors of angina-limited exercise time. Similarly, percentage stenosis diameter ($\beta$ -0.68, 95%CI -4.05 – 2.70, p=0.68 for univariate analysis) and stenosis length ($\beta$ 0.93, 95%CI -8.56 – 9.28, p=0.93 for univariate analysis) were not significant predictors of angina-limited exercise time.

The relationship between $E_{\text{angina}}$ and FFR, iFR, HSR and CFR are displayed in Table 5.05. All of the physiological indices were significant independent predictors of angina-limited exercise time. When entered into a multivariable linear regression model, only iFR remained predictive of angina-limited exercise time ($\beta$ 291, 95%CI 32.2 – 549, p=0.03 for multivariable analysis). The correlation between $E_{\text{angina}}$ and FFR, iFR, HSR and CFR values are
displayed in Figure 5.02. Both iFR (R=0.68, p<0.001) and FFR (R=0.52, p<0.01) correlated with angina-limited exercise time.

5.4.5 Predictors of the change in exercise time following PCI

The correlations between baseline FFR, iFR, HSR and CFR and the change in exercise time following PCI (ΔET) are displayed in Figure 5.03. ΔET was most predicted by the baseline iFR value (R=-0.51, p=0.02), with the greatest improvement in post-PCI exercise time demonstrated at the lowest baseline iFR value. The correlation between ΔET and baseline FFR was R=-0.42, p=0.06.

The correlations between ΔET and ΔFFR, ΔiFR, ΔHSR and ΔCFR following PCI are displayed in Figure 5.04. ΔET was most predicted by ΔiFR (R=0.53, p=0.01). The correlation between ΔET and ΔFFR was R=0.40, p=0.07.
5.5 Discussion

This Chapter sought to determine the relationship between physiological stenosis severity and angina-limited exercise capacity. The main findings of this Chapter are as follows. First, in patients with stable angina and single vessel coronary artery disease, physiological stenosis severity quantified by FFR, iFR, HSR or CFR predicted angina-limited exercise capacity. Second, stenosis severity quantified by anatomy alone did not predict angina-limited exercise capacity. Third, coronary pressure-based iFR and FFR demonstrated amongst the highest correlations with angina-limited exercise capacity. Last, physiological stenosis severity predicted the improvement in exercise capacity observed following PCI; most evident with baseline iFR and ΔiFR.

5.5.1 Using coronary physiology to predict angina-limited exercise capacity

Despite the recommended role for coronary physiology to guide revascularisation in stable CAD, the relationship between physiological indices of stenosis severity and angina-limited exercise capacity is poorly understood. As outlined in the Introduction to this thesis, this represents an important gap in knowledge relevant to the contemporary management of stable CAD.

In a small study by Tanaka et al, fifteen patients with stable angina and 75% angiographic stenosis underwent FFR measurement followed by cardiopulmonary exercise test. The authors demonstrated a significant correlation between FFR and peak oxygen consumption (R=0.53; p<0.05) (91). Furthermore, no relationship was demonstrated when percentage diameter stenosis was compared with maximal exercise capacity.

Eroglu et al investigated the association between echocardiography-derived CFR and exercise capacity tested by treadmill testing (92). In fifty patients the authors demonstrated
that CFR correlated with exercise time (R=0.38, p=0.007). However, all patients were without coronary artery disease or other cardiac disease. Therefore, the results of Eroglu et al primarily inform that coronary microvascular dysfunction may be a reason for reduced exercise capacity in patients without apparent cardiovascular disease. Accordingly, these results are not directly applicable to patients in whom revascularisation is contemplated.

Lastly, in a study of thirty-three patients with single-vessel disease and exertional angina, Handa et al demonstrated a good correlation between invasive CFR and exercise capacity determined by treadmill testing (93). Consistent with our own findings, the authors also reported that exercise capacity did not relate well with the degree of stenosis determined by quantitative coronary angiography.

Therefore, the present study is differentiated from the existing literature in a number of ways. Specifically, it is the only investigation to comparatively assess all clinically used coronary pressure and flow-based indices against angina-limited exercise capacity. Additionally, it is the only study to assess exercise capacity at the same time as physiological assessment; including an assessment immediately following PCI.

5.5.2 Using coronary physiology to predict the change in exercise capacity following PCI

The physiology-stratified analysis of the Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) trial is the only investigation of the relationship between FFR and iFR and the placebo-controlled change in treadmill exercise time following PCI (90). When assessed under blinded conditions, neither FFR (P_{interaction}=0.318) nor iFR (P_{interaction}=0.523) predicted the placebo-controlled change in treadmill exercise time following PCI (90). Conversely, within the present study, baseline
physiological stenosis severity was predictive of the improvement in exercise time following PCI. This was most seen with iFR (R=-0.51, p=0.02), however, an association was also noted with FFR (R=-0.42, p=0.06).

A number of reasons may explain this difference. Primarily, in ORBITA, patients were blinded as to whether they had received PCI or not. In contrast, in the present study, all patients were aware they had undergone successful PCI, and therefore may have had the greatest willingness to exert themselves maximally.

Second, patients in the present study were recruited from routine clinical coronary angioplasty waiting lists, without a pre-PCI protocol-mandated medical optimisation phase. Accordingly, at the time of revascularisation, the number of anti-anginal medications per patient were significantly fewer (1.4 ± 0.7 per patient) than in ORBITA (2.9 ± 1.1 per patient).

Last, the timing and mode of exercise testing was different between the two studies. In the present study post-PCI exercise testing was performed on a supine ergometer immediately following PCI. Conversely, within ORBITA, exercise treadmill testing was performed at six weeks post-PCI. Although speculative, it is possible that the relationship between coronary physiology and functional performance is strongest when assessed in immediate succession.

5.5.3 FFR, iFR and angina-limited exercise capacity – underlying physiological mechanisms

Exercise is the most important physiological stimulus for increased myocardial oxygen demand (85). Because the extraction of oxygen is already near maximal in the resting state, the increase in myocardial oxygen demand during exercise must principally be met by the augmentation of coronary blood flow (85).
The ability to increment flow during exercise is critically dependent on the vasodilator capacity of the microcirculation (87). In the absence of a hemodynamically significant coronary stenosis, this increase in flow is predominantly achieved by a large reduction in microvascular resistance (87). However, in the presence of a severe epicardial stenosis, in order to preserve resting coronary flow, vasodilatation of the microcirculation is enacted even at rest (39, 94). Accordingly, there is a reduced capacity of the microcirculatory bed to vasodilate during exercise and coronary flow is unable to meet the increase in myocardial oxygen demand.

By respectively quantifying the trans-stenotic pressure ratio during maximal hyperemia or the wave-free period of diastole at rest, both FFR and iFR provide coronary pressure-based estimates of flow. Figure 5.05 demonstrates that regardless of the method used, both FFR (R=0.69 [95% CI 0.24-0.82], p=0.003) and iFR (R=0.71 [0.41-0.87], p<0.001) positively correlate with coronary flow velocity measured during peak physical exercise at the onset of angina symptoms. This novel observation provides mechanistic understanding for the predictive capability of coronary pressure-based FFR and iFR to determine angina-limited exercise capacity.

5.5.4 Clinical implications

These findings further highlight the inadequacy of anatomical stenosis severity to accurately determine the hemodynamic (and functional) significance of a coronary stenosis. Compared to anatomy alone, coronary physiology provides superior ischemia detection (95), improved clinical patient outcomes when used to guide myocardial revascularisation (33) and, as demonstrated in the present study, a tool potentially capable of predicting the improvement in exercise capacity post-PCI in clinically representative settings (Figure 5.06).
5.6 Limitations

To avoid duplication, I will highlight only the limitations that are specific to this Chapter.

Intracoronary flow measurements are technically more demanding to perform than intracoronary pressure measurements. Therefore, compared to coronary pressure-based measurements, coronary flow-based measurements are potentially subject to a higher degree of measurement error. In theory, this may negatively bias the relationship between angina-limited exercise capacity and HSR/CFR as compared to angina-limited exercise capacity and FFR/iFR. However, all operators performing intracoronary flow measurements were well experienced in the technique and only high-quality Doppler flow data were included for analysis (Online video 1).

Lastly, this study did not blind patients to the presence of PCI. Following the results of the ORBITA trial (96), the first double-blind, placebo-controlled trial of PCI for stable angina, it is clear that functional improvement following PCI is mediated by a combination of physical and psychological effects. In the present unblinded study, the observed improvement in exercise time post-PCI must be considered to be inclusive of a placebo effect from the procedure itself. However, our study design mirrors that of routine clinical practice, where patients are aware they have undergone PCI.
5.7 Conclusions

In patients with stable angina and severe single-vessel coronary artery disease, physiological stenosis severity quantified by FFR, iFR, HSR or CFR predicted angina-limited exercise time. Conversely, no relationship was demonstrated between anatomical stenosis severity and functional exercise capacity. Physiological stenosis severity further predicted the improvement in exercise capacity observed following PCI. This relationship was most evident with baseline iFR and ΔiFR.

5.8 Chapter Synthesis

In this Chapter I assessed the relationship between FFR, iFR, HSR, CFR and angina-limited exercise time and whether any of these indices were capable of predicting the change in maximal exercise time following PCI.

My findings demonstrated that in patients with stable coronary artery and severe, single-vessel stenosis, clinically used indices of physiological stenosis severity predicted angina-limited exercise time. Interestingly, despite incorporating measurements of coronary flow velocity, CFR and HSR did not demonstrate superior relationships with angina-limited exercise time compared to coronary pressure-based FFR or iFR. Indeed, the numerically strongest correlation between physiological index value and angina-limited exercise time was demonstrated with iFR. Furthermore, immediately following PCI, both baseline iFR and ΔiFR predicted the improvement in exercise time.

I further investigated the mechanism by which coronary pressure-based FFR and iFR predicted angina-limited exercise time. This was performed by correlating baseline FFR and iFR against peak exercise coronary flow velocity, measured at the onset of angina symptoms. Positive correlations were identified for both FFR (R=0.69 [95% CI 0.24-0.82],...
p=0.003) and iFR (R=0.71 [0.41-0.87], p<0.001). Accordingly, this novel observation demonstrated the ability of both hyperemic and resting coronary pressure-based measurements to accurately inform about exercise coronary flow hemodynamics.

During the conduct of this study, I recruited a patient where the FFR (0.80) and iFR (0.98) values disagreed on the hemodynamic classification of physiological stenosis severity – so called FFR+/iFR- discordance. Discordance between FFR and iFR is frequently encountered in clinical practice, often presenting a diagnostic dilemma to the physician. Owing to the availability of combined coronary pressure and flow recordings within the present study, I was able to determine that the CFR in this patient with FFR+/iFR- discordance was normal (CFR 2.8).

This observation, that suggested that FFR/iFR discordance may be explained by differences in CFR, prompted me to investigate the physiological mechanism of FFR/iFR discordance further. In order to do this, I needed to use a larger collection of combined coronary pressure and flow measurements than was provided by the current exercise experiment dataset, where only a single case of FFR/iFR discordance was encountered.

In the following Chapter, by analysing data from the largest collection of combined coronary pressure and flow measurements currently available (94), I aim to determine the coronary flow characteristics of stenoses classified as discordant by FFR and iFR coronary pressure-based methods. Specifically, I test my hypothesis that FFR/iFR discordance was explained by differences in hyperemic coronary flow velocity.
Table 5.01: Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.6 (8.1)</td>
</tr>
<tr>
<td>Male</td>
<td>21 (91%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>LVEF &lt; 40%</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CCS class</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>II</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>III</td>
<td>13 (57%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>Statin</td>
<td>22 (96%)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>CCB</td>
<td>9 (39%)</td>
</tr>
</tbody>
</table>

PCI indicates percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society; bpm, beats per minute; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.
### Table 5.02: Overall anatomical and physiological stenosis characteristics

<table>
<thead>
<tr>
<th>Target vessel (LAD/Cx/RCA)</th>
<th>14/5/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis location (proximal/mid/distal)</td>
<td>13/8/2</td>
</tr>
<tr>
<td>Diameter stenosis by QCA</td>
<td>74.6% (10.4)</td>
</tr>
<tr>
<td>Stenosis length (mm)</td>
<td>10.7 (3.9)</td>
</tr>
<tr>
<td>FFR</td>
<td>0.54 (0.44 - 0.72)</td>
</tr>
<tr>
<td>iFR</td>
<td>0.53 (0.38 - 0.83)</td>
</tr>
<tr>
<td>CFR</td>
<td>1.35 (1.11 - 1.63)</td>
</tr>
<tr>
<td>HSR</td>
<td>1.67 (0.84 - 3.16)</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>23 (8.3)</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.4 (0.5)</td>
</tr>
<tr>
<td>Stent post-dilatation</td>
<td>83% (19/23)</td>
</tr>
<tr>
<td>FFR post-PCI</td>
<td>0.91 (0.85 - 0.96) *</td>
</tr>
<tr>
<td>iFR post-PCI</td>
<td>0.98 (0.94 - 0.99) *</td>
</tr>
<tr>
<td>CFR post-PCI</td>
<td>2.73 (2.50 - 3.12) *</td>
</tr>
<tr>
<td>HSR post-PCI</td>
<td>0.16 (0.06 - 0.37) *</td>
</tr>
<tr>
<td>ΔFFR</td>
<td>0.34 (0.21 - 0.42) *</td>
</tr>
<tr>
<td>ΔiFR</td>
<td>0.25 (0.09 - 0.54) *</td>
</tr>
<tr>
<td>ΔCFR</td>
<td>1.28 (0.74 - 1.50) *</td>
</tr>
<tr>
<td>ΔHSR</td>
<td>-1.37 (-2.38 - -2.08) *</td>
</tr>
</tbody>
</table>

Values are n, mean ± SD, median (IQR) or n (%). LAD indicates left anterior descending; Cx, circumflex; RCA, right coronary artery; QCA, quantitative coronary angiography; mm, millimetre; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; CFR, coronary flow reserve; HSR, hyperemic stenosis resistance; PCI, percutaneous coronary intervention. *Significant difference pre versus post-PCI, p<0.0001.
<table>
<thead>
<tr>
<th>Vessel</th>
<th>Proximal stenosis location</th>
<th>Diameter stenosis by QCA</th>
<th>FFR</th>
<th>CFR</th>
<th>ΔFFR</th>
<th>ΔCFR</th>
<th>ΔHSR</th>
<th>ΔIS</th>
<th>ΔIFR</th>
<th>ΔAFR</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>64% (8/14)</td>
<td>0.50</td>
<td>0.49</td>
<td>1.43</td>
<td>1.65</td>
<td>0.69</td>
<td>0.94</td>
<td>0.37</td>
<td>2.73</td>
<td>0.32</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>72.2% (11/13)</td>
<td>0.79</td>
<td>0.83</td>
<td>1.22</td>
<td>1.63</td>
<td>0.90</td>
<td>0.67</td>
<td>0.30</td>
<td>3.38</td>
<td>0.42</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>64% (8/14)</td>
<td>0.64</td>
<td>0.64</td>
<td>1.22</td>
<td>1.61</td>
<td>0.90</td>
<td>0.67</td>
<td>0.30</td>
<td>3.38</td>
<td>0.42</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>74.5% (5/8)</td>
<td>0.79</td>
<td>0.64</td>
<td>1.22</td>
<td>1.61</td>
<td>0.90</td>
<td>0.67</td>
<td>0.30</td>
<td>3.38</td>
<td>0.42</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>64% (8/14)</td>
<td>0.29</td>
<td>0.29</td>
<td>1.22</td>
<td>1.61</td>
<td>0.90</td>
<td>0.67</td>
<td>0.30</td>
<td>3.38</td>
<td>0.42</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>84.5% (7/3)</td>
<td>0.60</td>
<td>0.60</td>
<td>1.22</td>
<td>1.61</td>
<td>0.90</td>
<td>0.67</td>
<td>0.30</td>
<td>3.38</td>
<td>0.42</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values are n, mean ± SD, median (IQR) or n (%). All abbreviations as per Table 2.
Table 5.04: Univariate linear regression of baseline characteristics and anatomical stenosis characteristics on angina-limited exercise time.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-2.27</td>
<td>-6.5 – 1.94</td>
<td>0.27</td>
</tr>
<tr>
<td>Male</td>
<td>32.3</td>
<td>-88.5 – 153</td>
<td>0.58</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-48.8</td>
<td>-215 – 118</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-24.8</td>
<td>-94.1 – 44.6</td>
<td>0.47</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>-19.3</td>
<td>-93.3 – 54.7</td>
<td>0.59</td>
</tr>
<tr>
<td>History of smoking</td>
<td>-13.4</td>
<td>-83.4 – 56.6</td>
<td>0.70</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>-62.1</td>
<td>-160 – 35.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Number of antianginal medications</td>
<td>-3.84</td>
<td>-59.2 – 51.5</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Anatomical stenosis characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>3.93</td>
<td>-76.0 – 83.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Stenosis diameter (%)</td>
<td>-0.68</td>
<td>-4.05 – 2.70</td>
<td>0.68</td>
</tr>
<tr>
<td>Stenosis length (mm)</td>
<td>0.93</td>
<td>-8.56 – 9.28</td>
<td>0.93</td>
</tr>
</tbody>
</table>

\( ET_{\text{angina}} \) indicates the change in exercise time following PCI. All abbreviations as per Table 1.
Table 5.05: Univariate linear regression of physiological stenosis characteristics on angina-limited exercise time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate predictors of ET&lt;sub&gt;angina&lt;/sub&gt;</th>
<th>Multivariate predictors of ET&lt;sub&gt;angina&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>FFR</td>
<td>226</td>
<td>59.5 – 393</td>
</tr>
<tr>
<td>iFR</td>
<td>198</td>
<td>97.2 – 299</td>
</tr>
<tr>
<td>HSR</td>
<td>-17.4</td>
<td>-28.6 – -6.21</td>
</tr>
<tr>
<td>CFR</td>
<td>44.7</td>
<td>0.21 – 91.7</td>
</tr>
</tbody>
</table>

All abbreviations as per Table 2
Figure 5.01: FFR, iFR, HSR and CFR values before and after PCI
Boxplots of FFR (red), iFR (blue), HSR (green) and CFR (grey) before and after PCI. The horizontal black line indicates the mean value. The horizontal black line indicates the median value. The box indicates the inter quartile range and the whiskers indicate the range of values. FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; HSR, hyperemic stenosis resistance; CFR, coronary flow reserve. * p<0.0001.
Figure 5.02: The relationship between angina-limited exercise time and baseline FFR, iFR, HSR and CFR value

Scatter plots of the relationship between angina-limited exercise time ($E_{\text{angina}}$) and FFR (red), iFR (blue), HSR (green) and CFR (grey) value. All abbreviations as per Figure 1.
Figure 5.03: The relationship between the change in exercise time following PCI and baseline FFR, iFR, HSR and CFR value

Scatter plots of the relationship between the change in exercise time following PCI (ΔET) and FFR (red), iFR (blue), HSR (green) and CFR (grey) value. All abbreviations as per Figure 1.
Figure 5.04: The relationship between the change in exercise time and the change in FFR, iFR, HSR and CFR value following PCI

Scatter plots of the relationship between the change in exercise time following PCI (ΔET) and ΔFFR (red), ΔiFR (red), ΔHSR (green) and ΔCFR (grey) value. All abbreviations as per Figure 1.
Figure 5.05: The relationship between FFR, iFR and peak-exercise coronary flow velocity

Scatter plots of the relationship between peak-exercise coronary flow velocity, FFR (red) and iFR (blue). All abbreviations as per Figure 1.
Figure 5.06: Anatomical versus physiological coronary stenosis assessment
Schematic illustration of the differences between anatomical versus physiological coronary stenosis assessment in patients with stable angina.

This Chapter is part of the following publication:

Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance in Angiographically Intermediate Coronary Stenoses

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6.1 Abstract

6.1.1 Background

Discordance between FFR and iFR occurs in up to 20% of clinical cases of physiological stenosis assessment. The underlying physiological mechanism to explain FFR/iFR discordance is unclear. Specifically, no comparisons have been reported between the coronary flow characteristics of FFR/iFR discordant stenoses and unobstructed angiographic control vessels. The aim of this study was to determine the coronary flow characteristics of stenoses classified as discordant by FFR and iFR coronary pressure-based methods.

6.1.2 Methods

Baseline and hyperemic coronary flow velocity (cm/s) and coronary flow reserve (CFR) were compared across five vessel groups: FFR+/iFR+ (108 vessels, 91 patients), FFR-/iFR+ (28 vessels, 24 patients), FFR+/iFR- (22 vessels, 22 patients), FFR-/iFR- (208 vessels, 154 patients) and an unobstructed vessel group (201 vessels, 153 patients), in a post-hoc analysis of the largest combined pressure and Doppler flow velocity registry (IDEAL).

6.1.3 Results

FFR disagreed with iFR in 14% (50/366) Baseline flow velocity was similar across all five vessel groups, including the unobstructed vessel group (p=0.34 for variance). In FFR+/iFR- discordants, hyperemic flow velocity and CFR were similar to both FFR-/iFR- and unobstructed groups; 37.6cm/s (26.1 to 50.4) versus 40.0cm/s (29.7 to 52.3) and 42.2cm/s (33.8 to 53.2) and CFR 2.36 (1.93 to 2.81) versus 2.41 (1.84 to 2.94) and 2.50 (2.11 to 3.17), respectively (p>0.05 for all). In FFR-/iFR+ discordants, hyperemic flow velocity and CFR were similar to the FFR+/iFR+ group; 28.2cm/s (20.5 to 39.7) versus 23.5cm/s (16.4 to 34.9) and CFR 1.44 (1.29 to 1.85) versus 1.39 (1.06 to 1.88), respectively (p>0.05 for all).
6.1.4 Conclusions

FFR/iFR disagreement was explained by differences in hyperemic coronary flow velocity. Furthermore, coronary stenoses classified as FFR+/iFR- demonstrated similar coronary flow characteristics to angiographically unobstructed vessels.
6.2 Introduction

In determining the physiological significance of a coronary stenosis, the Fractional Flow Reserve (FFR) and instantaneous wave-Free Ratio (iFR) both quantify the trans-stenotic pressure ratio as a surrogate measure of coronary flow. FFR is measured under conditions of maximal pharmacological hyperemia (22) whereas iFR is measured in the resting state (97).

In up to 20% of cases, FFR and iFR disagree upon the functional significance of a stenosis (98). The recently reported DEFINE FLAIR (51) and iFR SWEDEHEART (52) trials demonstrated in over 4500 patients that iFR was noninferior to revascularisation guided by FFR with respect to major adverse cardiac events (MACE) at 1 year. Furthermore, patient-level pooled meta-analysis of both trials demonstrated significantly less revascularisation based on iFR versus FFR interrogation, but similar MACE in the both FFR and iFR deferred populations (99). This combination of findings have lead some to question whether, in comparison to iFR, FFR overestimates the true flow-limiting potential of angiographically intermediate coronary stenoses.

In this Chapter I perform a post-hoc analysis of stenosis classification discordance between FFR and iFR using combined coronary pressure-and-flow measurements from the multicentre IDEAL registry on coronary physiology (42). My aim is to determine the coronary flow characteristics of stenoses classified as discordant by FFR and iFR with comparison to an angiographically unobstructed vessel group.
6.3 Methods

6.3.1 Study population

This post-hoc analysis included a total of 567 vessels (301 patients), comprising 366 stenosed vessels (291 patients) and 201 unobstructed vessels (153 patients), as part of the Iberian–Dutch–English collaborators (IDEAL) dataset (42). IDEAL is the largest international, multicentre, nonrandomized, prospective analysis in patients with coronary artery disease undergoing physiological lesion assessment by combined pressure (FFR and iFR) and Doppler flow velocity measurements. All patients recruited were scheduled for elective coronary angiography with physiological stenosis assessment by FFR and gave written informed consent for acquisition of additional physiological data for study purposes. Stenosed vessels were defined as vessels that had an angiographically visible stenosis between 40-70% severity, as determined visually by the operating physician at the time of coronary angiography. Unobstructed vessels were defined as vessels with a complete absence of any angiographically visible stenosis. As part of the original IDEAL study protocol, all angiogram cines were reviewed and adjudicated by two independent assessors to ensure compliance with the aforementioned definitions (42).

Exclusion criteria were limited to severe valvular heart disease, acute myocardial infarction within 48 hours, previous coronary artery bypass surgery, vessels with angiographically identifiable myocardial bridging or collateral arteries and vessels with a previous myocardial infarction.

6.3.2 Coronary catheterisation and Measurement of Physiologic Indices

Physiological measurements of coronary stenoses were performed according to the existing IDEAL study protocol (42). Briefly, for pressure-based measurements the pressure sensor was first zeroed and equalized to aortic pressure, before being positioned at least 3 vessel
diameters distal to the stenosis and a recording of the baseline distal coronary and aortic pressures obtained. Adenosine was administered by intravenous infusion in 234 measurements (140 mcg/kg/min) and by intracoronary bolus injection in 333 measurements (60–150 mcg).

FFR was calculated as the ratio of mean distal coronary artery pressure to mean aortic pressure across the whole cardiac cycle during hyperemia. iFR was calculated as the mean pressure distal to the stenosis divided by the mean aortic pressure during the wave-free period of diastole.

Intracoronary nitrates (200–300 mcg) were administered in all cases prior to performing any physiological measurement. Resting indices were calculated at a time of stability, allowing for a return to stable baseline conditions after any preceding injection of contrast or saline. Hyperemic indices were calculated during stable hyperemia, excluding ectopy and conduction delay.

Significant drift was defined as ± 2mmHg (100) after pullback of the pressure wire transducer into the guiding catheter. If pressure drift was identified, measurements were repeated or corrected for upon analysis.

For flow-based measurements, Doppler signals were optimized carefully to ensure adequate tracking profiles were observed. Electrocardiogram (ECG), pressures, and flow velocity signals were directly extracted from the device console (ComboMap, Volcano Corporation, San Diego, CA, USA). Data were analysed off-line, using a custom software package designed with MATLAB (Mathworks, Inc, Natick, MA, USA). The calculations for the physiology indices used in the study are shown in Table 6.01.
6.3.3 Comparison of coronary flow characteristics between groups

Established cut-off values of pressure-derived physiologic indices (FFR ≤ 0.80 (33) and iFR ≤ 0.89 (101)) were used to dichotomize stenoses into concordantly classified (FFR+/iFR+ and FFR-/iFR-) and discordantly classified (FFR+/iFR- and FFR-/iFR+) groups. Baseline coronary flow velocity (cm/s), hyperemic coronary flow velocity (cm/s) and coronary flow reserve were compared across these groups, as well as in the unobstructed vessel group.

6.3.4 Statistical analysis

Categorical data were expressed as numbers and percentages, while continuous data were expressed as mean (± standard deviation) or median (inter quartile range) as appropriate. Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were compared with Student t or Mann-Whitney U tests, and categorical variables with chi-square or Fisher exact tests, as appropriate. Differences across the groups were compared with the Kruskal-Wallis H test, followed by post-hoc Mann-Whitney U tests with Bonferroni correction. Cohen’s kappa coefficient was used to assess agreement between dichotomous variables. Applicable tests were 2 tailed and p < 0.05 was considered statistically significant. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).
6.4 Results

6.4.1 Study population

A total of 366 stenosed vessels and 201 unobstructed vessels were derived from a total study population of 301 patients (age 60.6 ± 9.6 years old, 69% male, Table 6.02). The patient characteristics of the FFR/iFR discordant vessel groups are summarized in Table 6.03. In comparison to the FFR+/iFR- group, the FFR-/iFR+ group demonstrated a significantly higher prevalence of diabetes (p=0.03).

6.4.2 Stenosis and hemodynamic characteristics

The stenosis and hemodynamic characteristics of all groups are summarized in Table 6.04. In the stenosed vessel group, median physiological values were 0.85 (0.74 to 0.91) for FFR, 0.93 (0.84 to 0.97) for iFR and 1.99 (1.44 to 2.62) for CFR. In the unobstructed group, median CFR was 2.50 (2.10 to 3.17). The distributions of FFR, iFR and CFR values for the stenosed vessel group are shown in Figure 6.01.

6.4.3 Relationships between FFR and iFR

Figure 6.02 shows the scatter plot between FFR and iFR pressure-only indices of stenosis severity. The correlation coefficient between FFR versus iFR was \( r=0.89 \) (95% CI for the estimated correlation coefficient 0.86 to 0.90; \( p<0.0001 \)). In total, FFR agreed with iFR in 86% (316/366) of stenosed vessels, comprising 108 FFR+/iFR+ and 208 FFR-/iFR- cases. FFR disagreed with iFR in 14% (50/366) of stenosed vessels, comprising of 22 FFR+/iFR- and 28 FFR-/iFR+ discordant cases (Figure 6.02). Cohen’s kappa coefficient between FFR and iFR categorization was 0.71 (\( p<0.001 \)). Agreement between iFR and CFR was superior
compared to the agreement between FFR and CFR, as demonstrated by a Cohen’s Kappa coefficient of 0.47 (p<0.001) versus 0.30 (p<0.001), respectively.

6.4.4 Comparisons of baseline flow velocity, hyperemic flow velocity and coronary flow reserve

Boxplots demonstrating the variations in i) baseline and hyperemic flow velocity; and ii) coronary flow reserve according to FFR and iFR classification are shown in Figure 6.03 and Figure 6.04, respectively. Data from the unobstructed vessel group are also displayed.

Baseline coronary flow velocity was similar across all groups (p=0.34 for variance), with a median cross-population value of 16.6 cm/s (12.6 to 22.06) (Figure 6.03a). As would be expected, hyperemic coronary flow velocity was significantly lower in FFR+/iFR+ concordantly positive versus FFR-/iFR- concordantly negative and unobstructed groups; 23.5 cm/s (16.4 to 34.9) versus 40.0 cm/s (29.7 to 52.3) and 42.2 cm/s (33.8 to 53.2), respectively (p<0.001 for both comparisons) (Figure 6.03b). Accordingly, CFR was significantly lower in FFR+/iFR+ concordantly positive versus FFR-/iFR- concordantly negative and unobstructed groups; CFR 1.39 (1.06 to 1.88) versus 2.41 (1.84 to 2.94) and 2.50 (2.10 to 3.17), respectively (p<0.001 for both comparisons) (Figure 6.04).

For stenoses discordantly classified as positive by FFR and negative by iFR (FFR+/iFR-), no significant difference in hyperemic coronary flow velocity was observed in comparison with the FFR-/iFR- concordantly negative and unobstructed vessel groups; 37.6 cm/s (26.1 to 50.4) versus 40.0 cm/s (29.7 to 52.3) and 42.2 (33.8 to 53.2), respectively (p=0.12) (Figure 6.03b). Similarly, no significant difference was found in CFR between FFR+/iFR- stenoses and FFR-/iFR- concordantly negative and unobstructed vessel groups; 2.36 (1.93 to 2.81) versus 2.41 (1.84 to 2.94) and 2.50 (2.11 to 3.17), respectively (p=0.08) (Figure 6.04).
For stenoses discordantly classified as negative by FFR and positive by iFR (FFR-/iFR+), hyperemic coronary flow velocity and CFR were similar to the FFR+/iFR+ concordantly positive group; 28.2 cm/s (20.5 to 39.7) versus 23.5 cm/s (16.4 to 34.9) and 1.44 (1.29 to 1.85) versus 1.39 (1.06 to 1.88), respectively (p=0.09 and p=0.46, respectively).
6.5 Discussion

The main findings of this Chapter were as follows. First, differences in stenosis classification between FFR and iFR were explained by differences in hyperemic coronary flow velocity. Second, in comparison to patients with FFR+/iFR- discordant stenoses, patients with FFR-/iFR+ discordant stenoses had a significantly higher prevalence of diabetes. Last, stenoses discordantly classified as FFR+/iFR- demonstrated similar non-flow-limiting characteristics to angiographically unobstructed vessels.

6.5.1 Revascularisation guided by ischemia - flow is more important than pressure

Blood flow down the coronary arteries facilitates oxygen delivery and removal of waste metabolites from respiring myocardial cells. If this flow of blood is impeded by a coronary stenosis, supply-demand mismatch can occur, leading to myocardial ischemia and the onset of the symptoms of angina (98, 99). Positron emission tomography and stress echocardiography with Doppler assessment of coronary flow velocity all provide non-invasive measures of coronary flow. However, invasive measures of coronary flow are not routinely performed in clinical practice. Factors that contribute to this are that invasive coronary flow measurements are technically more challenging and time consuming to perform than intracoronary pressure measurements. For these reasons, despite the physiological importance of measuring intracoronary flow, the hemodynamic impact of a stenosis is most routinely assessed using pressure-based indices such as FFR and iFR.

6.5.2 The relationship between coronary pressure and flow

In order to understand the physiological mechanisms that underpin discordance between hyperemic (FFR) and non-hyperemic (iFR) pressure-only indices of stenosis severity, combined coronary pressure-and-flow measurements are required. The relationship
between pressure loss due to a stenosis ($\Delta P$) and arterial flow velocity ($V$) is related by the equation, $\Delta P = FV + S V^2$, where $F$ is the coefficient of pressure loss due to viscous friction in the stenotic segment and $S$ is the coefficient of pressure loss due to flow separation at the diverging end of the stenosis (104).

Therefore, if arterial flow velocity ($V$) increases by a large amount during hyperemia, the trans-stenotic pressure gradient ($\Delta P$) also increases. In this scenario, the $Pd$ value falls and the resultant FFR value is low; categorizing the stenosis as functionally significant despite demonstrably high coronary flow conditions (Figure 6.05).

Observations regarding this form of coronary pressure/flow mismatch are abundant in the literature (50, 77, 105–108) and date back to the very earliest days of coronary physiological assessment (25). However, the observations made in my study provide new evidence demonstrating that in angiographically intermediate stenoses classified as FFR positive but iFR negative, the flow characteristics are similar to angiographically unobstructed vessels. Furthermore, in stenoses classified as FFR negative but iFR positive, the flow characteristics are similar to FFR+/iFR+ concordantly positive cases.

Within this study cohort, these findings suggest that when FFR/iFR discordance occurs, the true hyperemic flow-limiting potential of a stenosis is more accurately discernible by the iFR rather than the FFR measurement. Although iFR categorisation in isolation cannot be used to fully determine coronary flow characteristics, in cases of FFR/iFR discordance, the FFR categorisation is inversely related to hyperemic flow velocity, coronary flow reserve and the prevalence of diabetes. In the FFR-/iFR+ discordant group, the association of low CFR and high prevalence of diabetes may reflect the attenuating influence of microvascular disease on adenosine-mediated vasodilatation. Conversely, in the FFR+/iFR- discordant group, the association of high CFR and low prevalence of diabetes may reflect the effect of profound adenosine-mediated vasodilatation in healthy microcirculations.
6.5.3 Discordance in stenosis classification by FFR and iFR—clinical perspectives and implications

The present study provides physiological observations that can be useful to interpret the result of large clinical trials comparing iFR and FFR. In the RESOLVE study (98), FFR and iFR disagreed upon the functional significance of an epicardial stenosis in approximately 20% of cases (98). More recently, Kobayashi et al reported that discordance between FFR and iFR was observed more frequently in left main or proximal left anterior descending artery lesions compared to other lesions (105). Therefore, discordance between hyperemic and resting indices is a common and important clinical finding, particularly as it occurs most frequently in vessels with the largest myocardial territories at stake.

The DEFINE FLAIR (51) and iFR SWEDEHEART (52) studies demonstrated in over 4500 patients that iFR was noninferior to revascularisation guided by FFR with respect to major adverse cardiac events (MACE) at 1 year. Based on these two studies and the demonstrated quicker procedure time and decreased incidence of unpleasant patient side effects, iFR has recently been proposed as the preferred pressure-based index for the assessment of angiographically intermediate severity, stable coronary lesions (110). A further observation from the trials was that despite significantly less revascularisation being performed based on iFR versus FFR interrogation, similar major adverse cardiac event rates were demonstrated in both FFR and iFR deferred populations (95) The findings of the present study do not extend to direct predictions of patient outcome, but do provide a possible mechanism to explain the higher revascularisation rate associated with FFR.
6.6 Limitations

In this study, discordance was identified by differences in functional classification determined according to a single binary cut point value. Although myocardial ischemia must surely be a continuum, the use of binary cutpoints to distinguish hemodynamic significance from non-significance is ubiquitous in the literature, clinical outcome trials (33, 51, 52, 111) and revascularisation and appropriate use criteria guidelines (7, 9, 112). This largely reflects the necessary design of clinical outcome trials, where revascularisation decision-making must be standardised according to binary values. However, in clinical practice, the strict use of cutpoints may not be most appropriate.

The total number of discordant stenoses from the IDEAL study was relatively small. However, the IDEAL study represents the largest collection of patients with coronary artery disease undergoing physiological lesion assessment by combined pressure-and-flow measurements. The requirements for statistical analysis for differences between hyperemic flow velocity and CFR between groups were satisfied by the sample size. However, a larger number of discordant lesions may have permitted additional statistical power to determine if vessel type or stenosis location influences discordance between FFR and iFR (as has been demonstrated in larger (pressure-only) datasets (109)).

In the FFR+/iFR- discordant group, the median FFR was 0.77 (0.74-0.80). Some readers may consider these to represent ‘gray zone’ FFR values. Although no gray zone is incorporated into coronary revascularisation guidelines (7, 9), clinicians do often apply a diagnostic gray zone in their practice in order to provide individualised patient decision-making. In such circumstances, readers may contest that additional information is required for 0.75 to 0.80 FFR values to be considered truly flow-limiting. In that regard, the direct measurement of intracoronary flow has been advocated (89), or as this study demonstrates,
in cases of FFR/iFR discordance, the iFR classification alone appears able to accurately determine the hyperemic flow-limiting potential of a coronary stenosis.

In this study, coronary flow reserve was used as the reference method for the determination of flow limitation of an angiographically intermediate coronary stenosis (Figure 6.04). Although many consider CFR ≤2 to be indicative of myocardial ischemia, there is no universal normal value for CFR. Whether this level of CFR is adequate for some patients who still have ischemic responses despite CFR >2 remains a possibility. Mindful of these limitations to the use of CFR as a reference method, the inclusion of an unobstructed vessel group provides a clinically meaningful comparator of normality, given that the angiographic appearance of a vessel during coronary angiography is the first step in the clinical decision-making process for the identification of ischemia (with a view to percutaneous coronary intervention). Furthermore, any potential criticism of using a ratio of coronary flow velocities to determine flow limitation are not founded in this dataset, as baseline flow velocities across all groups were comparable, including the unobstructed vessel group.

Lastly, in keeping with a previous large-scale study of discordance between hyperemic and resting pressure indices (77), the statistical unit of our analysis was vessels rather than patients. Accordingly, there is a potential for both statistical and biological interaction for different vessels analysed within the same patient. However, across both the FFR-/iFR+ and FFR+/iFR- discordant groups, all but 4 vessels were from individual patients, and no patient contributed more than one vessel to both discordant groups. In order to permit a per-patient analysis, patients with more than one stenosis would need to be excluded, or alternatively, only one of the vessels selected for analysis. Either measure might risk the introduction of bias as well as limit the power of the study. Furthermore, an analysis of only one vessel per patient does not reflect real-world experience, where treating physicians make revascularisation decisions on the vessel rather than patient level.
6.7 Conclusion

Stenoses classified as discordant by FFR and iFR could be rationalised by differences in hyperemic coronary flow velocity and CFR. Specifically, in comparison to FFR-/iFR+ discordant cases, FFR+/iFR- discordant cases were associated with higher hyperemic coronary flow velocity and CFR, and a lower prevalence of diabetes. Additionally, coronary stenoses discordantly classified as FFR+/iFR- demonstrated similar coronary flow characteristics to angiographically unobstructed vessels.
**Table 6.01: Definition of Physiological Indices**

<table>
<thead>
<tr>
<th>( \text{Pa} )</th>
<th>Proximal (aortic) pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Pd} )</td>
<td>Distal (coronary) pressure (mmHg)</td>
</tr>
<tr>
<td>( \text{FFR} )</td>
<td>( \frac{\text{Pd}}{\text{Pa}} ) at whole-cycle hyperemia</td>
</tr>
<tr>
<td>( \text{iFR} )</td>
<td>( \frac{\text{Pd}}{\text{Pa}} ) at baseline iFR window</td>
</tr>
<tr>
<td>Baseline coronary flow velocity</td>
<td>Mean baseline whole-cycle coronary flow velocity (cm/s)</td>
</tr>
<tr>
<td>Hyperemic coronary flow velocity</td>
<td>Mean hyperemic whole-cycle coronary flow velocity (cm/s)</td>
</tr>
<tr>
<td>( \text{CFR} )</td>
<td>( \frac{\text{Whole cycle hyperemic flow velocity}}{\text{Whole cycle baseline flow velocity}} )</td>
</tr>
</tbody>
</table>
Table 6.02: Patient demographics and stenosis characteristics

<table>
<thead>
<tr>
<th></th>
<th>N or mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>301</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.6 (±9.6)</td>
</tr>
<tr>
<td>Male</td>
<td>209 (69%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>157 (52%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>172 (57%)</td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>128 (43%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67 (22%)</td>
</tr>
<tr>
<td>Chronic renal impairment</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>129 (43%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>34 (11%)</td>
</tr>
<tr>
<td>Impaired LV function EF &lt; 30%</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Stable angina</td>
<td>290 (96%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>11 (4%)</td>
</tr>
<tr>
<td><strong>Vessels</strong></td>
<td>567</td>
</tr>
<tr>
<td>Angiographically stenosed vessels</td>
<td>366</td>
</tr>
<tr>
<td>Patients contributing 1 vessel</td>
<td>228/291 (78%)</td>
</tr>
<tr>
<td>Patients contributing 2 vessels</td>
<td>51/291 (18%)</td>
</tr>
<tr>
<td>Patients contributing 3 vessels</td>
<td>12/291 (4%)</td>
</tr>
<tr>
<td>Angiographically unobstructed vessels</td>
<td>201</td>
</tr>
<tr>
<td>Patients contributing 1 vessel</td>
<td>118/153 (77%)</td>
</tr>
<tr>
<td>Patients contributing 2 vessels</td>
<td>22/153 (14%)</td>
</tr>
<tr>
<td>Patients contributing 3 vessels</td>
<td>13/153 (8%)</td>
</tr>
<tr>
<td><strong>Coronary artery</strong></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>277 (49%)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>172 (30%)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>118 (21%)</td>
</tr>
</tbody>
</table>

Values are n, mean (SD), or n (%). CAD = coronary artery disease, EF = ejection fraction.
Table 6.03: Study Population Characteristics of the FFR/iFR Discordant Vessel Groups

<table>
<thead>
<tr>
<th></th>
<th>FFR-/iFR+ vessel group</th>
<th>FFR+/iFR- vessel group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels</td>
<td>28</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>24</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58.3 (±11.1)</td>
<td>65 (9.69)</td>
<td>0.08</td>
</tr>
<tr>
<td>Male</td>
<td>62.5% (15/24)</td>
<td>81.8% (18/22)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.3% (14/24)</td>
<td>50% (11/22)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>66.7% (16/24)</td>
<td>63.6% (14/22)</td>
<td>0.83</td>
</tr>
<tr>
<td>History of smoking</td>
<td>12.5% (3/24)</td>
<td>36.3% (8/22)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41.7% (10/24)</td>
<td>13.6% (3/22)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>0% (0/24)</td>
<td>4.5% (1/22)</td>
<td>n/a</td>
</tr>
<tr>
<td>Previous MI</td>
<td>12.5% (3/24)</td>
<td>18.8% (4/22)</td>
<td>0.59</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>29.2% (7/24)</td>
<td>31.8% (7/22)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Values are % (n) or mean (SD). CVD = cardiovascular disease, MI = myocardial infarction.
Table 6.04: Studied Vessel Characteristics

<table>
<thead>
<tr>
<th></th>
<th>FFR+/iFR+</th>
<th>FFR-/iFR+</th>
<th>FFR+/iFR-</th>
<th>FFR-/iFR-</th>
<th>Unobstructed</th>
<th>P value for variance across groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vessels</strong></td>
<td>108</td>
<td>28</td>
<td>22</td>
<td>208</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>91</td>
<td>24</td>
<td>22</td>
<td>154</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td><strong>Stenosis characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis diameter (%)</td>
<td>62.1 (±17.8)</td>
<td>48.7 (±21.7)</td>
<td>46.4 (±15.8)</td>
<td>40 (±20.0)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Reference lumen diameter (mm)</td>
<td>2.79 (±0.9)</td>
<td>2.81 (±0.93)</td>
<td>3.11 (±0.77)</td>
<td>2.85 (±0.67)</td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Minimal lumen diameter (mm)</td>
<td>0.97 (±0.40)</td>
<td>1.42 (±0.81)</td>
<td>1.58 (±0.61)</td>
<td>1.67 (±0.72)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stenosis length (mm)</td>
<td>19.2 (±15.8)</td>
<td>17.6 (±13.1)</td>
<td>18.9 (±6.32)</td>
<td>16.5 (±12.5)</td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>79 (±24)</td>
<td>72 (±11)</td>
<td>73 (±17)</td>
<td>75 (±18)</td>
<td>76 (±21)</td>
<td>0.25</td>
</tr>
<tr>
<td>Baseline Pa (mmHg)</td>
<td>98.9 (±14.4)</td>
<td>94.0 (±17.7)</td>
<td>103 (±17.4)</td>
<td>100 (±14.7)</td>
<td>98.8 (±15.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Baseline Pd (mmHg)</td>
<td>75.3 (±18.2)</td>
<td>85.9 (±16.6)</td>
<td>99 (±18)</td>
<td>97.8 (±14.8)</td>
<td>97.2 (±15.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Pressure measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>0.63 (0.51-0.72)</td>
<td>0.86 (0.84-0.88)</td>
<td>0.77 (0.74-0.80)</td>
<td>0.91 (0.87-0.95)</td>
<td>0.97 (0.94-0.99)</td>
<td></td>
</tr>
<tr>
<td>iFR</td>
<td>0.93 (0.92-0.94)</td>
<td>0.88 (0.84-0.89)</td>
<td>0.92 (0.91-0.93)</td>
<td>0.97 (0.94-0.99)</td>
<td>0.98 (0.96-1.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Flow measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline flow (cm/s)</td>
<td>16.4 (11.3-23.4)</td>
<td>19.3 (12.9-26.8)</td>
<td>15.1 (12.6-19.5)</td>
<td>16.9 (13.0-21.6)</td>
<td>16.5 (12.6-21.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Hyperemic flow (cm/s)</td>
<td>23.5 (16.4-34.9)</td>
<td>28.2 (20.5-39.7)</td>
<td>37.6 (26.1-50.4)</td>
<td>40.0 (29.7-52.3)</td>
<td>42.2 (33.8-53.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CFR</td>
<td>1.39 (1.06-1.88)</td>
<td>1.44 (1.29-1.85)</td>
<td>2.36 (1.93-2.81)</td>
<td>2.41 (1.84-2.94)</td>
<td>2.50 (2.11-3.17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proportion with CFR &lt;2 (%)</td>
<td>81.5</td>
<td>85.7</td>
<td>73</td>
<td>32.7</td>
<td>18.9</td>
<td></td>
</tr>
</tbody>
</table>
Figure 6.01: Distribution of FFR, iFR, and CFR values for stenosed vessels
Frequency histograms reveal unimodal data distributions of FFR, iFR and CFR values in the stenosed vessel groups. The solid red line indicates the median value. The solid black line indicates the mean value.
Figure 6.02: Scatter plot showing the relationship between FFR and iFR
The black line represents the line of best fit. The curve is fitted by second-order polynomial. The gray lines represent the respective cutoff values for FFR (≤0.80) and iFR (≤0.89). Concordant cases are colored blue, discordant cases are colored red.
Figure 6.03: Boxplot comparisons of baseline and hyperemic coronary flow velocity
The horizontal black line indicates the median value. The box indicates the inter quartile range and the whiskers indicate the range of values. FFR+/iFR+ (n=108) cases are colored red. FFR-/iFR+ (n=28) and FFR+/iFR- (n=22) discordant cases are colored amber. FFR-/iFR- (n=208) cases are colored light green. Unobstructed reference vessel (n=201) cases are colored dark green. (A) Baseline coronary flow velocity was similar across all groups. (B) Hyperemic coronary flow velocity was similar in FFR+/iFR+ and FFR-/iFR+ groups. Hyperemic coronary flow velocity was similar in FFR+/iFR-, FFR-/iFR- and unobstructed reference vessel groups.
Figure 6.04: Boxplot comparisons of coronary flow reserve

The horizontal black line indicates the median value. The box indicates the inter quartile range and the whiskers indicate the range of values. CFR values ≤2 and >2 are colored red and green, respectively. CFR was significantly higher in the FFR+/iFR- versus FFR-/iFR+ discordant group (and similar to FFR-/iFR- and unobstructed reference vessel groups).
Figure 6.05: FFR+/iFR- discordance attributed to high coronary flow reserve – Clinical case

The coronary angiogram image displays a proximal circumflex (Cx) stenosis. QCA derived percentage diameter stenosis, area stenosis and minimal lumen diameter were 62%, 85% and 1.20mm, respectively. Invasive pressure-based coronary physiology assessment revealed discordant iFR (negative) and FFR (positive) results. Upon measuring combined coronary pressure-and-flow data, the FFR+/iFR- discordant result can be attributed to high coronary flow reserve.
7.0 Synthesis

This thesis investigated intracoronary hemodynamics in stable coronary artery disease during rest, adenosine hyperemia and maximal exercise stress; immediately before and after percutaneous coronary intervention.

In this series of studies, I have demonstrated that in patients with coronary stenosis, invasive hemodynamic responses were markedly different during adenosine versus physical exercise stress. Following this, I described the invasive hemodynamics of rate-limiting angina and demonstrated that PCI immediately normalised exercise hemodynamic responses across systemic, coronary and microvascular circulations. I then established that physiological indices of stenosis severity were capable of predicting angina limited exercise time and the improvement in exercise time following PCI. Lastly, I demonstrated that FFR/iFR discordance could be rationalised by differences in hyperemic coronary flow velocity and CFR.

In the following sections I synthesise these findings and present them in a clinical context relevant to the physiological stenosis assessment of stable coronary artery disease with FFR and iFR.

7.1 Challenging the rationale for hyperemic stress in coronary pressure-based stenosis assessment

The pathophysiology of myocardial ischemia has long been appreciated as the deficiency of coronary blood flow to meet myocardial oxygen demand (85). However, in clinical practice, to quantify ischemia and guide treatment decision-making, physiological stenosis
assessment is performed using coronary pressure. As explained in the Introduction to this thesis, this is a practical consideration based on the ease and reproducibility of performing coronary pressure measurements.

The accepted notion that coronary pressure can be used as a surrogate measure of flow is based on a landmark study by Pijls at el during the development and validation of FFR (22). Their work identified that when microvascular resistance was stable and minimal, a linear relation between perfusion pressure of the myocardium and blood flow was observed. In these early days of physiological stenosis assessment, in order to stabilise microvascular resistance, transient vasodilatation of the microcirculation using pharmacological agents (most commonly adenosine) was advocated. Subsequently, the need for vasodilatation of the microcirculation was deemed critical in order to permit hemodynamic stenosis assessment using coronary pressure.

Recently, this paradigm has been challenged by the introduction of iFR. By quantifying the trans-stenotic pressure ratio during a specific portion of diastole, where microvascular resistance has been demonstrated to be naturally stable (97), iFR permits pressure-based hemodynamic stenosis assessment without a need for pharmacological hyperemia. Since the introduction of iFR in 2012, multiple studies have been conducted that demonstrate equivalent diagnostic performance between FFR and iFR for ischemia detection (44, 46, 48–50). Furthermore, large prospective randomised clinical outcome trials have recently demonstrated the non-inferiority of iFR-guided compared to FFR-guided revascularisation (51, 52).

Notwithstanding the developing body of evidence supporting the use of iFR as a hyperemia-independent index of hemodynamic stenosis severity, pervasive arguments persist against the use of resting coronary pressure measurements to predict ischemia. Paramount among these is the belief that FFR may be the physiologically more representative index of
ischemia, owing to its measurement under conditions of maximal pharmacological stress - a condition believed to be similar to the vasodilation caused by physical activity (10).

Within this thesis I present novel data that challenges this commonly-held belief. Specifically, in patients with stable angina and coronary stenosis, hemodynamic responses recorded invasively during maximal adenosine versus maximal exercise stress were markedly different across systemic, coronary and microcirculatory circulations. These findings are additive to those of Lumley et al, who previously conducted the only other comparative assessment of invasive hemodynamics during adenosine versus exercise stress in asymptomatic, healthy controls without stenosis (62).

In summary, aside from its practical role in the stabilisation of microvascular resistance to facilitate FFR measurement, adenosine stress does not accurately replicate physical stress conditions during physiological stenosis assessment. In view of this, and the clinical availability to measure coronary pressure during a period of the cardiac cycle where microvascular resistance is naturally stable (97), the rationale for pharmacological stress in coronary pressure-based physiological stenosis assessment is questioned (114).

7.2 Challenging the notion that hyperemia is required to ‘unmask’ true stenosis severity

Proponents of pharmacological hyperemia additionally question the ability of resting coronary pressure measurements to inform about coronary flow hemodynamics during physical activity – a criterion for the diagnosis of chest pain of cardiac origin (8). Examples of this are common in the literature, where the presence of maximal hyperemia is considered a requirement to ‘unmask’ the true severity of a coronary stenosis (115–117). In these situations, the term ‘unmasking’ appears apt, because often it may only be the hyperemic
FFR measurement that indicates ischemia, while other tests such as the resting pressure measurements, non-invasive ischemia tests or anatomical quantifications of angiographic severity suggest hemodynamic insignificance of the lesion. ‘Unmasking’ of the lesion by hyperemia is a compelling argument because it is aligned with the natural will of the physician to want to diagnose a problem and provide an effective therapy (revascularisation). An anxiety naturally present in the mind of the interventional cardiologist is that resting pressure measurements may ‘miss’ ischemia, whereas hyperemic pressure measurements may be required to ‘unmask’ the ischemic potential of a stenosis.

The findings of this thesis challenge this way of thinking. To date, efforts to dismiss this have been limited by the lack of physical exercise as an available stressor within the coronary catheter laboratory. However, by incorporating the use of a supine ergometer during coronary catheterisation, I was able to investigate the relationship between resting coronary pressure measurements and coronary flow hemodynamics during exercise stress. During these studies, I invasively assessed exercise hemodynamics in patients with coronary stenosis up until the development of rate-limiting angina symptoms. By subsequently demonstrating positive relationships between peak-exercise coronary flow velocity and both baseline iFR (R=0.71, p<0.001) and FFR (R=0.60, p=0.003), I have dispelled the falsehood that resting coronary pressure measurements do not inform about exercise stress hemodynamics.

This novel finding challenges the notion that hyperemia is required to unmask the ischemic potential of a stenosis. Indeed, it prompts discussion that in situations of unmasking (i.e. when only FFR indicates the presence of ischemia where other tests do not), the hemodynamic severity of the stenosis may in fact be overestimated by the very use of pharmacological hyperemia. Prompted by an observation consistent with this, where a case of FFR+/iFR- discordance was explained by high hyperemic coronary flow velocity (and thus
a normal CFR), I used FFR/iFR discordance as a model to test the hypothesis that FFR may overestimate the flow-limiting potential of a stenosis in situations of ‘unmasking’.

Using the world’s largest collection of combined coronary pressure and flow measurements, I demonstrated that differences in stenosis classification between FFR and iFR were explained by differences in hyperemic coronary flow velocity. Furthermore, I demonstrated that stenoses discordantly classified as FFR+/iFR- (those that may be consider ‘unmasked’ by hyperemia) displayed similar non-flow-limiting characteristics to angiographically unobstructed vessels.

In summary, by demonstrating that resting coronary pressure measurements maintain a close relationship to coronary flow hemodynamics during stress (both physical and pharmacological), I have challenged the notion that hyperemia is required to ‘unmask’ true stenosis severity.

To take this observation beyond simply a mechanistic critique of hyperemic coronary pressure measurements, clinical trials could be designed to test these findings against patient outcomes. Specific examples could include trials that focus only on patients in whom FFR/iFR discordance is observed, with subsequent treatment decisions randomly assigned according to either the FFR or iFR classification. Furthermore, given the known higher prevalence for FFR/iFR discordance in proximal LAD and left main stem lesion locations (owing to larger downstream myocardial territories and thus higher hyperemic flow rates) (109), a prospective randomised controlled trial of FFR versus iFR-guided revascularisation in left main stem patients remains an important population to consider.
7.3 (Reappraising) the therapeutic role of coronary angioplasty in stable coronary artery disease

During the course of this thesis, results from the first double blind, placebo-controlled trial of the therapeutic efficacy of coronary angioplasty in stable angina (ORBITA) were reported (98). ORBITA demonstrated that under blinded conditions, the efficacy of PCI to improve exercise time was not significantly greater than that achieved by a sham PCI procedure (+16.6 seconds, 95% CI -8.9 - 42.0 seconds, p=0.20).

Following ORBITA, vigorous debate has ensued in the cardiology community regarding the therapeutic role of coronary angioplasty for symptom relief in stable coronary artery disease. Specifically, it has prompted renewed interest in defining the pathophysiological mechanisms of exertional angina and scrutinising the biological plausibility of PCI as an effective therapy for ischemia. As a result, this thesis provides a timely and relevant contribution to this ongoing debate and must additionally be considered in the context of the ORBITA trial findings.

Within this thesis I performed the first invasive assessment of the hemodynamic impact of PCI assessed during exercise. Prior to PCI, I demonstrated that in patients with hemodynamically severe coronary stenosis, coronary flow plateaued early during exercise. This failure to augment coronary flow to meet myocardial oxygen demand was secondary to both mechanical limitation to flow imposed by the stenosis, manifesting as high stenosis resistance, and premature maximal dilatation of the microcirculatory vascular bed. Immediately after PCI, flow increased almost linearly with exercise and was significantly higher at all stages of exertion by comparison with the corresponding pre-PCI measurements. This was due to a large fall in stenosis resistance and a corresponding increase in microcirculatory resistance at rest. These physiological adaptations following PCI
restored the coronary vessel to its primary role as a conduit (86) and also restored the capacity of the downstream microcirculatory bed to progressively vasodilate during exercise.

These objective improvements in exercise hemodynamics following PCI clearly demonstrate the physiological rationale for coronary stenting in stable CAD. Furthermore, as is routinely observed in clinical practice, these hemodynamic improvements were associated with a reduction in rate-limiting angina and a significant improvement in exercise capacity following PCI (+67 seconds, 95% CI 31-102 seconds, p<0.0001). Although long considered the primary indication for PCI in stable CAD, it is these latter findings of a significant improvement in symptoms and exercise time that contrast with the results of ORBITA.

Critiques of the ORBITA trial exist (118, 119). Specifically, claims have been made that the trial was underpowered to detect a clinically meaningful difference in exercise time against placebo. Furthermore, imbalance in pre-PCI exercise times between those patients randomised to angioplasty versus sham has been mentioned as a potential reason for the neutral findings of the trial, owing to a potential regression to the mean effect. Lastly, despite the trialists following international treatment guidelines, some observers have criticised the high intensity of pre-PCI anti-anginal therapy as not being representative of real world clinical practice. However, all of these critiques have been successfully rebutted by the ORBITA investigators (120, 121). Accordingly, the neutral result of the trial must be upheld as the first demonstration of a significant placebo effect associated with undergoing PCI for symptom relief in stable angina.

The results of ORBITA may at first be interpreted as directly in contrast with those of this thesis. However, a binary interpretation of ‘for’ or ‘against’ PCI is an oversimplified view of both studies. What ORBITA has taught us is that despite the resolution of markers of ischemia following PCI, as extensively characterised within this thesis, if the patient is unaware they have received the stent, then the improvements in physiology alone are not
sufficient to translate into symptom and exercise time improvement. Thus, the more nuanced amalgamation of the findings of ORBITA and the present study is that the therapeutic benefit of PCI in routine unblinded clinical practice is a combination of both physical and non-physical factors.

In summary, the appreciation that part of the therapeutic effect of PCI for angina relief comes from placebo does not invalidate coronary angioplasty as a treatment in stable coronary artery disease. Indeed, utilisation of this knowledge, for example by emphasising to the patient how effective the PCI has been both anatomically and physiologically, can be a valid method used by the physician in order to maximise the overall therapeutic effect of coronary angioplasty in stable angina patients.

Lastly, following ORBITA, it is likely that we are entering a new era of medical device research; where irrespective of the biological plausibility of a therapy, new devices must be tested against sham controls in order to meaningfully interpret their clinical effectiveness. When considering future avenues of sham-controlled research, the therapeutic benefit of PCI for chronic total occlusions (CTO) assessed under blinded conditions seems a pertinent choice. Currently I am involved in the design of a sham-controlled supine ergometer protocol that could be used in a CTO patient population (with bi-radial arterial access).

### 7.4 A new application for coronary physiology in the assessment of stable coronary artery disease?

Because the majority of physiology-guided PCI for stable CAD is performed for symptomatic rather than prognostic benefit, one of the primary aims of this thesis was to determine the relationship between physiological stenosis severity and angina-limited exercise capacity.
The pre-PCI component of the study protocol was designed to test this relationship using both coronary pressure and flow-based physiological indices. Additionally, the post-PCI component of the study protocol was designed to test the capability of these indices to predict the improvement in exercise capacity assessed immediately following PCI.

In this first study of its kind, I have demonstrated that physiological indices of stenosis severity were able to predict angina-limited exercise time. Conversely, no relationship was demonstrated between anatomical measures of stenosis severity and functional exercise capacity. Despite the additional measurement of coronary flow velocity (in order to calculate the flow-based indices of CFR and HSR), coronary pressure-based FFR and iFR demonstrated closer relationships with angina-limited exercise time. Additionally, when used to predict the improvement in exercise time assessed immediately post-PCI, only coronary pressure based iFR (and ΔiFR) predicted this change.

The synthesis of these findings is three-fold. Firstly, they further validate the role of coronary physiology in the assessment of stable CAD, by expanding their application to prediction of the likely gain in functional improvement from coronary angioplasty in single vessel disease patients. Secondly, they further highlight the inadequacy of anatomical stenosis severity to accurately determine the hemodynamic (and functional) significance of a coronary stenosis. Thirdly, by demonstrating that resting coronary pressure measurements associate with exercise stress capacity, as well as exercise stress hemodynamics, they clinically reinforce the earlier findings of this thesis.

Final comment is reserved for discussion of the contrasting nature of these results with those of the physiology-stratified sub-analysis of the ORBITA trial; where no relationship was observed between either baseline FFR (Pinteraction=0.318) or iFR (Pinteraction=0.523) and the placebo-controlled change in treadmill exercise time following PCI.
As per the main ORBITA trial findings, the act of blinding seems to have been critical in neutralised the capability of FFR and iFR to predict the change in exercise time following PCI. Specifically, although both FFR and iFR markedly improved following PCI, closely tracking the improvement in ischemia as documented by dobutamine stress echo, this did not translate into an ability to predict the improvement in exercise time when assessed under blinded conditions.

An important distinction between the present study and that of ORBITA physiology sub-analysis is in the assessment and reporting of the relationship between coronary physiology and the pre-PCI exercise time. Because angioplasty had not yet been performed, relationships observed in this pre-PCI phase are theoretically independent of the blinding status of the patient. Within the present study, both FFR and iFR positively correlated with pre-PCI exercise time. Furthermore, both FFR and iFR positively correlated with pre-PCI peak exercise coronary flow velocity. This latter observation provides a mechanistic rationale to support the first. However, when considering the differing findings of the two studies for the predictive capability of coronary physiology for the post-PCI change in exercise time, the issue of blinding becomes relevant and paramount.

This can be viewed one of two ways. From a scientific viewpoint, it must be appreciated that in the absence of blinding, bias towards an improvement in exercise time following known PCI cannot be excluded. Accordingly, this may lessen the scientific certainty of observations made under these unblinded conditions. Conversely, from a clinical viewpoint, all coronary angioplasty is performed with the full knowledge, indeed consent, of the patient. Therefore, although bias and placebo may be included under such conditions, these appear critical factors in determining the beneficial therapeutic effect observed in real world clinical practice.
8.0 Conclusions

Invasive assessment of coronary pressure and flow during maximal physical exercise demonstrates that physiological stenosis severity predicts exercise-limited angina time and the improvement in functional exercise capacity immediately post PCI in patients with stable angina and single vessel coronary stenosis. These findings potentially expand the remit of coronary physiology in the contemporary management of stable coronary artery disease to include prediction of those patients most likely to obtain functional improvement following revascularisation in routine, unblinded clinical practice.

Beyond these central conclusions, additional findings of this thesis further challenge the need for pharmacological hyperaemia in coronary pressure-based physiological stenosis assessment. Specifically, beyond its role in stabilising microvascular resistance, adenosine stress does not accurately reproduce the vasodilatation associated with physical exercise stress in patients with stable angina and coronary stenosis. Furthermore, both FFR and iFR demonstrate similar positive relationships with peak exercise coronary flow velocity, indicating that pharmacological hyperemia is not required for coronary pressure measurements to inform about exercise stress hemodynamics.

Lastly, the incorporation of maximal supine exercise into invasive cardiac catheterisation was found to be both safe and tolerable to patients. This experimental model is adaptable to the further investigation of angina-limited exercise capacity in more complex stable coronary artery disease subsets, particularly where the therapeutic benefit of PCI is debated (e.g. chronic total occlusions). Future supine exercise experiments should focus on the incorporation of a sham-control arm as part of the study protocol. Such methods will provide a novel means to determine the efficacy of medical devices or procedures under patient blinded conditions.
9.0 References


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71. Pijls NHJ, Hospital C. THEORY AND PRACTICAL SET-UP OF FFR. :103.


10.0 Appendix

10.1 Publications arising from this thesis

First author:

Impact of Percutaneous Revascularization on Exercise Hemodynamics in Patients With Stable Coronary Disease


J Am Coll Cardiol. In press

The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve.

**Cook CM**, Götberg M, Sen S, Nijjer S, Escaned J, Davies JE2

J Am Coll Cardiol. 2017 Sep 12;70(11):1379-1402


Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Predicts Hemodynamic Outcome In Humans With Coronary Artery Disease: Primary Results of the International Multicentre iFR GRADIENT Registry.


Diagnostic Accuracy of Computed Tomography-Derived Fractional Flow Reserve: A Systematic Review.


JAMA Cardiol. 2017 Jul 1;2(7):803-810


Fractional Flow Reserve in Angiographically Insignificant Stenoses: Unmasking the Lesion or Creating Disease?

**Cook CM**, Davies JE.

J Am Heart Assoc. 2017 Aug 22;6(8)
Co-author:


Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials.
Eur Heart J. 2018 May 7;39(18):1638-1649

**The impact of coronary chronic total occlusion percutaneous coronary intervention upon donor vessel fractional flow reserve and instantaneous wave-free ratio:**
Implications for physiology-guided PCI in patients with CTO.


**Past, Present and Future of Coronary Physiology.**
Warisawa T, **Cook CM**, Akashi YJ, Davies JE.

**Coronary autoregulation and assessment of stenosis severity without pharmacological vasodilation.**
de Waard GA, **Cook CM**, van Royen N, Davies JE.

**Diagnostic Performance of Resting and Hyperemic Invasive Physiological Indices to Define Myocardial Ischemia: Validation With 13N-Ammonia Positron Emission Tomography.**
Optimal antiplatelet strategy after transcatheter aortic valve implantation: a meta-analysis.

Coronary physiological parameters at a crossroads.
Davies JE, Cook CM, Piek JJ.

Is FFRCT Ready to Assume the Crown Jewels of Invasive FFR?
Davies JE, Cook CM.

Resolving the paradox of randomised controlled trials and observational studies comparing multi-vessel angioplasty and culprit only angioplasty at the time of STEMI

Effect of study design on the reported effect of cardiac resynchronization therapy (CRT) on quantitative physiological measures: stratified meta-analysis in narrow-QRS heart failure and implications for planning future studies.
J Am Heart Assoc. 2015;4:e000896.

**ECG-Independent Calculation of Instantaneous Wave-Free Ratio**


**A new method of applying randomised control study data to the individual patient: A novel quantitative patient-centred approach to interpreting composite end points.**


**The ischaemic constellation: an alternative to the ischaemic cascade—implications for the validation of new ischaemic tests**

Maznyczka A, Sen S, Cook CM, Francis DP.
Open Heart. 2015;2:e000178.
10.2 Awards

- European Association of Percutaneous Cardiovascular Interventions (EAPCI), Committee Member, 2018

- EuroPCR, Committee Member, 2018

- PCR Clinical Research, Board Member, 2018

- Eurointervention, International Editorial Board Member, 2018

- PCR’ Got Talent Winner - Best Oral Abstract Award, 2015

- Imperial Valve and Cardiovascular Course Young Cardiologist of the Year, 2015

- Medical Research Council, Clinical Training Fellowship Award, 2015
10.3 Patient Information sheet

Patient Information Leaflet

EXERT PCI study
Assessment of exercise capacity and exercise coronary flow velocity pre and post percutaneous coronary intervention

Chief Investigator: Dr Justin Davies

Version 1.4 IRAS ID: 213758 24/11/2016

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?

You are being invited to participate in this study because your cardiologist has referred you for a stenting procedure (also called coronary angioplasty or percutaneous coronary intervention). Stenting is a recommended treatment for improving symptoms of angina (chest pain/shortness of breath). The vast majority of patients referred for stenting report a worsening of their symptoms of angina when exercising (for example, symptoms are worse when climbing stairs/walking up a hill). Despite this well-known link between symptoms and exercise, stenting procedures are almost always performed with patients lying still. This means we do not currently have a good understanding of the effect of exercise on blood flow in the heart, or what changes occur after stenting.

We are conducting a research study that aims to better understand the effect of coronary stenting on capacity, and more specifically, the effect of exercise on the flow of blood in your coronary arteries (the blood vessels that supply blood to your heart).

Why have I been chosen?

You have been invited to take part because you have been scheduled to have a coronary stenting procedure. Because you are having a coronary stent it provides an ideal opportunity to perform our measurements of blood flow during exercise before and after your treatment. This provides an opportunity to gather lots of useful scientific data whilst only adding a small amount of additional time to your procedure (approximately 15 minutes).

Do I have to take part?

No. Your decision whether to participate in this study is entirely voluntary. You have the right to refuse as well as to withdraw your participation at any time (even if you agree today) without giving a reason.
If you decide not to participate or to withdraw, it will not affect the quality of your care or treatment, nor the relationship you have with your doctor and nursing team.

**What do I have to do?**

You may be requested to stop taking some of your medications for 48 hours prior to your planned procedure date. These medications include beta-blockers, calcium channel blockers and oral nitrate preparations. The study doctor will review all of your medications with you to determine if there is any need to withhold any of them, so you will not need to worry about the various medication names that can often be confusing. The reason for withholding these types of medications is that they can limit your capacity to exercise fully. Withholding of these medications is routine practice for patients before any exercise based test (for example an exercise treadmill test) and is not associated with any increased risk.

On the day of your planned coronary stenting procedure, you will attend the hospital as planned. Essentially the only difference you will appreciate from being part of the study will be that you will be asked to exercise at 2 specific points during you procedure. Aside from that, the experience is the same as for a routine stenting procedure.

To aid your understanding of the stenting procedure and the clinical study in general, a short summary is provided for you:

The cardiologist (heart specialist) will pass wires to the heart via the artery in your right wrist. Once the cardiologist has taken pictures of your heart arteries, measurements of the flow of blood in your arteries will take place. As mentioned above, blood flow measurements will be made while a) you are lying still; b) we give you a routine medicine called adenosine; and c) you are pedalling on an exercise bike. Only the measurements on the exercise bike are an extra step in this hospital – the other parts are routine.

The exercise bike is attached to the catheter laboratory table and you will pedal it with your legs while you are lying down. You will only need to do this for a few minutes, until you feel tired and want to stop. You will then proceed to have your stent in the normal routine manner. Once the stent has been successfully placed in your coronary artery, the same flow measurements you had at the start of your procedure will be repeated and you will be invited to pedal again until you feel tired and want to stop. This will allow us to compare the results pre and post stenting. Once these few additional measurements have been performed, both the procedure and the study will be completed and you will return back to the day ward for routine monitoring before you go home.

**What are the possible disadvantages and risks of taking part?**

We do not expect you to experience any significant side effects as a result of participating in this study. The measurement of blood flow as part of the study does not add any additional risk over the procedure that your Doctor has recommended to you and what is needed for your treatment.

Patients who undergo coronary stenting as part of their routine medical care have a risk of 1 in a 100 (1%) of a serious complication due to the procedure. This means 1 person in a 100 having this procedure would have a complication. This includes damage to blood vessels needing immediate treatment, heart attack or stroke that needs immediate treatment, urgent or emergency surgery or death. The risk of any of these complications on their own is smaller than 1 in a 100 which is the combined risk. These risks are all part of the procedure your doctor has recommended for you and the heart specialist explaining the procedure will describe them in detail to you.

Since these procedures are performed under x-ray guidance you should be aware that the mean effective doses from these procedures are equivalent to about 10 years of natural background radiation and increases the natural risk of lifetime cancer by 0.17%.

The exercise component of the study is designed to place addition stress on your heart, by making it beat harder and faster. For this reason, exercise based tests are sometimes referred to as ‘stress tests’. Stress tests are a routine investigation in patients with known/suspected heart problems.
Exercise based stress tests are very safe, and carry a 1 in 10,000 (0.0001%) risk of precipitating a heart attack. In the unlikely scenario of this occurring, you will be able to receive immediate treatment.

What are the possible benefits of taking part?

You will not directly benefit from this study, but the information we gain will give a much better understanding of how exercise effects coronary blood flow pre and post stenting.

What if something goes wrong?

Imperial College Healthcare NHS Trust holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College Healthcare NHS Trust is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone’s negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Justin Davies 020 7594 1264). The normal National Health Service complaint mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

Will my taking part in this study be kept confidential?

If you agree to take part, data collected about you will be anonymised and stored on password protected computers, which are kept in a secure room, behind a swipe card protected door. Hard copies of data e.g. ECGs will be recorded in a case-record data file for each participant, with identifiable data stored separately from other records in swipe care protected secure rooms. It is expected that the data will remain valid for at least 10 years (in line with Imperial College London policy). After this point it will be destroyed using specialist confidential waste removal services. We will also ask your permission to inform your GP that you are participating in this study.

What will happen to the results of the research study?

Scientific data from this study may be presented at meetings and published so that the information can be used to help others, but your participation in the study will not be made known and will be kept strictly confidential. If you wish, we will give you a summary of the results.

Who is sponsoring the study?

The study will be sponsored by Imperial College London.

Who is organising and funding the research?

This study is organised and supported by financial support from The Foundation for Circulatory Health.

Who has reviewed the study?

This study has been reviewed and given a favourable ethical opinion by the Research Ethics Committee.

Contact for further information

If you have any further questions please do not hesitate to contact:

Dr Christopher Cook on 07709430794, christopher.cook@nhs.net, or Dr Justin Davies on 0207 594 1264, justin.davies@imperial.ac.uk
10.4 Consent form

Imperial College London,
The Hammersmith Hospital,
B block South, 2nd floor, NHLI – Cardiovascular Science,
London W12 0NN

CONSENT FORM

EXERT PCI study
Assessment of exercise capacity and exercise coronary flow velocity immediately post percutaneous coronary intervention
Chief Investigator: Dr Justin Davies

I have read the Patient Information Sheet (Version 1 Date 08/08/2016) for the above study. I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions.

I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care.

I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the NHS Trust. I give permission for these individuals to access my records.

I agree to my GP being informed about my participation in this research study

I agree to take part in this research study.

Name of Patient/Participant

Signature

Date

Name of Person taking consent
(if different from Principal Investigator)

Signature

Date
10.5 HRA ethical approval

Dr Justin Davies
Consultant Cardiologist & Senior Research Fellow
Imperial College Healthcare NHS Trust
Hammersmith Hospital
Du Cane Road
London
W12 0HS

24 November 2019

Dear Dr Davies

Letter of HRA Approval

Study title: Assessment of exercise capacity and exercise coronary flow velocity pre and post percutaneous coronary intervention
IRAS project ID: 213758
REC reference: 16/LO/1928
Sponsor Imperial College London and Imperial College Healthcare NHS Trust

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England
The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. Please read Appendix B carefully, in particular the following sections:

- Participating NHS organisations in England – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- Confirmation of capacity and capability - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria) - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.