The University Of Sheffield.

Virtual Coronary Intervention: *In-Silico* Treatment Planning in Coronary Artery Disease

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

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Submission Date: November 2019

I. Acknowledgments

First, I would like to thank my supervisors Professor Julian Gunn and Professor Rodney Hose for their constant support and encouragement. I could not have got this far without their expertise, patience and guidance. I would also like to thank Professor Pat Lawford and Dr Paul Morris for always being available for advice and providing additional support and supervision. I would like to thank the whole of the Mathematical Modelling in Medicine team of which there are too many to mention individually.

Importantly, I owe a big thanks to my family, especially my Mum and Brother Daniel for their everlasting support. A very special thank you goes to David, my Husband, for supporting everything I do and keeping me smiling along the way.

Finally, I dedicate this to my Dad, who I know would have been so proud to see me get to the end of this journey.

II. Abstract

Using Fractional Flow Reserve (FFR) to guide Percutaneous Coronary Intervention (PCI) improves patient outcomes and reduces costs, yet is currently used in less than 10% of all cases. Utilising computational fluid dynamics modelling techniques, it is possible to model a virtual FFR (vFFR) based upon imaging alone, removing the need for invasive instrumentation. Several groups have developed models to achieve this based upon either computed tomography coronary angiography or invasive angiographic imaging. These models could increase the availability of physiological assessment and also lend themselves to virtual coronary intervention (VCI); the ability to model the insertion of stents and predict the physiological outcome. This would be advantageous in treatment planning as a number of strategies could be trialled, allowing the operator to select the optimal procedure, before committing to intervention in the patient. This thesis describes the development and validation of a VCI tool as an add-on to the existing VIRTUheart^{TM} angiography based vFFR system that has been developed at the University of Sheffield. The tool is initially validated against invasively acquired post PCI FFR values in a prospective study. Subsequent chapters assess the ability of this tool to impact 'real world' stenting, by predicting the best possible FFR on a vessel by vessel basis, determining the optimal strategy and impacting decision making in a virtual clinic setting.

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VI. Declaration

I, the author, confirm that the Thesis is my own work. I am aware of the University's Guidance on the Use of Unfair Means (www.sheffield.ac.uk/ssid/unfair-means). This work has not previously been presented for an award at this, or any other, university. I would like to confirm that all of the work presented in this thesis is my own with the exception of the following:

- Description of work by Morris et al in developing and validating the VIRTUheart^{TM} software in chapter 2
- Development of code and software which was performed by Dr Daniel Silva-Soto and Vignesh Rammohan under the supervision of Professor Rodney Hose.

VII. Publications

The work presented in this thesis is complemented by a series of publications which are listed below. The thesis chapter to which the publication relates is also referenced under the citation where relevant.

1. R Gosling, P Morris, P Lawford, DR Hose and J Gunn (2018) Predictive Physiological Modeling of Percutaneous Coronary Intervention – Is Virtual Treatment Planning the Future?. *Front Physiol*. 2018 Aug 13;9:1107.

   Chapter 1

2. R Gosling, P Morris, D Silva-Soto, P Lawford, D.R.Hose, J Gunn. Virtual coronary intervention; a treatment planning tool based upon the angiogram. *JACC Cardiovasc Imaging*. 2019 May;12(5):865-872.

   Chapter 2

3. R Gosling, P Morris, P Lawford, D. R Hose and J Gunn. Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation. *EuroIntervention*. 2019 Oct;15:707-713.

   Chapter 3

VIII. Published abstracts

1. R Gosling, P Morris, P Lawford, et al. 53 Virtual (computed) FFR and Virtual Coronary Intervention (VCI) vs angiography for guiding PCI: a virtual study. *Heart* 2019;105:A45. **Chapter 4**

Permission to reproduce elements of these publications in this thesis has been granted by the co-authors of the above publications (Appendix) and appropriate copyright permission has been sought from the publishers.

IX. Abbreviations

2D	2-Dimensional
3D	3-Dimensional
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
BMS	Bare Metal Stent
BSR	Basal Stenosis Resistance
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CFD	Computational Fluid Dynamics
CFR	Coronary Flow Reserve
CHD	Coronary Heart Disease
CI	Confidence Interval
COX-1	Cyclooxygenase 1
CMR	Cardiac Magnetic Resonance
CMRA	Cardiac Magnetic Resonance Angiography
CMVR	Coronary Microvascular Resistance
CT	Computed Tomography
CTCA	Computed Tomography Coronary Angiography
CTO	Chronic Total Occlusion
CVP	Central Venous Pressure
DES	Drug-eluting Stent

DICOM	Digital Imaging and Communications in Medicine
Dx	Diagonal
ECG	Electrocardiogram
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FD –OCT	Frequency Domain Optical Coherence Tomography
FFR	Fractional Flow Reserve
FFR_{CT}	CT based Fractional Flow Reserve
FFR_{max}	Maximal Achievable Fractional Flow Reserve
FFR_{pers}	Personalised Fractional Flow Reserve
GUI	Graphical User Interface
HR	Hazard Ratio
HSR	Hyperaemic Stenosis Resistance
ICA	Invasive Coronary Angiography
iFR	Instantaneous wave-free Ratio
IQR	Inter-Quartile Range
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending
LAO	Left Anterior Oblique
LCX	Left Circumflex
LVEDP	Left Ventricular End Diastolic Pressure
MACE	Major Adverse Cardiac Events
MDT	Multi-Disciplinary Team
mFFR	Measured Fractional Flow Reserve

MI	Myocardial Infarction
MPS	Myocardial Perfusion Scintigraphy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
NSTEMI	Non-ST segment elevation Myocardial Infarction
OCT	Optical Coherence Tomography
OM	Obtuse Marginal
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
Pa	Proximal (aortic) Pressure
Pd	Distal Pressure
Pv	Venous Pressure
PET	Positron Emission Tomography
PPV	Positive Predictive Value
Q	Flow
QCA	Quantitative Coronary Angiography
QFR	Quantitative Flow Ratio
RAO	Right Anterior Oblique
RCA	Right Coronary Artery
ROM	Reduced Order Model
RR	Relative Risk
RVD	Reference Vessel Diameter
SD	Standard Deviation
SPECT	Single Photon-Emission Computed Tomography

STEMI	ST segment Elevation Myocardial Infarction
STL	Sterolithography
T2DM	Type 2 Diabetes Mellitus
TIMI	Thrombolyis in Myocardial Infarction
UA	Unstable Angina
UK	United Kingdom
VCI	Virtual Coronary Intervention
vFFR	Virtual Fractional Flow Reserve
$vFFR_{PersBC}$	Virtual Fractional Flow Reserve using personalised boundary conditions
$vFFR_{genericBC}$	Virtual Fractional Flow Reserve using generic boundary conditions
vFAI	Virtual Functional Assessment Index
VRML	Virtual Reality Modelling Language

Chapter 1 - Background

1.1 Coronary heart disease

Coronary heart disease (CHD) remains a major cause of death in the United Kingdom (UK) and worldwide. In 2016, it was responsible for an estimated 9.43 million deaths, making it the leading cause of death globally. In the UK, it is responsible for approximately 65,000 deaths annually, a third of which occur in people under the age of 75. An estimated 2.3 million people are currently living in the UK with CHD. There has been an overall decline in deaths over the past decade due to significant advances in investigation and treatment. The current mortality rate is approximately 1.2-2.4% per annum (Boden et al., 2007). In addition, CHD confers a significant economic burden with substantial costs relating to investigation and treatment. In 2014, £8.7 billion of healthcare costs was attributed to CHD in the UK.

CHD describes a spectrum of clinical syndromes caused by the accumulation of atherosclerotic plaque within the coronary arterial walls. As the plaque develops, it can impinge upon the arterial lumen resulting in a reduction in coronary blood flow and subsequent myocardial ischaemia.

1.2 Pathophysiology

The atherosclerotic process begins in early life with the appearance of fatty streaks within the arterial wall as a result of intracellular lipid deposition. Over decades, this can progress with further lipid addition and an increase in smooth muscle and collagen. A mature atherosclerotic plaque consists of a lipid core surrounded by a connective tissue matrix. This process is illustrated in Figure 1.1. Atherosclerosis is a multifaceted disease process and the rate and degree of progression is highly variable and dependent upon a number of genetic, biological and environmental influences. Epidemiologic

studies have identified a number of significant risk factors including smoking, diabetes mellitus, hypertension and dyslipidaemia in the pathogenesis.

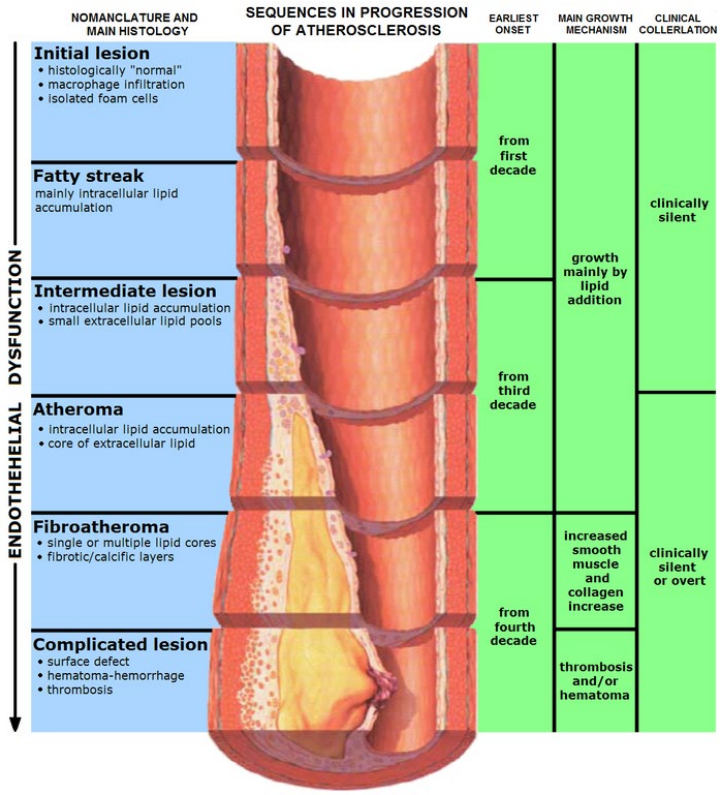


Figure 1.1: Endothelial dysfunction in atherosclerosis

The atherosclerotic process begins in early life with macrophage infiltration into the vessel wall. Over time, lipid accumulates, developing the lesion into an atheroma. Later, the plaque matures with addition of smooth muscle and collagen. Complicated lesions develop when surface defects attract thrombus and/or haematomas. A mature atherosclerotic plaque consists of a lipid core, mainly released from necrotic foam cells (monocyte derived macrophages) which migrate into the intima and ingest lipids. The connective tissue matrix is derived from smooth muscle cells, which migrate from the media into the intima where they proliferate to form a fibrous capsule around the core. Reproduced from Wikimedia commons under creative commons attribution-share alike 3.0 unported licence.

1.3 Clinical presentation and management

Early plaque accumulation is associated with a compensatory increase in vessel size. The arterial media and external elastic membrane expand to accommodate the growing plaque in a process of positive remodelling. Therefore, in the initial stages of plaque growth, the size of the arterial lumen is unaffected

(Glagov et al., 1987). However, a threshold is reached whereby the vessel can no longer compensate and further plaque deposition impinges upon the lumen. This creates a luminal stenosis, which can become 'flow-limiting' predisposing myocardial ischaemia. Myocardial ischaemia is caused by an oxygen supply-demand mismatch. Symptoms are typically first recognised on exertion, or in other situations with an increased myocardial oxygen demand. In the absence of a stenosis, coronary flow is increased to match demand through an autoregulation process (Figure 1.2). This regulation of coronary blood flow is complex and is dictated by a number of mechanisms including myogenic, metabolic, endothelial, neural and hormonal influences (Goodwill et al., 2017).

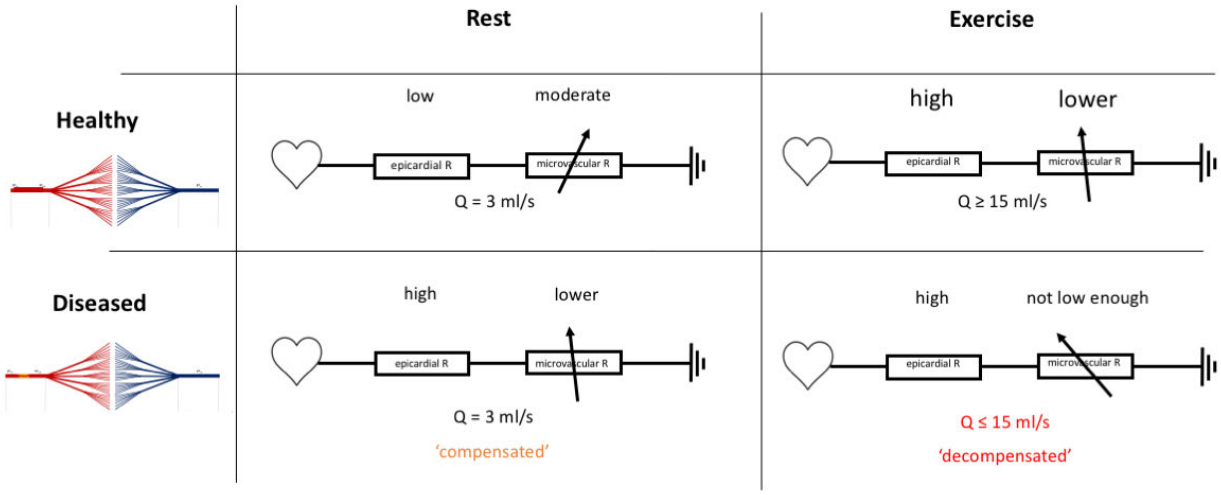


Figure 1.2: Coronary autoregulation

Based on Ohms law, Coronary flow (Q) is equal to perfusion pressure (P)/Resistance (R). As pressure is tightly controlled, it is resistance that is the biggest determinant of coronary blood flow. The coronary arterial system is represented as an electrical analogue with two resistors in sequence representing the two components of myocardial blood supply; the epicardial arteries and the microvasculature. It is the relationship between the two that determines coronary blood flow (Q). In a healthy system, the epicardial resistance (R) is negligible therefore flow is determined solely by the microvascular resistance. At rest, flow is maintained at about 3ml/s (Top left). On exercise, the microvasculature resistance decreases to allow flow to be increased to match the increased metabolic demand (top right). In the presence of epicardial disease, the epicardial resistance is high. Therefore, at rest, the microvascular resistance is lower to allow flow to be maintained at 3ml/s (bottom left). On exercise, the microvascular resistance decreases to try and allow increased flow, however there comes a point when the ability to lower the microvascular resistance becomes exhausted, and the system can no longer compensate for the increased epicardial resistance. Flow can no longer meet metabolic demand and the myocardium becomes ischaemic. The only way to reverse this is to rest, thus reducing the myocardial demand.

In the presence of a stenosis, a threshold is reached whereby flow can no longer be increased and ischaemia ensues. This leads to characteristic ischaemic chest pain. When the patient is at rest, blood flow can be maintained and symptoms resolve. This syndrome is known as stable angina or chronic coronary syndrome. Acute coronary syndromes (ACS) occur when disruption of the plaque provokes thrombus formation and subsequent vessel occlusion. This presents with acute ischaemic chest pain, often occurring at rest. Thrombosis formation occurs via a number of mechanisms. Contact with the

collagen within the extracellular matrix can trigger platelet activation and tissue factor produced by macrophages and smooth muscle cells can activate the coagulation cascade.

The management of CHD is aimed at reducing the symptoms of ischaemia, halting disease progression and preventing thrombosis formation and its sequelae. This can be achieved through medical and interventional strategies.

1.3.1 Medical management

'Anti-anginal' medications aim to relieve ischaemia either by reducing myocardial oxygen demand or enhancing myocardial blood flow (supply). Several classes of anti-anginals have been approved. The most commonly used in clinical practice include beta blockers, nitrates and calcium channel blockers. Beta blockers reduce heart rate and inotropy therefore reducing myocardial oxygen demand. Additionally, the reduction in heart rate leads to an increase in the time spent in diastole, which translates to an overall increase in coronary flow as coronary flow predominates in diastole. In patients with previous myocardial infarction (MI), the introduction of beta blockers into a standard treatment regimen is associated with a 30% reduction in cardiovascular death and MI (Yusuf et al., 1988). They may also be protective in patients with stable angina but there is a lack of evidence from placebo based trials. Nitrates cause arteriolar and venous vasodilatation which increases coronary blood flow and reduces preload. Similarly, calcium channel blockers work through vasodilatory mechanisms reducing afterload. The second aim of medical management in CHD is to reduce the risk of future thromboembolic events or ACS. This is primarily achieved with antiplatelet therapy and the aggressive management of risk factors. Aspirin is the most commonly used antiplatelet and acts by irreversible inhibition of platelet cyclooxygenase 1 (COX-1) and therefore thromboxane production. This decreases platelet aggregation and may prevent the formation of coronary thrombus. The addition of aspirin therapy to standard CHD treatment regimens has been demonstrated to be associated with a significant reduction in MI or death

compared to placebo without any increase in major bleeding (Juul-Moller et al., 1992). Risk factor modification is also important in preventing ACS and in slowing the rate of progression of non-flow limiting lesions. The benefits of smoking cessation have been extensively reported and is potentially the most effective of all preventative measures (Critchley and Capewell, 2004). Additionally, lipid management and blood pressure control remain important factors.

1.3.2 Interventional management

Coronary revascularisation is aimed at restoring blood flow to the distal myocardium and can be achieved through coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI).

CABG surgery restores blood flow to the distal myocardium by diverting blood through a surgically inserted graft, therefore bypassing the flow limiting disease. Vein or arterial grafts can be used, most commonly the left internal mammary artery, radial artery or saphenous veins. A section of the blood vessel is grafted from the aorta to the distal coronary artery to bypass the region of disease (Figure 1.3). Early CABG trials demonstrated the ability of the surgery to relieve angina and improve quality of life (Mathur et al., 1975, Guinn and Mathur, 1976, Kloster et al., 1977, Murphy et al., 1977). However, most were not powered to detect survival differences between CABG and optimal medical therapy (OMT). Meta-analyses suggested a potential 4.3 month increase in survival over 10 years which is increased further in patients with left main-stem disease (19.3 months) and those with impaired left ventricular function (10.6 months) (Yusuf et al., 1994).

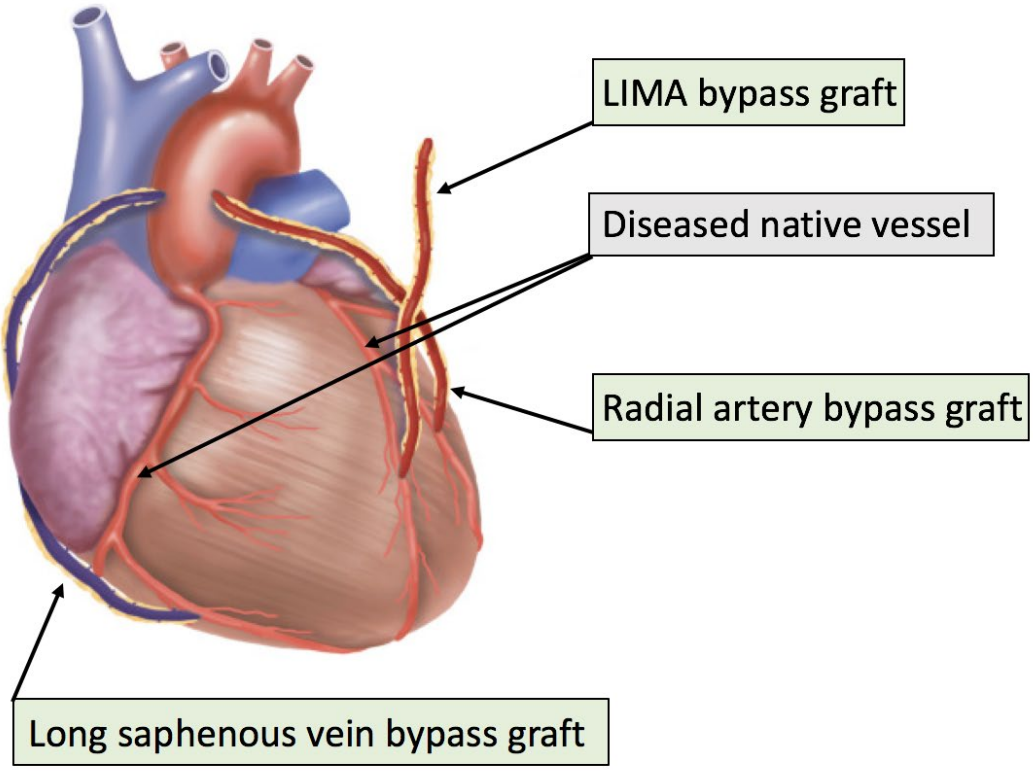


Figure 1.3: CABG surgery
Venous and arterial grafts are grafted from the aorta to the distal coronary artery allowing blood flow to be diverted away from the diseased native vessel. The LIMA graft is attached directly to the distal coronary artery without reattaching the proximal end. Adapted from J Am Coll Cardiol, 66(15), Gaudino et al, The choice of conduits in coronary artery bypass surgery, 1729-37., Copyright (2015), with permission from Elsevier.

PCI is the insertion of a stent(s) into the coronary artery to re-open a stenosis thereby restoring blood flow. An arterial puncture is made (typically femoral or radial) through which a catheter is passed. The catheter is specially shaped to facilitate engagement with the coronary ostia. A stent can then be delivered over a wire into the coronary artery (Figure 1.4). This is performed under X ray guidance.

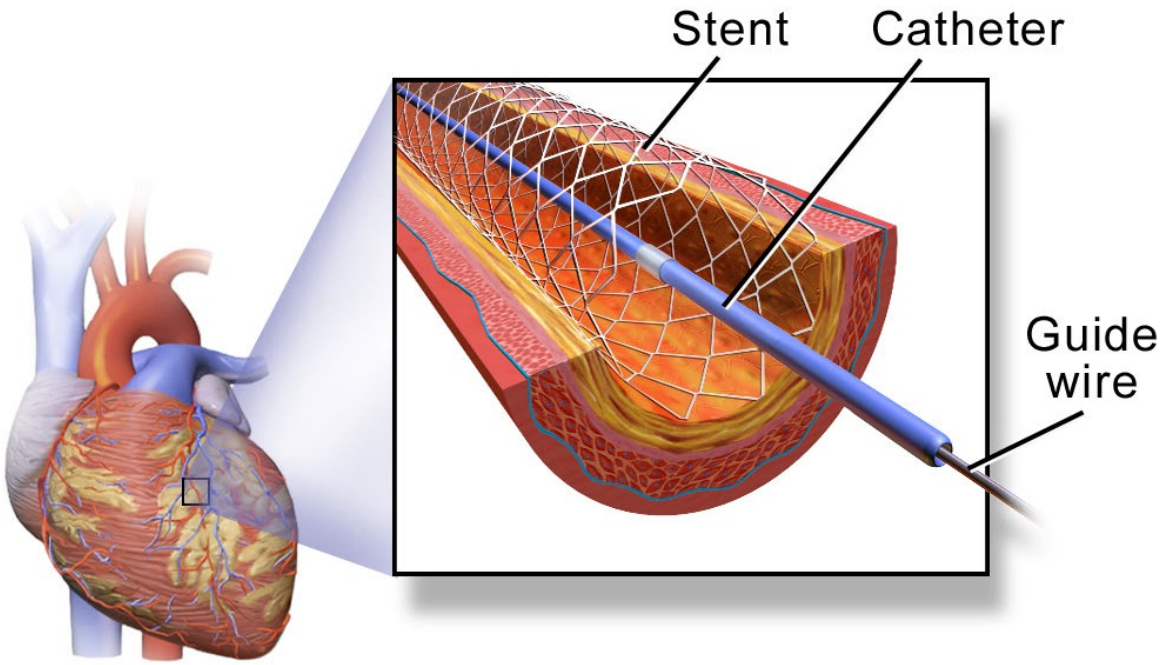


Figure 1.4: Percutaneous coronary intervention
A catheter is passed into the coronary arteries. A guide wire is then inserted, over which a stent can be positioned and then inflated within the vessel. The aim is to re-open areas of significant stenosis, restoring coronary blood flow. Reproduced from Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014" Wikijournal of Medicine 1 (2) under creative commons license CC BY 3.0.

Like CABG, the goal of PCI is to restore blood flow to the myocardium and therefore to improve symptoms of ischaemia. A number of studies have demonstrated the ability of PCI to improve symptoms (Henderson et al., 2003, Rogers et al., 1990). However, the potential impact on survival is less clear. In the RITA-2 (the Second Randomised Intervention Treatment of Angina) trial, 1,018 patients were randomised to PCI or OMT (Henderson et al., 2003). There was no significant difference between the groups in terms of risk of death or MI. However, an initial PCI strategy was associated with improved angina symptoms and exercise times. The landmark COURAGE (Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation) trial randomised 2,287 patients with stable coronary artery disease (CAD) to undergo either PCI (with bare metal stent (BMS)) with OMT or OMT alone (Boden et al., 2007). The authors reported no significant difference between the PCI group and the OMT

group in the composite outcome of death, MI and stroke (20.0% versus 19.5%; hazard ratio (HR), 1.05; 95% CI, 0.87 to 1.27; P=0.62). In the BARI2D (Bypass Angioplasty Revascularisation Investigation in Type 2 Diabetes) trial, patients with diabetes mellitus were randomised to receive OMT or revascularisation. There was no difference in survival at five years with either CABG or PCI (Group et al., 2009). In the MASS II (Medicine, Angioplasty or Surgery Study) trial (Hueb et al., 2010), 611 patients with proximal multi-vessel disease and documented ischaemia were randomised to CABG, PCI or OMT. At 10 year follow up, OMT was associated with a higher incidence of MI, revascularisation and cardiac events. However, since many of the large trials were conducted, technology of both CABG and PCI have developed, most notably the move away from BMS to drug-eluting stents (DES) in PCI. More recently, the FAME-2 (Fractional Flow Reserve Guided PCI plus optimal medical therapy versus optimal medical therapy alone in patients with stable coronary artery disease) trial demonstrated a significant survival benefit with selective PCI (with DES), after confirming the presence of ischaemia (fractional flow reserve (FFR) <0.80) compared to OMT (De Bruyne et al., 2014). The recent ORBITA (Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina) trial was the first 'blinded', placebo controlled PCI study (Al-Lamee et al., 2018). Two hundred and thirty-one patients were randomised to undergo PCI or a placebo procedure. The authors found no significant differences in the primary endpoint of exercise time increment between the two groups, concluding that the common clinical observation of symptomatic improvement from PCI might contain a placebo component. However, this was a relatively small study that excluded patients with multi-vessel disease; a common group. Moreover, medical therapy in both arms was optimised by thrice weekly telephone consultation with a cardiologist supported by home blood pressure and heart rate monitoring. This level of optimisation is unrealistic in standard National Health Service (NHS) care and may be a factor in the results. Furthermore, follow up was limited to 6 weeks. Previous studies used different assessment criteria and endpoints and had larger numbers, so there is no comparator trial. Fractional Flow Reserve (FFR) was measured, but not used to guide treatment. Twenty nine percent of cases had

a FFR >0.80. Poor patient selection for PCI may be another factor in the perceived lack of symptomatic improvement from PCI.

Current guidelines recommend that the decision for revascularisation be based upon the presence of significant obstructive disease, the amount of ischaemia and the expected benefit and impact upon prognosis taking into consideration clinical, technical and anatomical factors. The European Society of Cardiology (ESC) guidelines are shown in Table 1.1.

Table 1.1: Summary of 2013 European Society of Cardiology Guidelines for revascularisation in patients on OMT

Indication	To improve prognosis:		To improve symptoms:	
	Class	Level	Class	Level
A heart team approach to revascularization is recommended for patients with unprotected left main, 2-3 vessel, diabetes or comorbidities	I	C	I	C
Left main >50% diameter stenosis	I	A	I	A
Any proximal LAD >50% diameter stenosis	I	A	I	A
2-3 vessel disease with impaired LV function/CHF	I	B	IIa	B
Single remaining vessel (>50% diameter stenosis)	I	C	I	A
Proven large area of ischaemia (>10% LV)	I	B	I	B
Any significant stenosis with limiting symptoms or symptoms non- responsive/intolerant to OMT	NA	NA	I	A
Dyspnoea/cardiac heart failure with > 10% ischaemia/viability supplied by a stenosis >50%	IIb	B	IIa	B
No limiting symptoms with OMT in vessel other than left main or proximal LAD or single remaining vessel or vessel subtending area of ischaemia <10% myocardium or with FFR >= 0.80.	III	A	III	C

LAD = Left anterior descending; LV = left ventricle; CHF = chronic heart failure; OMT = optimal medical therapy; FFR = fractional flow reserve. Adapted from 2013 ESC guidelines on the management of stable coronary artery disease(Task Force et al., 2013).

1.4 Investigation

The primary goal of investigation is to diagnose the presence of CAD and plan revascularisation. Invasive coronary angiography (ICA) remains the gold standard investigation. Due to its invasive nature, it is typically reserved as a first line investigation for patients with a high pre-test probability of CAD. The remainder of patients would usually undergo a form of non-invasive testing, in the first instance, proceeding to ICA if results are positive or inconclusive. The preservation of ICA for those at high risk of CAD inevitably means that a greater proportion of patients require alternative investigation. Prior to November 2016, the National Institute for Health and Care Excellence (NICE) guidelines recommended initial investigation to be determined by the calculation of the pre-test likelihood of CAD which is based upon the clinical history and patient demographic data. Those with an estimated likelihood of CAD of >10% proceeded to further investigation. Those estimated at 10-29% were offered computed tomography (CT) calcium scoring, proceeding to CT coronary angiography (CTCA) if the result was greater than 400 Agatston units. Those estimated at 30-60% were offered functional imaging and those 61-90% were offered ICA as first line. Those over 90% proceeded to ICA if they remained symptomatic despite OMT. Adopting this approach resulted in fewer patients proceeding to ICA, however the presence of CAD remained significantly over-estimated. A large study of over 400,000 patients showed that up to 62% of patients undergoing ICA had no obstructive disease (Patel et al., 2010). Of those with a positive stress test, two thirds had no obstructive disease. A revision of the guidelines in November 2016 has seen CTCA recommended as the first line of investigation for all patients (NICE, 2016). In an analysis performed by NICE, CTCA out performed all functional imaging tests in predicting the presence of a >50% diameter stenosis at ICA which was considered the gold standard. Furthermore, in a recent cost-effectiveness analysis, CTCA was found to be the most cost-effective diagnostic strategy (Petersen, 2016). Functional imaging is recommended in patients with confirmed CAD to determine the presence of ischaemia or in patients for whom CTCA has demonstrated CAD of uncertain significance

or is not diagnostic. ICA is recommended as third-line when the results of non-invasive functional imaging are inconclusive. Each of these modalities will be discussed in more detail.

1.4.1 Computed tomographic coronary angiography

CTCA is a primary anatomical test that permits the non-invasive quantification of CAD. The technology of CTCA has evolved in recent years allowing increased volume coverage, shorter gantry rotation times, improved diagnostic utility and reduced radiation exposure. Despite this, CTCA remains a challenging procedure. Heart rate control with appropriate electrocardiogram (ECG) gating and accurate timing of contrast injection are key components for successful image acquisition. The diagnostic accuracy of CTCA has been assessed in a number of prospective trials. The ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial assessed the ability of ECG gated 64 multi-detector row CTCA to predict the presence of obstructive CAD as seen at ICA (Budoff et al., 2013). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to detect lesions >50% at ICA were 95%, 83%, 64% and 99% respectively. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multi-Detector Computed Tomography Angiography) study showed similar accuracy with 64 row, 0.5mm multi-detector CT (Miller et al., 2008). The authors demonstrated a sensitivity, specificity, PPV and NPV to detect a stenosis of > 50% severity of 85%, 90%, 91% and 83% respectively. However, patients with a calcium score of greater than 600 Ageston units were excluded potentially explaining the slightly higher PPV. Meijboom et al conducted a prospective multi-centre study of 360 symptomatic patients that had been referred for diagnostic coronary angiography (Meijboom et al., 2008). Unlike CORE-64, no patients were excluded because of calcium or image quality. CAD was again defined as the presence of a lesion >50% at ICA. A patient-based analysis demonstrated a sensitivity, specificity, PPV and NPV of 99%, 64%, 86% and 97% respectively. All of the prospective studies have demonstrated a high NPV but a low PPV. Therefore, it is a useful test in ruling out CAD but CAD severity is frequently over-estimated.

The low PPV is likely due to calcium 'blooming' artefacts that affect interpretation. Of note, all of these studies used anatomical findings at ICA as the 'gold standard' comparator.

Two recent trials have evaluated a CTCA focused diagnostic approach on clinical outcomes. The PROMISE (PROspective Multi-center Imaging Study for Evaluation of chest pain) trial evaluated anatomic testing with CT compared to functional non-invasive imaging among patients with a low to intermediate risk of CAD (Shah et al., 2016). A total of 10,003 patients were randomised to either 64 slice CTCA or a functional strategy which could be exercise ECG, exercise imaging or pharmacological stress imaging. The primary outcome was all-cause mortality, MI, hospitalisation for unstable angina (UA) or a major complication from a cardiovascular procedure. The authors reported no difference in the primary outcome at a median follow up of two years between the two groups (3.3% versus 3.0%, P=0.75). However, in the CTCA group, fewer patients had a negative ICA (absence of obstructive CAD) compared with the functional imaging group (3.4% versus 4.3%, P=0.02). In the SCOT-HEART (Scottish CT of the Heart) trial, patients were randomised to receive standard care (whereby investigation was determined by the clinician based on local and national guidelines and clinical expertise) or standard care with CTCA (investigators, 2015). The primary endpoint was the certainty of diagnosis of angina secondary to CAD at six weeks. The standard group received routine clinical assessment, exercise ECG if appropriate, and a clinical decision regarding functional imaging. After a median of 1.7 years, CTCA was associated with a 38% reduction in non-fatal and fatal MI (P=0.05). Additionally, CTCA doubled the clinician's certainty of diagnosis (Relative Risk (RR) 2.56, 95% Confidence Interval (CI) 2.33 to 2.79) and led to the cancellation of unnecessary investigation or changed pharmacological therapy in 25% of patients. This resulted in an improvement in the selection of patients for ICA with rates of normal coronary angiography almost halved. A large Danish cohort study compared patients undergoing CTCA or functional investigation (exercise ECG or single photon emission computed tomography (SPECT)) (Jorgensen et al., 2017). Those in the CTCA group had a

29% lower risk of MI over a median of 3.6 years follow up. These patients were also more likely to undergo revascularisation and to be initiated on treatment. Moreover, overall management costs were an estimated 39% higher in the CTCA group. A major limitation of CTCA is the inability to provide functional assessment. Most studies to date have compared CTCA findings to anatomical findings at ICA, so it is unsurprising that correlation is reasonable. However, the presence of ischaemia is now recognised to be an important factor in determining the potential benefit from revascularisation and indeed impacts prognosis. The addition of myocardial perfusion, or more recently CT based fractional flow reserve (FFR_{CT}), may increase the relevance of CTCA. CT perfusion imaging is a relatively new technique. Used together with CTCA it can provide anatomical and functional evaluation of CAD with a higher diagnostic accuracy compared to CTCA alone (George et al., 2012). Combination with CTCA appears to offer prediction of haemodynamically significant lesions with >90% accuracy (Ko et al., 2012). A major limitation of CT perfusion is the higher dose profile due to the time-resolved acquisition of multiple phases. It is also subject to problems with artefact; for example, motion artefacts, breathing and beam hardening. Further work is required but this could be a promising tool for the future. FFR_{CT} involves the addition of computed FFR to coronary segments on CTCA. This technology is discussed in more detail in section 1.9.1.

1.4.2 Myocardial perfusion imaging

Myocardial perfusion scintigraphy (MPS) involves using SPECT or positron emission tomography (PET) imaging to identify the uptake of a radioactive tracer by the myocardial tissue. Comparison between rest and stress imaging allows identification of potentially reversible ischaemia. SPECT has been widely used in clinical practice in patients with intermediate risk of CAD. Patients with positive MPS tests have been shown to have a higher rate of obstructive CAD compared with those who do not undergo MPS prior to ICA (74.4% versus 45.6%). Stress SPECT has a pooled sensitivity of 87% and specificity of 73% (Klocke et al., 2003). A major drawback, however, is the unreliability in discerning

three vessel disease or left main stem disease. In situations with globally reduced flow, it is unable to detect a focal perfusion defect therefore potentially providing falsely normal results. Furthermore, spatial resolution is poor and it requires long acquisition protocols and considerable radiation exposure. PET consists of perfusion imaging with a perfusion tracer and functional metabolic imaging. Mismatch between flow and metabolism suggests reversible ischaemia. PET has a higher spatial and temporal resolution than SPECT and allows for accurate quantification of myocardial blood flow, consistently yielding superior results to SPECT with a pooled sensitivity of 84% and specificity of 81% (Mc Ardle et al., 2012). However, it remains limited in its ability to quantify the extent of a trans-mural myocardial perfusion defect. Additionally, costs are high and there is currently a low availability of scanners. Furthermore, it cannot distinguish between small vessel ischaemia or ischaemia from an epicardial stenosis.

1.4.3 Stress echocardiography

Stress echocardiography is based upon the detection of regional wall motion abnormalities to indicate ischaemia induced by exercise or pharmacological stress. The sensitivity and specificity have been reported as 80% and 86% respectively (Beleslin et al., 1999). A pooled meta-analysis demonstrated that it has superior specificity to SPECT but a lower sensitivity (Schinkel et al., 2003). However, stress echocardiography is largely dependent upon operator ability and is not available at all centres.

1.4.4 Cardiac MRI

Cardiac magnetic resonance (CMR) imaging allows radiation-free assessment of coronary arteries and is therefore an attractive alternative, but is limited by resources and cost. CMR exhibits superior spatial resolution compared to SPECT, thereby allowing depiction of even small perfusion defects confined to the sub-endocardium. Myocardial perfusion is assessed qualitatively using visual and semi quantitative analysis with time intensity curves. A meta-analysis demonstrated a pooled sensitivity of 89% and

specificity of 80% in detecting significant CAD (Hamon et al., 2010). A combined stress perfusion and delayed enhancement sequence had a higher specificity and accuracy compared to stress perfusion CMR alone. Coronary Magnetic Resonance Angiography (CMRA) allows direct visual assessment of the coronary arteries. A multicentre study demonstrated that whole heart CMRA can detect significant CAD with a sensitivity of 88% and specificity of 72% (Kato et al., 2010). However, its clinical utility is limited by the fact that it is time consuming and up to 30–50% of segments cannot be evaluated. The CE-MARC (Cardiac Magnetic Resonance and Single photon Emission Computed Tomography for Diagnosis of Coronary Heart Disease) study recruited 752 patients with suspected angina and at least one risk factor, and compared CMR and SPECT with ICA (Greenwood et al., 2012). The CMR protocol consisted of rest and adenosine stress perfusion, cine imaging, late gadolinium enhancement and CMR coronary angiography. The sensitivity, specificity, PPV and NPV were 86.5%, 83.4%, 77.2% and 90.5% respectively compared to 66.5%, 82.6%, 71.4% and 79.1% for SPECT, leading the authors to conclude that CMR was superior to SPECT. In the CE-MARC-2 (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2) trial, the primary end point was protocol-defined unnecessary coronary angiography (normal FFR (>0.80) or quantitative coronary angiography [QCA] showing no stenosis of ≥70% percentage diameter in one view or ≥50% in two orthogonal views in all coronary vessels ≥2.5 mm diameter) within 12 months (Greenwood et al., 2016). The investigators randomised 1,202 patients to receive functional imaging based care (CMR or MPS) or NICE guidelines directed care. The CMR group had a lower probability of unnecessary angiography within 12 months compared to those who underwent guideline directed care (7.5% versus 28.8%). There was no difference between CMR and MPS (7.1%). There was no detected difference in clinical outcomes. The development of major adverse cardiac events (MACE) at 12 months was 1.7% in the NICE group compared to 2.5% in the CMR group and 2.5% in the MPS group. However, the authors concluded that a broader use of functional imaging may reduce the number of patients undergoing unnecessary invasive investigation.

1.4.5 Hybrid imaging

More recently, it has been suggested that, in order to improve results, hybrid imaging combining CTCA with SPECT or PET could be utilised to obtain accurate co-localisation, combining anatomical and functional data. In 98 patients, hybrid analysis increased specificity from 62% to 95% and increased the PPV from 77% to 96% compared to CTCA alone in detecting CAD (Schaap et al., 2013). A recent analysis compared CTCA, SPECT, PET as well as hybrid CTCA-SPECT and hybrid CTCA-PET to invasive FFR. A combined hybrid approach did not add incremental diagnostic value. The highest accuracy was seen with PET (85% versus 74% for CTCA, 77% for SPECT, 76% for SPECT/CTCA and 84% for PET/CTCA) (Danad et al., 2017). More recently CMR has been allied with PET combining the advances in functional and morphological CMR imaging with PET application of myocardial perfusion and tissue viability. Its potential to emerge in the diagnostic pathway in CAD has yet to be fully explored. However, adopting a hybrid approach is more costly and time consuming therefore the search continues for an imaging modality that can assess anatomy and function in a single test.

1.5 Invasive coronary angiography

Although non-invasive imaging is rapidly advancing, the spatial and temporal resolution of ICA is unsurpassed, and ICA remains the gold standard investigation for the diagnosis of CAD. In 2014, 260,808 diagnostic coronary angiograms were undertaken in the UK, and 100,483 PCI procedures (BCIS, 2016) were performed. To perform an invasive ICA, an arterial puncture is made (typically via the radial or femoral artery) and a catheter is then passed to the aortic root, from which the coronary arteries emerge. The catheters are specially shaped to facilitate engagement with the coronary ostia. Radio-opaque contrast medium is then injected into the coronary arterial lumen whilst a series of x ray images are recorded. The goal of ICA is to capture an impression of the 3 dimensional (3D) arterial anatomy with a series of 2 dimensional (2D) images. This is achieved by rotating a radiological C arm

around the patient, capturing static 2D images at each position, with the patient placed on a central table (Figure 1.5).

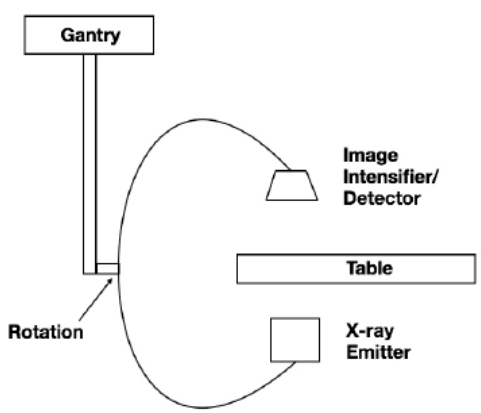


Figure 1.5: The radiological C arm
The patient is positioned on the table and the C arm rotated around the patient, allowing images to be acquired from different angles.

Although ICA remains the gold standard for diagnosing CAD, acquiring and interpreting images accurately can be challenging. Inadequate opacification of the arterial lumen can occur due to poor injection of contrast, poor catheter engagement, obesity and calcification (especially in the ageing population). Interpretation can also be hampered by the presence of overlying branches or artefacts and vessel foreshortening. ICA has a tendency to overestimate the severity of lesions and interpretation is both subjective and variable. Another drawback of ICA alone is its inability to determine physiology and biology, both known to contribute to the clinical significance and prognosis of CAD. Methods for intravascular imaging and the assessment of coronary physiology exist, but are currently underused.

1.5.1 Intravascular imaging

Intravascular imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have been developed to facilitate more detailed visualisation of the coronary artery lumen. These techniques offer incremental information that can be used to optimise stent implantation

and minimise stent related complications. They are particularly useful prior to PCI to accurately size the vessel, and post procedurally to provide strut level evaluation of the stent result permitting optimisation (Raber et al., 2018).

IVUS is a catheter based imaging technique that allows transluminal visualisation of the coronary arteries aiding both assessment and stent deployment. IVUS has been shown to contribute to decreased rates of in-stent re-stenosis and repeat revascularisation (Nissen and Yock, 2001). There is increasing evidence that using IVUS to guide PCI is associated with improved clinical outcomes (Elgendy et al., 2016, Buccheri et al., 2017). More recently, OCT was introduced in to the cardiac catheter laboratory. OCT measures backscatter of light derived from an infrared light source directed at the arterial wall allowing higher resolution images compared to IVUS but with less tissue penetration depth. This allows superior delineation of the fibrous cap and circumferential extent of necrotic cores, allowing identification of high risk plaques. Its use is associated with superior stent coverage (Lee et al., 2018b), improved post PCI physiology (Meneveau et al., 2016) and reduced cardiac death/MI compared with angiography alone (Prati et al., 2012). Furthermore, the ILUMIEN III: OPTIMIZE PCI (Optical Coherence Tomography Compared with Intravascular Ultrasound and with Angiography to Guide Coronary Stent Implantation) and OPINION (Optimal Frequency Domain Imaging Versus Intravascular Ultrasound in Percutaneous Coronary Intervention) trials have demonstrated non-inferiority compared to IVUS with respect to procedural result and mid-term outcomes (Ali et al., 2016, Otake et al., 2018). Its use will be explored further in the ongoing ILUMIEN IV: OPTIMAL PCI (Optimal Coherence Tomography Guided Coronary Stent Implantation Compared to Angiography: A Multicentre Randomised Trial in PCI) (NCT0350777) and OCTOBER (European Trial on Optical Coherence Tomography Optimized Bifurcation Event Reduction) (NCT03171311) trials. New generation frequency domain OCT (FD-OCT) enables long coronary segments to be assessed within a few seconds during contrast injections. A recent *ex-vivo* study has demonstrated the feasibility of a hybrid IVUS and

OCT catheter for intracoronary imaging and this may be a new avenue for research in the future (Task Force et al., 2013). However, in general, these techniques have only a small role in diagnosing CAD.

1.6 Fractional Flow Reserve (FFR)

One of the major drawbacks of ICA is that ICA alone does not reliably discern ischaemia-provoking lesions from haemodynamically non-significant lesions. FFR is a physiological measure that can be obtained during ICA. It is a measure of the pressure drop across a lesion at maximal hyperaemia and is used as an index of the effect of a lesion on coronary blood flow and therefore the ability to induce ischaemia. A pressure wire is passed down the artery and the pressure is recorded proximal (at the catheter tip) and distal to the lesion being assessed. The measurements are taken following pharmacological induction of maximal hyperaemia. The potential significance of the pressure drop across a lesion was first noted by Grüntzig in the 1970s (Gruntzig et al., 1979). He attempted to measure pressure using fluid filled catheters. However, the catheter was so large it occluded the vessel and could not be placed in the distal vessel leading to an over-estimation of the pressure drop. It was then not until 1993 that Pijls et al first laid out the experimental basis of FFR (Pijls et al., 1993). Since then, the concept has gained significant momentum and using FFR to guide decision making has been shown to improve patient outcomes and reduce costs, establishing itself as part of national and international guidelines.

1.6.1 Physiological basis of FFR

To understand the concept and limitations of FFR it is important to understand the principles of coronary blood flow. Coronary blood flow is carefully maintained by an extensive autoregulation process and in normal circumstances is well controlled to match the oxygen requirements of the heart. This is achieved by altering the calibre of the resistance vessels (arterioles). This involves mechanisms intrinsic to the vascular wall in combination with neuro-hormonal and metabolic mechanisms. A unique feature of coronary blood flow is that it occurs predominantly in diastole. This is a result of the compressive forces

exerted by the myocardium on the embedded microvasculature during systole (ventricular contraction) which increases resistance and impedes blood flow, but also the 'suction' effect of diastole itself. Blood flow therefore predominates when the resistance is lower (in diastole). The total resistance to flow in diastole consists of the resistance from the epicardial vessels and from the microvasculature and it is the relationship between the two that under pins the basis of many physiological indices, including FFR. Flow through the coronary arteries is driven by pressure and can be described using the Hagen-Poiseuille law:

$$Q = \Delta P\ \pi r^4 / 8\eta l.$$

Q= flow, ΔP=pressure drop, r= vessel radius, η=viscosity, l=vessel length

In coronary arteries, the length is fixed and viscosity can be considered constant (assuming no major variation in haematocrit), therefore this can be simplified to:

$$Q = c\Delta P\ \pi r^4$$

Thus, the important factors affecting coronary flow are the pressure gradient and the radius of the vessel. In the presence of a stenosis, the radius of the vessel is reduced. From the Hagen-Poiseuille equation, it is apparent that any effect on radius will have a large impact on flow as flow is related to the fourth power of the radius. A number of things happen in the presence of a stenosis. Due to a reduction in the radius, parabolic flow accelerates across the narrowing. A pressure drop then occurs as pressure energy is converted to kinetic energy. Distal to the stenosis, as flow slows, some of the pressure is recovered. However, this pressure recovery is not complete due to the development of eddy currents and flow separation which results in energy loss. This is illustrated in Figure 1.6.

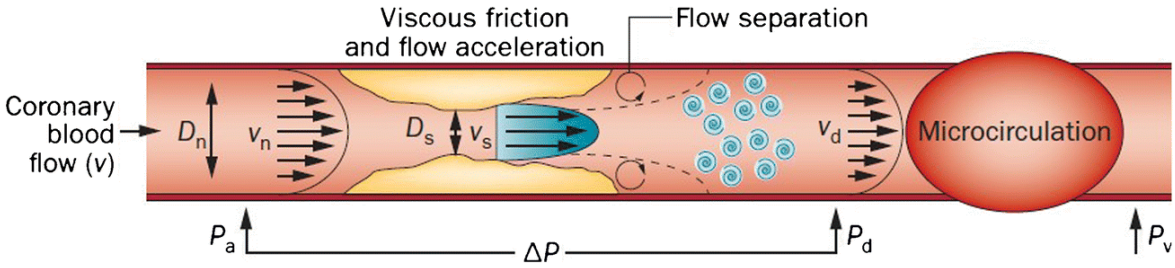


Figure 1.6: Trans-stenotic flow dynamics

Developed parabolic flow accelerates across the stenosis. Flow separation and eddy currents occur in the post-stenotic region resulting in energy loss. Pressure recovery is therefore not complete. The pressure gradient across a stenosis is determined by the sum of the viscous and separation losses. Dn = Normal Diameter, Ds = Diameter at stenosis, Vn = proximal velocity, Vs = stenosis velocity. Reproduced from van De Hoef TP et al., Nature Reviews Cardiology. 2013;10(8)439-52(64) (van de Hoef et al., 2013)with Permission.

The total pressure drop is made up of viscous losses (Poiseuille's law) and those of convective acceleration (Bernoulli's law). Poiseuille losses are linear, whereas Bernoulli losses are quadratically related to flow.

Poiseuille law:

$$\Delta P = \frac{8Q\mu\pi}{A_{ave}^2} L_{seg}$$

Pressure (P) losses increase linearly with flow but are also dependent upon blood viscosity (μ), length (L_{seg}), and critically, on the square of cross-sectional area (A_{ave})

Bernoulli law

$$\Delta P = \frac{1}{2}\rho(V_2^2 - V_1^2)$$

ρ=density of the fluid, V= velocity at a particular point

Whilst these laws describe the relationship between vessel geometry, flow and pressure, a more sophisticated mathematical model is needed to fully describe the haemodynamics. The relationship between pressure drop and velocity can be described by the quadratic equation:

$$\Delta P = Av \text{ and } Bv^2$$

A is a coefficient for of viscous friction loss and is dependent on blood viscosity, the diameter of the stenotic segment, the stenosis length and the ratio of the cross sectional area of the normal coronary artery proximal to stenotic segment (Gould, 1978). B is the coefficient of pressure loss due to flow separation and is dependent on blood density, the ratio of the cross-sectional area to the normal artery distal to the stenosis and on the divergence (exit -angle).

The first term (A) accounts for Poiseuille losses and the second (B) accounts for Bernoulli losses. In the absence of a stenosis, the nonlinear exit losses are removed and the equation reduces to the linear (Poiseuille) part (Figure 1.7).

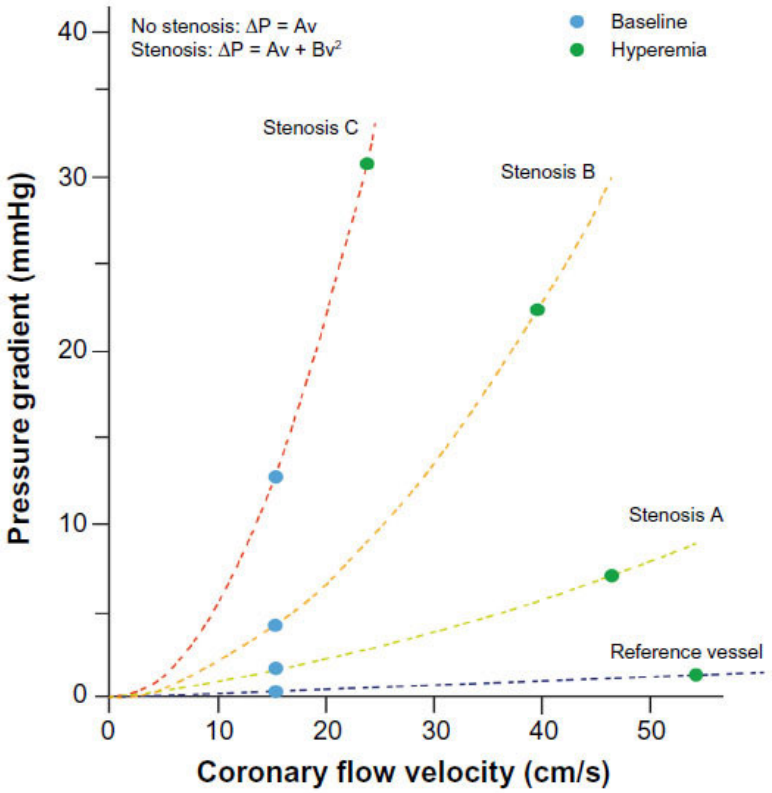
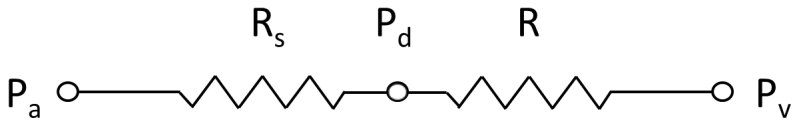


Figure 1.7: Pressure gradient - flow velocity relationship

Pressure loss over an epicardial vessel without a stenosis is negligible, and therefore increases linearly with flow (reference vessel). With increasing stenosis severity (A-C) the curve becomes steeper. This curve is described by the quadratic equation $\Delta P = Av + Bv^2$. Figure reproduced from van De Hoef TP, et al. Fractional flow reserve-guided percutaneous coronary intervention: where to after FAME 2? Vascular health and risk management (van de Hoef et al., 2015a) with permission from Dove Medical Press LTD.

1.6.2 Derivation of FFR

FFR is described as the maximal flow through a vessel in the presence of a stenosis compared to the maximal flow in the hypothetical absence of the stenosis. Pressure-flow relationships are analogous to an electrical circuit and are often described in this way where pressure is represented by voltage, flow by current and physical resistance by electrical resistance. Using such a model, flow down a diseased coronary artery can be described as below.



Pa is the aortic pressure. Rs is the resistance provided by the stenosis. Pd is the pressure distal to the stenosis. R is the myocardial resistance and Pv is venous pressure.

According to Ohm's law:

$$R = \frac{V}{I}$$

and

$$R = \frac{\Delta P}{Q}$$

therefore:

$$P_a - P_d = QR_s$$

and

$$P_d - P_v = QR$$

Therefore, by combining these two circulations:

$$P_a - P_v = Q\ (R_s + R)$$

which can be rearranged to: $Q = \frac{P_a - P_v}{R_s + R}$

FFR by definition is equal to:

$$\frac{Q_{stenosis}}{Q_{normal}}$$

It represents the ratio of flow through the stenosed artery ($Q_{stenosis}$) to that in a hypothetical normal artery (with no stenosis) (Q_{normal}).

Therefore:

$$Q_{stenosis} = \frac{Pa-Pv}{Rs+R}$$

$$Q_{normal} = \frac{Pa-Pv}{R}$$

$$FFR = \frac{P_a-P_v}{R_s+R} \cdot \frac{R}{P_a-P_v}$$

Which simplifies to:

$$FFR = \frac{R}{R_s+R}$$

Which expands to:

$$FFR = \frac{P_d-P_v}{Q} \cdot \frac{Q}{P_a-P_v}$$

Which can be reduced to:

$$FFR = \frac{P_d-P_v}{P_a-P_v}$$

Since *Pv* is assumed to be zero:

$$FFR = \frac{P_d}{P_a}$$

1.6.3 FFR in clinical studies

The impact of FFR guided treatment has been assessed in a number of outcome studies, summarised in Table 1.2. Initial studies focused on the role of FFR-guided management in stable patients. More recently there has been an increased interest in the role in ACS.

1.6.3.1 FFR in stable coronary disease

The DEFER (Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis) study was the first to report that it was safe to refrain from treating lesions with a FFR >0.75 in a cohort of stable patients with single vessel disease (Pijls et al., 2007). In DEFER, 325 patients who were scheduled for PCI to an intermediate lesion underwent FFR assesment. If the FFR was >0.75, they were randomised to 'deferral' (no treatment) or 'performance' (PCI). If the FFR was <0.75, PCI was performed as planned (reference). There was no difference in event free survival at five years between the 'defer' and 'perform' groups (80% and 73% respectively, P=0.52). The composite rate of cardiac death and MI in the 'defer', 'perform' and 'reference' groups were 3.3%, 7.9% and 15.7% respectively. The authors concluded that it was safe to refrain from treating lesions with a FFR >0.75, but due to the study design, were unable to demonstrate a benefit of FFR over traditional management. Moreover, as all patients with a FFR <0.75 were treated, no conclusions could be drawn about the risk of leaving these untreated. At 15 year follow up, there was no significant difference in death between the 'defer' and 'perform' groups (33% versus 31.1%, P=0.79) but the rate of MI was significantly lower in the 'defer' group compared to 'perform' (2.2% versus 10.0%, P=0.03).

Table 1.2: Summary of clinical studies of FFR

Study	N	Outline	Significant results
DEFER (Bech et al., 2001)	325	All patients underwent FFR. If <0.75 PCI performed. If >0.75 randomised to defer (no PCI) or perform (PCI).	No difference in event free survival at 5 years in 'defer' and 'perform' groups (80% vs 73%, P=0.52).
FAME (Tonino et al., 2009)	1005	Patients with multi-vessel disease randomised to either FFR-guided or angiography-guided management.	Significant reduction in MACE at 1 year in FFR-guided group (18.3% versus 13.2%, P=0.02).
FAME-2 (De Bruyne et al., 2012)	888	FFR-guided revascularisation versus optimal medical management.	Significant reduction in MACE at one year in FFR group (4.3% versus 12.7%, P<0.001).
R3F (Van Belle et al., 2014)	1075	Treatment strategy prior to FFR was compared to treatment strategy after FFR measurement.	Change in strategy in 43% of cases. No difference in outcomes at one year based on whether angiogram and FFR agreed or not.
RIPCORD (Curzen et al., 2014)	200	Treatment strategy prior to FFR was compared to treatment strategy after FFR measurement.	Management changed in 26% patients and 32% vessels.
POST-IT (Baptista et al., 2016)	918	Treatment strategy prior to FFR was compare to treatment strategy after FFR measurement.	Management decision changed in 44.2% patients and 45.2% lesions.
FAMOUS-NSTEMI (Layland et al., 2015)	350	Patients with NSTEMI were randomised to receive FFR-guided or angiographically-guided management. FFR measured in all cases but only revealed to operator in the FFR-guided group.	The percentage of patients initially treated with OMT was higher in the FFR-guided group (22.7% vs 13.2%, p=0.02). At 12 months, revascularisation remained lower in the FFR group (79% vs 86.8%, p=0.054). There was no significant difference in MACE rates at one year (8.0% (FFR) versus 8.6% (angio), p=0.89).
COMPARE-ACUTE (Smits et al., 2017)	885	Patients with STEMI randomised to FFR-guided revascularisation or culprit-lesion revascularisation only.	MACE free survival significantly reduced in FFR-guided revascularisation group (7.8% vs 20.5%, P<0.001).
DEFER-DES (Park et al., 2015)	229	Patients with angiographically intermediate stenosis randomised to FFR-guided or routine-DES management. Those in FFR group, if FFR<0.75 underwent DES implantation, if >0.75 treatment was deferred.	No significant difference in MACE between FFR-guided and routine-DES groups at 2 years (7.9% versus 8.8%, p=0.80) or 5 years (11.6% versus 14.2%, P=0.55).

DES = Drug-eluting stent; FFR = Fractional Flow Reserve; MACE = Major Adverse Cardiac Events; OMT = Optimal Medical Therapy; PCI = Percutaneous Coronary Intervention.

The landmark FAME (Fractional Flow Reserve versus Angiography for Multi-Vessel Evaluation) study was the first large prospective study to report favourable outcomes with a FFR-guided approach (Tonino et al., 2009). The simple design allowed a direct comparison between FFR-guided and angiographically-guided treatment. Unlike DEFER, in which only patients with single vessel disease were studied, FAME recruited patients with multi-vessel disease. Patients were randomised to receive standard treatment guided by angiography alone or FFR-guided treatment. Those in the angiography group did not undergo FFR assessment. One thousand and five patients were recruited. Patients were included if they had a stenosis of >50% diameter in at least two of the major epicardial arteries. The authors reported a significant reduction in MACE at one year in the FFR group (18.3% versus 13.2%, P=0.02). FFR-guided treatment was also associated with a significant reduction in cost ($6007 (±2819) versus $5332 (±3261), P<0.001) and in the number of stents placed per patient (2.7 (±1.2) versus 1.9 (±1.3), P<0.001). The favourable outcomes persisted at two year follow up; mortality and MI (12.9% versus 8.4%, P=0.02), MACE (22.4% versus 17.9%, P=0.08). From two to five years the risks in both groups developed similarly. At five years, there was no significant difference in MACE between angiographically guided and FFR-guided management (31% versus 28%, P=0.31). In FAME-2, FFR guided PCI was compared to OMT. The study was halted early due to a significant difference in the primary end point (MACE at one year). This was 4.3% in the PCI group compared with 12.7% in the OMT group (HR PCI 0.32, P<0.001). This was mostly driven by a lower rate of urgent revascularisation in the PCI group (1.6% versus 11.1%). At three years, MACE remained significantly lower in the PCI group compared to the medical therapy group (10.1% versus 22.0%, P<0.001), primarily as a result of a lower rate of urgent revascularisation (4.3% versus 17.2%, P<0.001) (Fearon et al., 2018).

The R3F (Registre Français de la FFR) study was the first to investigate the direct clinical relevance of using FFR as part of diagnostic routine. One thousand and seventy-five consecutive patients underwent diagnostic angiography including FFR at 20 French centres (Van Belle et al., 2014). Investigators were

asked to give their treatment strategy prior to FFR measurement. FFR was then measured and the final management decision, taking into account the FFR, was recorded. The final strategy differed from the *a priori* strategy in 43% of cases. There was no difference in outcomes at one year based on whether the initial and final treatment strategy agreed. The RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography) study, published shortly afterwards, investigated the same concept. In RIPCORD, 200 patients underwent clinically indicated ICA (Curzen et al., 2014). A management plan was made based upon the coronary angiogram. FFR was then measured and the consultant was asked to make a second management plan with FFR results available. Knowledge of the FFR led to a change in management plan in 26% of patients and 32% of vessels. The POST-IT (Portuguese Study on the Evaluation of FFR Guided Treatment of Coronary Disease) study was a prospective registry of FFR use in an unselected 'real world' population (Baptista et al., 2016). In this study, the decision to use FFR was entirely at the operator's discretion. The operators were asked to provide a management strategy both before and after FFR measurement. Nine hundred and eighteen patients were enrolled and a total of 1,293 lesions were evaluated. The management decision changed based upon FFR in 44.2% of patients and 45.2% of lesions. At the lesion level, deferral of treatment in a lesion with a FFR <0.80 was associated with a 3.1-fold increase in MACE (P=0.01). Freedom from the primary end point at 12 months was 94.6% in patients whom management decisions changed based on FFR versus 91.9% in those with concordant decisions (P=0.12). The lowest MACE rate was seen in those who had all lesions deferred based on FFR (5.3%) compared to 7.3% in those that had at least one vessel revascularised and 13.6% in those that were untreated despite an FFR <0.80. The authors concluded that FFR assessment can allow management decisions to be changed safely and can help to identify those that can safely be deferred from treatment. Interestingly, in POST-IT, the proportion of patients ultimately undergoing revascularisation after FFR was known was higher than planned at baseline (34.8% versus 44.0% for PCI and 4.1% versus 8.3% for CABG). This differs from FAME which saw a reduction in PCI with FFR. This is most likely explained by the fact that a much broader

population was studied in POST-IT, including patients who were initially being considered for OMT or CABG. R3F, RIPCORD and POST-IT all have very comparable results and re-affirm the role of FFR in a DES era.

1.6.3.2 FFR in ACS

The majority of early FFR studies focused on its role in stable patients in the elective setting. However, approximately two thirds of patients undergoing PCI in the UK present with ACS (BCIS, 2016). There were initial concerns about the applicability of FFR in ACS, as the responsiveness of the coronary microvasculature can be reduced in this setting and the validity of FFR is contingent on minimising microvascular resistance (through the administration of adenosine). The FAMOUS-NSTEMI (Fractional Flow Reserve versus Angiography in Guiding Management to Optimise Outcomes in Non-ST-segment Elevation Myocardial Infarction) study was designed to assess the role of FFR-guided treatment in the acute setting in 350 patients (Layland et al., 2015). Patients were randomised to either FFR-guided or angiography-guided management. FFR was measured in all patients, but the results were not disclosed to the operator in those in the angiography group. FFR disclosure resulted in a change in management in 21.6% of patients (between OMT, PCI or CABG). The percentage of patients initially treated with OMT instead of revascularisation was higher in the FFR-guided group (22.7% versus 13.2%, P=0.02). At 12 months, revascularisation remained lower in the FFR group (79.0% versus 86.8%, P=0.05). There was no significant difference in MACE rates at one year (8.0% versus 8.6%, P=0.89). In the COMPARE-ACUTE (Fractional Flow Reserve-Guided Multi-Vessel Angioplasty in Myocardial Infarction) study, 885 patients with ST segment elevation myocardial infarction (STEMI) and multi-vessel disease were randomised to receive either complete revascularisation guided by FFR or culprit only PCI (Smits et al., 2017). The primary endpoint was a composite of death, non-fatal MI, revascularisation and cerebrovascular events at one year. There was a significant reduction in MACE with the FFR-guided approach (HR 0.35, 95% CI 0.22-0.55, P<0.001). Similarly to the FAME trial, this

difference was mostly driven by repeat revascularisations (6.1% versus 17.5%, P<0.001). The FAME study, unlike many of the earlier studies, did include patients with ACS. Three hundred and twenty-eight patients had UA or Non ST segment Elevation Myocardial Infarction (NSTEMI), and were included if troponin titres were less that 1,000 units per litre. Although the study was not powered to detect subgroup differences, the results suggested a similar absolute risk reduction of MACE in the UA/NSTEMI group compared to stable angina group (5.1% versus 3.7%, P=0.92) (Sels et al., 2011).

1.6.4 What is the significance of post-PCI FFR?

The benefit of measuring the baseline FFR to indicate the need for revascularisation has become well established. More recently, the relevance of measuring the post PCI FFR has been addressed. This is occasionally performed in clinical practice by operators wishing to assess or quantify the 'success' of their PCI procedure. However, how the value should be interpreted and indeed its prognostic value is less clear. It is intuitive that post intervention physiology would be a better measure of procedural success than anatomical assessment. Despite growing evidence that post PCI physiology is predictive of clinical outcome, as of yet there has been a failure to reach a consensus on the target FFR value that should be used. One of the earliest descriptions of the importance of post PCI FFR was by Pijls et al who, in 2002, reported that following PCI with BMS, a post treatment FFR of <0.90 was associated with a higher rate of MI and revascularisation at six months (Pijls et al., 2002). This was followed by a number of studies in relatively small patient populations using cut offs anywhere between 0.86 and 0.96 for the prediction of clinical events (Nam et al., 2011). The most relevant studies are summarised in Table 1.3. Li et al undertook a large prospective study of 1,476 patients undergoing PCI for either stable angina or UA without biomarker rise (Li et al., 2017). The primary endpoint was target vessel failure at one year. A post PCI FFR value of ≤0.88 was predictive of target vessel failure (8% versus 4%, P=0.001). This was mainly driven by target vessel revascularisation (8.8% versus 3.8%, P=0.005) and cardiac death (1.3% versus 0.2%, P=0.02). The difference was maintained through three year follow up (P=0.002).

Disease in the left anterior descending (LAD) artery was identified as an independent predictor of a suboptimal post PCI FFR and in these patients, a value of ≤0.905 was found to be predictive of target vessel failure at one year. A couple of meta-analyses have also been published. One meta-analysis consisting of 105 studies and 7,470 patients demonstrated that achieving a post PCI FFR of ≥0.90 was associated with a lower risk of repeat PCI (Odds Ratio = 0.43, 95% CI 0.34-0.56, P<0.001) and MACE (Odds Ratio = 0.71, 95% CI 0.59-0.85, P=0.003) (Rimac et al., 2017). Another similarly demonstrated that FFR after stenting has an inverse relationship with prognosis (HR: 0.86, 95% CI 0.80 to 0.93, P<0.001) (Johnson et al., 2014).

A study of 621 patients also examined the relevance of the percentage increase in FFR from the baseline value. The investigators demonstrated a significant reduction in target vessel failure if the post PCI FFR was >0.84 (1.0% versus 2.6%; HR=3.367, 95% CI 1.412 to 8.025, P=0.006) and if the percentage increase in FFR was > 15% (9.2% versus. 3.0%; HR=3.613, 95% CI 1.543 to 8.458, P=0.003) (Lee et al., 2018a).

Table 1.3: Summary of clinical studies of post PCI FFR

Authors, year of publication	Indication for PCI	N =	FFR cut off	Follow up	Findings
(Nam et al., 2011)	2/3 ACS, 1/3 stable angina	80 patients, 99 lesions	≤0.90	1 year	Reduced MACE in higher FFR group (12.5% versus 2.5%, P<0.01).
(Li et al., 2017)	Stable angina or UA	1,476 patients	≤0.88	3 years	TVF at 1 year 8% versus 4% (P=0.001)
(Pijls et al., 2002)	All comers	750 patients	≤0.90	6 months	Post PCI FFR predictive of MACE. FFR >0.95 = 4.9%, 0.90-0.95 = 6.2%, <0.90 = 20.3%.
(Leesar et al., 2011)	Stable angina	66 patients	<0.96	24 months	Event free survival higher if FFR > 0.96 (94% versus 72%, P=0.02)
(Ito et al., 2014)	92% stable angina, 8% unstable angina	97 patients	≤0.90	Median 17.8 months	Post PCI FFR lower in patients with MACE (0.86 v 0.91). Optimal threshold for predicting MACE identified as FFR =0.90.
(Doh et al., 2015)	1/3 ACS, 2/3 stable angina	107 patients, 115 lesions	<0.89	3 years	Higher target vessel survival at 3 years in patients with FFR ≥0.89 (89.3% vs 61.1%, P=0.03).
(Reith et al., 2015)	SA	66 patients	≤0.905	20 months	MACE greater if FFR ≤0.905 (35.9% versus 5.3%)
(Rimac et al., 2017)	Meta-analysis	105 studies, 7470 patients	< 0.90	30 months	Post PCI FFR ≥ 0.90 associated with lower risk of repeat PCI (OR = 0.4, P<0.0001) and MACE (OR 0.71,P=0.003)
(Lee et al., 2018a)	44% ACS, 56% stable angina	621 patients	< 0.84	2 years	Reduction in target vessel failure if FFR >0.84 (9.1% versus 2.6%, P=0.006).
(Johnson et al., 2014)	Meta-analysis	6961 patients	-	14 months	Post PCI FFR has an inverse relationship with prognosis (HR = 0.86, P<0.001)
(Piroth et al., 2017)	FAME 1 and FAME 2 patients	838 vessels 639 patients	0.92	2 years	Post PCI FFR significantly lower in patients with MACE (0.88 versus 0.90, P=0.019).
(Agarwal et al., 2016)	32% ACS, 68% stable angina.	574 patients, 664 lesions	≤0.86	Median 31 months	FFR ≤0.86 predictive of MACE and TVR
(Wolfrum et al., 2016)	Meta-analysis	1,337 patients	Variable as per study		Low FFR associated with higher MACE rate (OR = 4.95, P<0.001), MI, death and repeat revascularisation

ACS = Acute Coronary Syndrome; FFR = Fractional Flow Reserve; MACE = Major Adverse Cardiac Events; TVF = Target Vessel Failure; TVR = Target Vessel Revascularisation; UA = Unstable Angina.

1.6.5 Causes of a suboptimal post PCI FFR

With a growing body of evidence supporting the predictive role of post-PCI physiology, it is increasingly important to understand the cause of suboptimal physiology and whether this can be improved. The recent DEFINE PCI (Physiological Assessment of Coronary Stenosis Following Percutaneous Coronary Intervention) study demonstrated that nearly one in four of all patients leave the cardiac catheter laboratory with suboptimal post PCI physiology (Jeremias et al., 2019). Out of 467 patients in which they measured post PCI instantaneous wave free ratio (iFR), 112 (24%) had a post treatment iFR <0.90. In 82% of cases, this was deemed to be due to untreated focal disease. Determining the location of the residual pressure drop is important in determining the cause and indeed optimising the result. A residual pressure drop across the stented segment can suggest that the procedure can be optimised. A recent study assessed the ability of OCT guidance to be used to optimise PCI. Two hundred and forty patients presenting with NSTEMI were randomised to PCI guided by angiography alone or OCT guided PCI (Meneveau et al., 2016). Post PCI FFR was measured in all patients and was significantly higher in the OCT group (0.94 versus 0.92, P=0.005). OCT revealed the residual pressure gradients to be due to stent under expansion (42%), stent malopposition (32%) and incomplete lesion coverage (20%). In the ILUMIEN 1 (Optical Coherence Tomography Imaging During Percutaneous Coronary Intervention Impacts Physician Decision Making) trial, a statistically non-significant increase in post-PCI FFR from 0.86 to 0.90 was achieved with OCT driven optimisation (Wijns et al., 2015).

Another important cause of a residual pressure drop is the presence of diffuse disease outside the region of the stent. A gradual pressure drop in the presence of diffuse disease can be associated with increased mortality, and is not usually amenable for intervention (Tonino and Johnson, 2016). It has been demonstrated that, in these situations, an optimal physiological result is seldom achieved following PCI, despite the use of long (>30mm) and ultra-long (>50mm) drug-eluting stents (Baranauskas et al., 2016). In patients with a lesion length >30mm, less than a third achieved a post PCI FFR of >0.90 and only

11% achieved a FFR of >0.95. Eight (11%) vessels remained haemodynamically significant (FFR ≤0.80). In another study, 17.8% of vessels remained ischaemic (FFR <0.80) immediately after treatment, and 9.5% continued to be ischaemic despite further attempts at PCI optimisation. Diffuse disease was a predictor of a post-PCI FFR ≤0.80 (Agarwal et al., 2017). The ongoing TARGET FFR (How Often Can Optimal Post PCI FFR Results be Achieved? – a Randomised Controlled Trial of FFR Targeted PCI) trial, which is due to report in March 2020, aims to assess the ability of routine post PCI FFR measurement to optimise the final PCI result. All patients will have pre- and post-PCI FFR measured. In the study arm, the post PCI FFR will be disclosed to the operator to allow further intervention if deemed necessary, whereas in the control arm the post PCI FFR will not be disclosed. The investigators hypothesise that revealing post PCI FFR will increase the proportion of patients achieving a post PCI FFR of ≥0.90.

1.6.6 Caveats of FFR

Despite being supported by outcome data, FFR is based upon a number of assumptions which may affect its interpretation. First, FFR uses measurement of pressure as a surrogate for flow. It is myocardial flow that determines ischaemia, not the perfusion pressure. However, due to complexities associated with invasive flow measurement, it is pressure that is measured. Using pressure as a surrogate for flow assumes a linearity between pressure and flow when coronary resistance is minimal and constant. However, the regulation of coronary vessel tone is complex, and 'minimal and constant' microvascular resistance is not always achieved with the pharmacological methods used (administration of adenosine). Furthermore, even if resistance is minimal and constant, the relationship is not proportional-linear. In fact, it has been shown to have a non-zero pressure intercept and is incrementally linear in the physiological range (Figure 1.8).

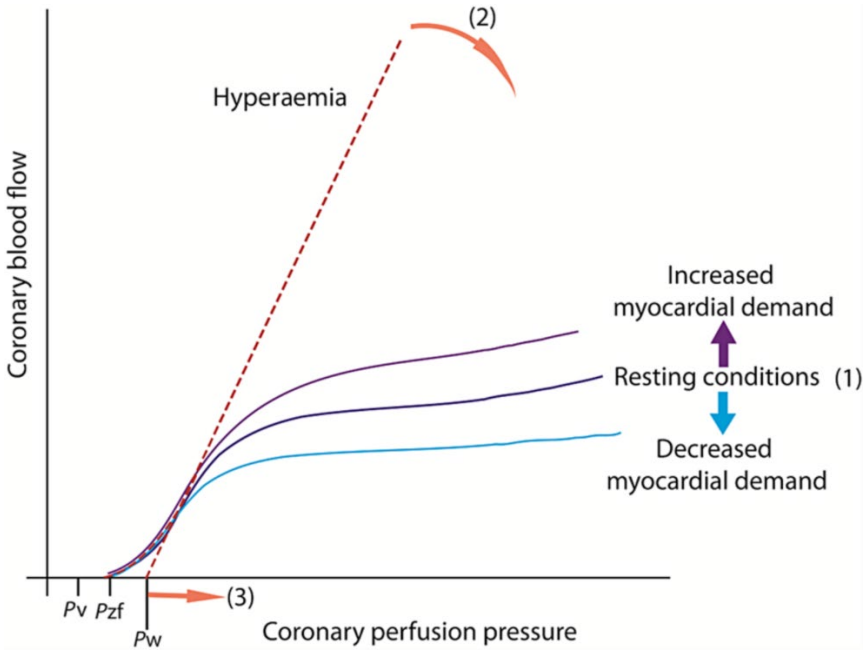


Figure 1.8: The coronary pressure-flow relationship

The coronary pressure–flow relationship. Coronary blood flow at rest (solid lines) is controlled to match myocardial oxygen demand and to counteract variations in perfusion pressure by parallel changes in microvascular resistance, resulting in an auto regulatory plateau (1). During coronary vasodilatation, control is exhausted and blood flow depends upon perfusion pressure (dotted line). The coronary pressure–flow relationship is concave at low perfusion pressures. The zero-flow intercept on the pressure axis (Pzf) slightly exceeds venous pressure (Pv). Straight extrapolation of the hyperaemic pressure–flow relationship results in an incremental–linear relationship that intercepts the pressure axis at the coronary wedge pressure (Pw), which incorporates collateral flow, heart rate, and ventricular wall tension, which may vary widely in the human coronary circulation (3). Small vessel disease or abnormal left ventricular function decreases the slope of the pressure–flow relationship (curved arrow (2)). Elevated left ventricular end-diastolic pressure or left ventricular hypertrophy cause a parallel shift to the right (straight arrow (3)). Adapted by permission from Springer Nature customer service centre GmbH: Springer Nature, Nat Rev Cardiol, Fractional Flow Reserve as a surrogate for inducible myocardial ischameia. Van de Hoef et al. Copyright (2013).

Second, the accuracy of FFR measurement is contingent upon minimising microvascular resistance, and therefore achieving the maximal hyperaemic response. In patients with microvascular disease, microvascular resistance is increased and hyperaemia cannot be reliably achieved. This has an impact upon FFR measurement. Maximal coronary blood flow is impaired, so FFR will 'under-estimate' the lesion severity (Meuwissen et al., 2001); even though, of course, it accurately predicts the futility of treating a lesion in such conditions. Myocardial resistance can also be affected by a number of other factors such as extravascular compression, venous back pressure and left ventricular loading conditions.

All of these can compromise the linearity between pressure and flow (a key assumption in FFR measurement). The response to pharmacological agents which induce hyperaemia is also important. Patients react differently and at different doses, and yet a standard protocol is recommended for all patients. Moreover, the derivation of FFR assumes that microvascular resistance is the same in the presence of a stenosis as in the absence of the same stenosis. However, this may not be correct. Verhoeff et al reported a fall in minimal microvascular resistance in response to coronary perfusion pressure restoration after PCI (Verhoeff et al., 2005). Third, neglecting venous pressure is another potential source of error. Basic FFR metrics require that venous pressure is simultaneously measured (FFR = (pd-Pv)/(Pa-Pv)). However, as central venous pressure is typically close to zero, the simplified equation of FFR = Pd/Pa is used. This may be satisfactory in most cases, but omission of central venous pressure can lead to an over estimation of the FFR index in patients with a particularly raised central venous pressure (Layland et al., 2013). However, a recent study demonstrated that taking into account the right atrial pressure in the FFR calculation led to minimal differences even in patients with markedly increased right atrial pressure suggesting the impact to be negligible (median difference 0.01 (Inter-Quartile Range IQR) 0.01-0.02) (Toth et al., 2016). Moreover, FFR values above the grey zone (0.75-0.85) did not yield values below the grey zone (<0.75). Fourth, FFR measurement is also impacted by procedural difficulties, most notably pressure drift. Pressure drift can occur where there is loss of equalisation over time that is not related to the coronary stenosis and typically only noted when the wire is pulled back to the catheter. This is mostly related to changes in the piezoelectric sensor during measurement and can be minimised by flushing the wire before use. One study suggested that drift affects up to 20% of all measurements (Matsumura et al., 2017). Finally, the use of a dichotomous cut off has also been criticised. FFR represents a marker on the ischaemic continuum yet the recommendation for a FFR of 0.79 is different than that for a FFR of 0.81. It is for this reason that values in the 'grey-zone' are treated with caution. This is particularly important when one considers that FFR has an intrinsic variation of approximately 4% (de Bruyne et al., 1996).

1.7 Other physiological indices

FFR relies upon a number of assumptions because it uses invasive pressure measurement as a surrogate for flow. It would be preferable to assess coronary flow directly. However, flow is much more difficult to measure because invasive flow measurements are technically demanding. Current methods for assessing flow in the cardiac catheter laboratory use techniques based upon Doppler velocity ultrasound or thermodilution, both of which are impractical, challenging and often inaccurate (Cole and Hartley, 1977, Wilson et al., 1985, Sibley et al., 1986, Barbato et al., 2004). Thermodilution requires administration of saline boluses to obtain thermodilution curves and allow the calculation of the mean transit curves. Doppler allows a more direct assessment of flow velocity (not flow volume) but is prone to error, because the wire position is critical to align with the peak velocity profile and requires significant experience and technical skill (van de Hoef et al., 2015c). Recently, improved thermodilution methods using an infusion catheter and thermo- and pressure-sensitive wire have been introduced (Aarnoudse et al., 2007). Whilst this catheter measures volumetric flow rate, it requires additional hardware and is unlikely to enter widespread routine clinical practice. Therefore, whilst coronary flow is an important physiological parameter, limitations of current assessment methods have prevented its adoption into routine clinical practice (van de Hoef et al., 2012, Kern et al., 2006, Kousera et al., 2014, van de Hoef et al., 2015b, Doucette et al., 1992, Barbato et al., 2004). Despite these difficulties, invasive measurements of flow have been tested and validated along with a number of other physiological indices which will be discussed in more detail.

1.7.1 Coronary flow reserve

Coronary Flow Reserve (CFR) is a measure of the ratio of maximal to baseline flow velocity distal to a stenosis. It is a measure of the capacity of the resistance vessels to achieve maximal blood flow in the presence of a hyperaemic stimuli (Kern et al., 2006). A CFR of <2.0 is regarded as abnormal and has been demonstrated to be a prognostic indicator of adverse outcomes in those with and without epicardial

CAD (Pepine et al., 2010). CFR is a measure of both the epicardial and microvascular components and cannot, on its own, distinguish between the two. The uncertainty of the microvascular contribution to CFR makes CFR alone less useful in epicardial lesion assessment. However, its use alongside FFR can improve understanding of patient-specific physiology and has been shown to provide incremental prognostic value. Significant discordance between CFR and FFR has been repeatedly demonstrated and found to occur in up to 30-40% of cases (Figure 1.9). This is thought to reflect the fact that CFR and FFR integrate different domains of the vasculature. A normal FFR with an abnormal CFR can occur in situations with diffuse disease or significant microvascular disease. With diffuse disease, there is less flow separation caused by the stenosis resulting in a smaller pressure drop despite a significant impact on flow. Additionally, in the presence of microvascular disease, low flow can occur despite a minimal pressure drop. Increased microvascular resistance results in a higher distal pressure and therefore a falsely elevated FFR (Figure 1.9). More recently, CFR has been shown to add incremental prognostic value to FFR. Van de Hoef et al studied 157 patients that had been evaluated using FFR and CFR and in whom revascularisation had been deferred. The authors demonstrated discordance between FFR and CFR in 37% of cases (van de Hoef et al., 2014). In cases with a normal FFR, but abnormal CFR, MACE rates at follow up were significantly increased compared to those where both CFR and FFR were normal (46% versus 4% at 3 years, $P<0.001$). In contrast, the group with abnormal FFR and normal CFR had equivalent outcomes to the concordant normal group (8% versus 4%, $P=0.73$). The main disadvantage of CFR is the technical difficulty associated with its measurement. Furthermore, direct outcome data for flow measurements are limited. This is the focus of the DEFINE-FLOW (Combined Pressure and Flow Measurements to Guide Treatment of Coronary Stenoses) trial (NCT02329920) that is expected to report in November 2019. This study is investigating the prognostic value of combining pressure and flow measurements, whereby only lesions with a simultaneous reduction in FFR and CFR will be treated with PCI.

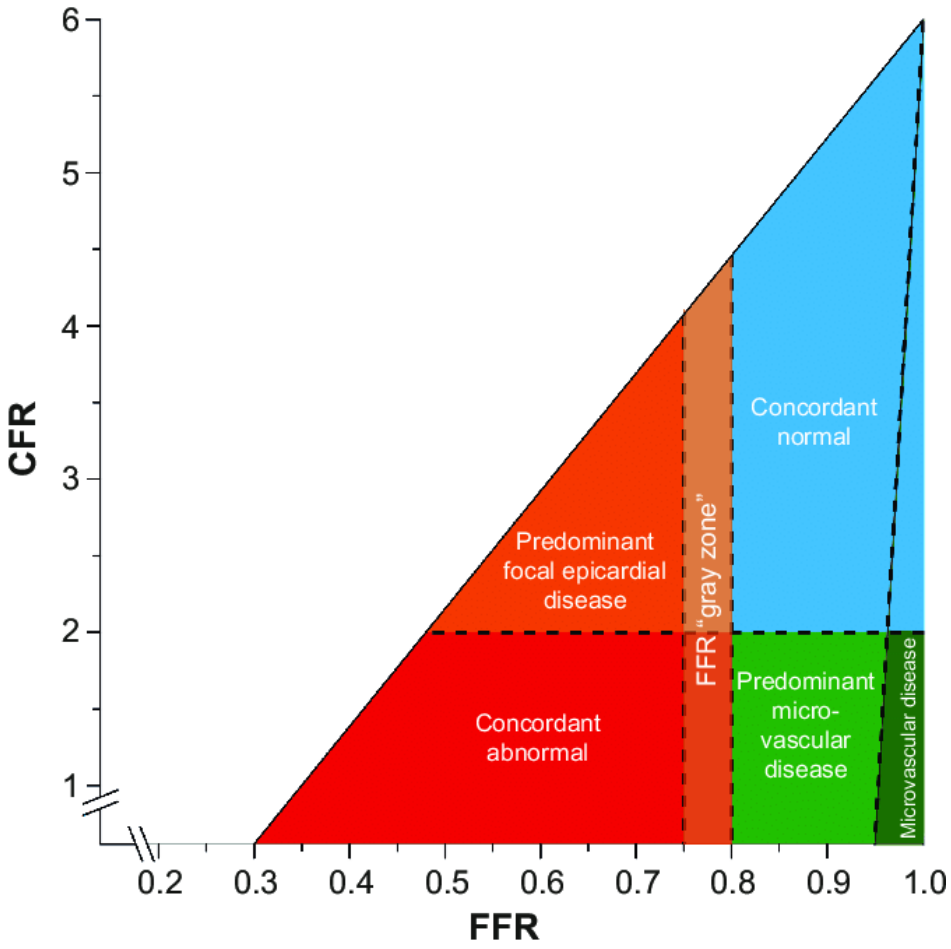


Figure 1.9 FFR-CFR discordance

Conceptual plot of the fractional flow reserve (FFR)–coronary flow velocity reserve (CFR) relationship. Four main quadrants can be identified by applying the clinically applicable cut-off values for FFR and CFR, indicated by the dotted lines. Patients in the upper right blue area are characterized by concordantly normal FFR and CFR, and patients in the red lower left area are characterized by concordantly abnormal FFR and CFR. Patients in the upper left orange area and lower right light green area are characterized by discordant results between FFR and CFR, where the combination of an abnormal FFR and a normal CFR indicates predominant focal epicardial, but non flow-limiting, coronary artery disease, and the combination of a normal FFR and an abnormal CFVR indicates predominant microvascular involvement in coronary artery disease. The small dark green region in the lower right is characterized by an FFR near 1 and an abnormal CFR, indicating sole involvement of the coronary microvasculature. The FFR grey zone indicates the equivocal 0.75 to 0.80 FFR range. Reproduced from van de Hoef et al. Circulation: Cardiovascular Interventions under creative commons license CC BY-NC 3.0.

1.7.2 Stenosis resistance indices

Because of the problems discussed above with using pressure or flow individually, a number of methods have been proposed that combine pressure and flow measurement. This has been assisted by advances in guidewire technology allowing simultaneous flow and pressure measurement with a single wire. The hyperaemic stenosis resistance index (HSR) is defined as the ratio between the average pressure drop over the stenosis and the average flow velocity during hyperaemia. This index gives a refined measurement quantifying the degree of impediment of flow caused exclusively by a stenosis (Gould, 1978). Furthermore, it is independent of basal conditions making it free from some of the limitations of CFR. It has been demonstrated to have high reproducibility and excellent accuracy. In a study of 151 patients, Meuweissen et al compared HSR with FFR and CFR against SPECT as the gold standard (Meuwissen et al., 2002). A deferral threshold of a HSR <0.8mmHgcm-1 was established. HSR had an overall accuracy to identify reversible ischaemia as detected by SPECT of 87% which was significantly higher than FFR (75%, P=0.007) and CFR (75%, P=0.005). The gain in accuracy was predominantly seen in intermediate lesions where there was conflict between CFR and FFR.

The basal stenosis resistance (BSR) index is calculated as the ratio of the pressure gradient to distal flow velocity at baseline. Its main advantage is that it is not dependent on hyperaemia. This measure has been demonstrated to have equivalent diagnostic accuracy for inducible myocardial ischaemia, as determined by SPECT, as FFR and CFR (van de Hoef et al., 2012). However, it was inferior to HSR suggesting hyperaemia is required to demonstrate the full flow limitation of a stenosis. In a subsequent study, accuracy was similar for all (van de Hoef et al., 2016). The ischaemic threshold was determined at 0.66mmhg/cm/s. Although promising, a lack of outcome data is available limiting the use of these measures in clinical practice.

1.7.3 Instantaneous wave-free ratio (iFR)

IFR is a resting index of stenosis severity that is measured during a period of diastole known as the wave-free period. During this period, flow velocity is intrinsically high and the relationship between flow and pressure becomes linear. Therefore, an assessment of pressure ratios can give a good indication of stenosis severity (as determined by the limitation in flow). The ADVISE (Adenosine Vasodilatation Independent Stenosis Evaluation) study compared iFR with FFR in 157 stenoses demonstrating good correlation (R = 0.90). The authors demonstrated a classification match of 80%, which is similar to the classification match between repeated measures of FFR in the DEFER study (85% match) (Petraco et al., 2013). The CLARIFY (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease) study compared iFR and FFR to HSR. CLARIFY showed that iFR and FFR have equal diagnostic efficiency to match HSR (Sen et al., 2013). IFR has also been shown to have a stronger correlation with CFR compared to FFR (Petraco et al., 2014). IFR can also be calculated during pressure wire pullback. Because iFR does not require induction of hyperaemia, iFR pullback may be more accurate is assessing tandem lesions than FFR pullback (Stone et al., 2005) (Nijjer et al., 2014). This is because it is not affected by distal disease which acts a fixed resistor, affecting the ability to achieve 'true' hyperaemia. 'Virtual PCI' algorithms have been developed that can 'remove' a stenosis on a pullback trace and then compute the residual gradients to estimate an expected post-PCI iFR (Nijjer et al., 2014). Two large multi-centre outcome studies DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndromes) have recently reported demonstrating non-inferiority of iFR compared to FFR. In DEFINE FLAIR, 2,492 patients were randomly assigned to undergo iFR-guided or FFR-guided revascularisation (Davies et al., 2017). The investigators demonstrated non-inferiority of iFR versus FFR in the primary outcome of MACE at one year (6.8% versus 7.0%, P<0.001 for non-inferiority). Adverse procedural symptoms and clinical signs were lower in the iFR group (3.1% versus 30.8%, P<0.001). In a similar design, iFR SWEDEHEART recruited

2,037 patients with stable angina or ACS who had an indication for physiologically guided assessment of a coronary stenosis (Gotberg et al., 2017). Patients were randomised to iFR-guided or FFR-guided management. There was no significant difference in MACE at one year (6.7% in iFR and 6.1% in FFR, P=0.007 for non-inferiority).

1.7.4 Resting Pd:Pa

IFR requires software from a specific vendor that identifies the 'wave-free' period. However, a resting Pd:Pa can be calculated using the mean pressures over several cycles, and is universally available. Its use was examined in a post hoc analysis of the CONTRAST (Can Contrast Injection Better Approximate FFR compared to Pure Resting Physiology) study (Kobayashi et al., 2017). Seven hundred and sixty three patients were studied and Pd:Pa was compared with iFR. The investigators demonstrated that Pd:Pa was highly correlated with iFR (R^2 =0.93) with good agreement (mean difference: 0.00 ± 0.03; 95% limits of agreement: −0.06 to 0.06), and with a scatter similar to repeated iFR measurements. Using the diagnostic treatment threshold value of an iFR ≤0.89, they demonstrated excellent agreement with a Pd:Pa <0.91. The area under the curve was 0.98. Diagnostic accuracy, sensitivity, specificity, PPV and NPV were 93.0%, 91.4%, 94.4%, 93.3%, and 92.7% respectively. Lee et al also compared resting Pd:Pa and iFR with percentage diameter stenosis in 1,024 vessels (Lee et al., 2019). They demonstrated a similarly high correlation between iFR and Resting Pd:Pa (R=0.97).

1.8 Coronary physiology in the guidelines

The renewal of interest in coronary physiology and the improvements in clinical outcome shown in the DEFER and FAME trials have led to FFR being included in clinical guidelines. In the ESC guidelines, FFR or iFR is recommended as a class 1A recommendation to identity haemodynamically relevant coronary lesions in stable patients when evidence of ischaemia is not available. The 2017 American College of Cardiology (ACC) appropriate use criteria for coronary revascularisation in stable ischaemic

heart disease also recognise the advances in coronary physiology (Patel et al., 2017). Not only is FFR-guided treatment recommended, but iFR can be substituted for FFR, reflecting the outcomes of the recent DEFINE-FLAIR (Davies et al., 2017) and iFR-Swedeheart (Gotberg et al., 2017) trials. Despite incorporation into the guidelines, FFR is estimated to be used in just 5-10% of all PCI procedures (Dattilo et al., 2012), and almost no purely diagnostic angiograms. There are a number of proposed reasons for this poor uptake including the cost of pressure wires, the technical steps and additional procedural time required, the requirement for adenosine and the operator underestimating the importance of physiology. Additionally, FFR is only available at PCI-capable centres, yet a number of diagnostic angiograms in the UK are performed at district general hospitals by non-interventional cardiologists. In an attempt to increase availability of coronary physiology, many groups have sought to find a method of virtual FFR that does not require passage of a pressure wire or administration of adenosine.

1.9 Virtual FFR

Several groups have applied computational fluid dynamics (CFD) allied to 3D anatomical models based upon different modalities of coronary imaging to calculate FFR (a 'virtual' FFR, vFFR) without requiring the passage of a pressure wire. CFD is a numerical technique that predicts and analyses mechanical responses of fluids to external (and other) forces allowing the quantification of physiological parameters such as blood flow velocity and pressure. For incompressible fluids, the majority of the methods solve the Navier-Stokes equations which are the governing equations describing the conservation of mass, momentum and energy.

In order to compute vFFR using CFD, both anatomical and physiological inputs are required. Although different groups have employed slightly different methods, the overall principles and key steps remain the same. First, a 3D reconstruction of the arterial anatomy is created from coronary imaging in a process known as segmentation. This surface geometry is then discretised (meshed) into a finite number of

volumetric elements. The boundary conditions of the model must then be defined. The boundary conditions represent the physical conditions at each of the boundaries of the model, which in the case of coronary artery models are the inlet, outlet and vessel wall. Assumptions about these boundaries, especially the outlet, must be made and how different groups approach this varies. A CFD solver is then used to generate predictions of pressure and flow along the vessel. Initial models were based upon CTCA, but more recently invasive coronary angiography models have emerged.

1.9.1 FFR_{CT}

CT based FFR solutions combine image based modelling and CFD techniques. An anatomical model is generated from the CTCA data. Mathematical principles are applied to derive the boundary conditions and a numerical solution for the fluid dynamics laws provide the simulation of pressure and flow. The greatest success in FFR modelling to date has been achieved by Heartflow inc, Redwood City, California with their method of FFR_{CT} that was the first model to achieve Food and Drugs Agency (FDA) and European Medicines Agency (EMA) approval. In their model, the boundary outlet pressure and resistance is derived from the diameter of the coronary outlets and the myocardium subtended. The hyperaemic coronary microvascular resistance (CMVR) is then assumed to be 0.24 of the CMVR at rest (Taylor et al., 2013). FFR is then computed using a 3D CFD solver. The predictive value of this method of FFR_{CT} has been assessed in a number of large clinical studies. In the DISCOVER-FLOW (Diagnosis of Ischaemia Causing Stenosis Obtained Via Non-invasive FFR) study, 103 patients with known or suspected CAD underwent CTCA, ICA and FFR. In this study, modelled FFR was more accurate than CTCA alone at detecting significant CAD (84% versus 59%) (Koo et al., 2011). A FFR_{CT} value of <0.80 had an accuracy of 84.3%, sensitivity of 87.9%, specificity of 82.2%, PPV of 73.9% and NPV of 92.2%. In the DeFACTO (Diagnostic Accuracy of Fractional Flow Reserve from Anatomic CT Angiography) study, patients with stable or suspected CAD who were scheduled for ICA underwent FFR_{CT} (Min et al., 2012). This multicentre study assessed 252 patients, and demonstrated a diagnostic accuracy of FFR_{CT}

of 73%. The NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial included 251 patients with stable angina (Norgaard et al., 2014). This trial used an improved computational algorithm with increased automation and improved segmentation. Accuracy, sensitivity, specificity, PPV and NPV were 81%, 86%, 79%, 65% and 93% respectively. Curzen et al took the 200 CTCAs from NXT and performed a retrospective analysis akin to the methodology of RIPCORD (Curzen et al., 2016). They asked cardiologists to make a management plan based on the CTCA alone, then revealed the FFR_{CT} and asked for their revised decision. The management strategy changed in 36% cases, which is a similar result as reported in the original RIPCORD study. The recently reported SYNTAX 3 trial also examined the ability of FFR_{CT} to impact decision making (Cavalcante et al., 2017). In this trial, the treatment of 233 patients was considered by two separate heart teams. The first had non-invasive imaging data only, including FFR_{CT} whereas the second had conventional invasive angiography data. There was a very high concordance between the treatment recommendations of the two groups. Addition of FFR_{CT} changed the treatment decision in 7% and modified treatment planning in 16% (Modolo et al., 2018). The largest, and first prospective, FFR_{CT} trial to date was the PLATFORM (Prospective Longitudinal Trial of FFR-CT Outcome and Resource Impacts) trial (Douglas et al., 2015). This was a prospective cohort study of 585 patients. Patients were divided into those initially recommended to undergo ICA and those recommended to have a functional test. Patients within each group were randomised to receive standard care (ICA or functional tests) versus CTCA with FFR_{CT}. In the cohort initially recommended for ICA, FFR_{CT} reduced the number of patients proceeding to ICA as well as the proportion of negative ICAs (73% versus 12%, $P<0.001$). The recent NICE guidelines recognise the promise of FFR_{CT} and state it should be considered for patients with stable, recent onset chest pain who are offered CTCA as part of their diagnostic pathway (NICE, 2016).

1.9.1.1 Limitations of FFR_{CT}

However, FFR_{CT} is not without limitation. First, the results are very dependent on the quality of the CTCA from which the anatomical model is created. In DEFACTO, NXT and PLATFORM 11%, 13%

and 12% of datasets respectively were unsuitable due to artefact, motion and extensive coronary calcification. This is likely to be higher in the real world. Second, processing times are long. Third, translation of findings to those seen at ICA can be challenging. Fourth is the lack of data focusing on cases in the grey zone (FFR between 0.75-0.85, where decision making is particularly challenging). A large systematic review analysed results from five studies comprising 908 vessels that had been assessed with FFR_{CT} (Cook et al., 2017). The authors demonstrated significant variation in the diagnostic accuracy achieved across the range of FFR values. The overall diagnostic accuracy was 81.9%; but when FFR_{CT} values were within the range of 0.70-0.80, the diagnostic accuracy was significantly lower at 46.1%. The majority of studies of FFR_{CT} have focused on the diagnostic accuracy of FFR_{CT} compared to CTCA alone, to which it is superior at predicting significant lesions at seen at angiography. But few studies have examined its ability to achieve equivalence, or to replace invasive FFR. The role of FFR_{CT} in different disease states is also less clear. A recent study by Gaur et al examined the use of FFR_{CT} to assess non-culprit vessels in patients with recent STEMI (Gaur et al., 2017). Accuracy in this cohort was lower than previously described (72%). Although better than CTCA (66%, $P<0.001$), there was no advantage over ICA alone (70%) ($P=0.10$). Moreover, the correlation between FFR_{CT} and invasive FFR was just 0.57. This exposes the vulnerability of FFR_{CT} in different disease states. It was hypothesised that the key assumptions used in determining the boundary conditions do not apply in this cohort, explaining the reduction in accuracy. The authors demonstrated that these patients had a lower 'volume to mass ratio' compared to those studied in the NXT trial. Volume to mass ratio was determined by dividing the total coronary artery lumen volume (calculated from combined image based and morphometric data) by the left ventricular myocardial mass.

Other groups have described slightly different methods, with the main focus being on improving the long processing times seen with FFR_{CT} (Heartflow). Ko et al utilised a reduced order one dimensional (1D) model, which is significantly less computationally intense (Ko et al., 2017). They derived boundary conditions by accounting for structural deformation changes in the coronary lumen and the adjacent

aorta across the entire diastolic phase. Their method requires 320 detector CT, but can be performed in 30 minutes on a standard desktop computer. Diagnostic accuracy was 83.9% with a mean bias of 0.065 (± 0.137). Giannopoulos et al aimed to develop and validate a fast FFR_{CT} algorithm utilising the Lattice Boltzman method for blood flow simulation. Lattice-Boltzman is a class of CFD that instead of solving the Navier-Stokes equations, solves the discrete Boltzman equation. The average computational time of their method was 40 mins. In a study of 64 patients, they demonstrated a diagnostic accuracy of 90.4% and a mean bias of 0.009 in predicting invasive FFR (Giannopoulos et al., 2018). Despite some promising results, no other group has achieved regulatory approval or demonstrated clear outcome data.

1.9.2 Angiography-based vFFR

A number of angiography-based vFFR solutions have emerged. These methods, instead of utilising CTCA data, utilise images acquired during ICA as the basis of the 3D reconstruction. Following the anatomical reconstruction, similar methods (using CFD or mathematical formulae) can be utilised to predict the vFFR. One of the key differences, other than the reconstruction, is the composition of boundary conditions. Many CT models use data from the CTCA to inform the distal boundary condition (i.e. myocardial mass). In angiography-based solutions, this is not possible, so other methods are employed.

1.9.2.1 The VIRTUheart™ system

A vFFR based upon ICA, using similar CFD techniques, has been developed by our group (Figure 1.10).

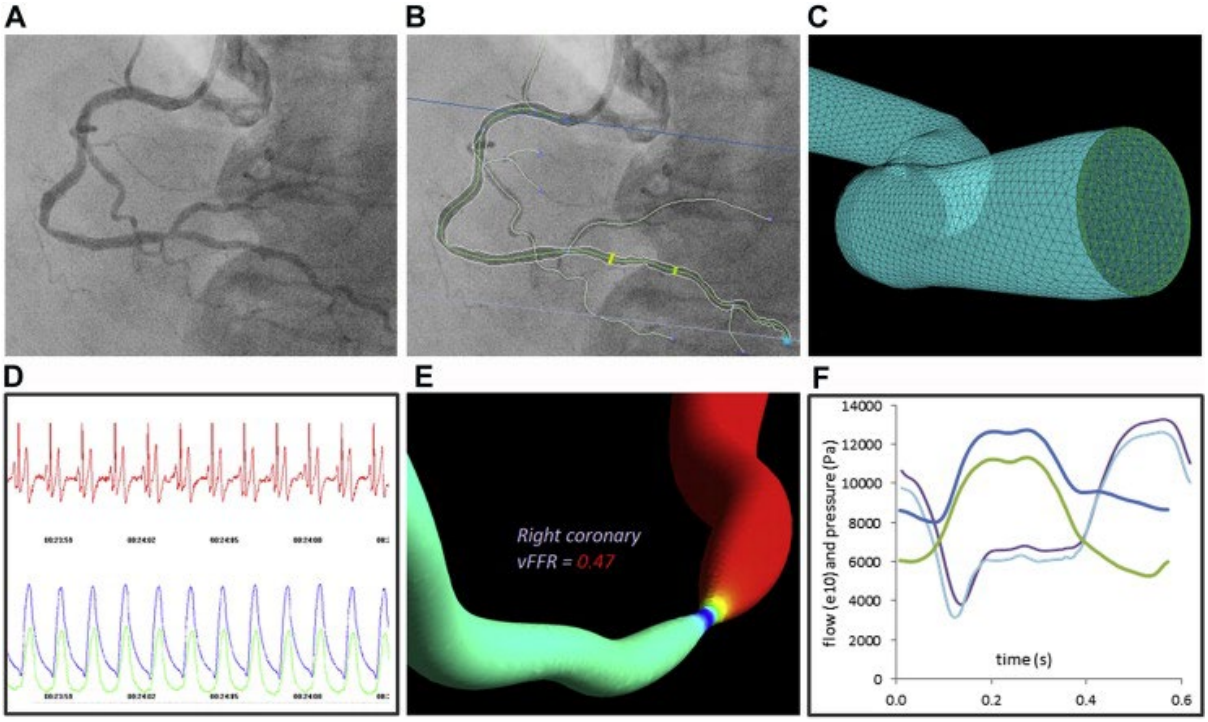


Figure 1.10: The Sheffield VIRTUheart™ workflow

*A Coronary angiogram **(A)** is "segmented" and reconstructed **(B)** into a 3-dimensional (3D) model **(C)**. Surface and volumetric meshing "discretize" the patient-specific geometry **(C)**. The physiological conditions beyond the modelled section must be represented at each boundary, that is, "boundary conditions" **(D)**. Computational fluid dynamics simulation computes the pressure gradient, using the anatomical 3D model "tuned" with physiological parameters. Pressure ratio is computed from output data **(E)**. Results are validated against invasive measurements during development **(F)**. vFFR = virtual fractional flow reserve." Figure reproduced from Morris et al (Morris et al., 2015) https://doi.org/10.1016/j.jcin.2015.04.006 under creative commons attribution license (CCBY) https://creativecommons.org/licenses/by/4.0/..*

This system has a diagnostic accuracy to predict significant lesions (FFR <0.80) of 97% and precision (predicting the actual FFR value) of ±0.06 (Morris et al., 2013). This system permits vFFR measurements to be made for any patient undergoing an angiogram. Currently a number of manufacturers offer software for estimating FFR using CFD techniques.

1.9.2.2 Medis quantitative flow ratio

The Medis model produces a quantitative flow ratio (QFR) and is based upon TIMI (flow grades based on results of the Thrombolysis in Myocardial Infarction trial) frame counting (Tu et al., 2014). Mean hyperaemic flow is determined from TIMI frame counting to assess the rapidity of the contrast wave

front during injection. This flow is then used as the input to a 3D CFD simulation. Their initial model still required induction of hyperaemia and as it is only an estimate of mean flow it can only be applied to steady-state CFD simulations. However, they were able to demonstrate good correlation with invasive FFR ($R=0.81$, $P<0.001$) and an overall diagnostic accuracy of 88%. In a follow-up study, they examined the ability of using contrast flow without inducing hyperaemia, demonstrating good agreement with their original technique (Tu et al., 2016). This method was then examined further in the FAVOR II (Functional Diagnostic Accuracy of Quantitative Flow Ratio in On-line Assessment of Coronary Stenosis) study (Xu et al., 2017). Three hundred and eight patients were studied and a diagnostic accuracy of 92.7% was achieved. Furthermore, the authors demonstrated good agreement between QFR and FFR (mean difference = -0.01 (±0.06), $P=0.006$). However, the absolute difference was >0.10 in 8.5% of cases and >0.05 in 31.4% of cases. The mean computational time was 4.36 mins per case.

1.9.2.3 PIE Medical

Within the past few years the CAAS 3D QCA workstation (Pie Medical Imaging, Maastricht, Netherlands) has been adapted to incorporate physiological lesion assessment. One of the first studies validating the software was performed by Papafaklis et al (Papafaklis et al., 2014). In this work, the authors utilised 3D-QCA to derive a virtual functional assessment index (vFAI). They demonstrated good agreement with invasive FFR (mean difference of -0.0039 (±0.085)) and an accuracy, sensitivity and specificity of 88%, 90% and 86% respectively. Their method utilised CFD analysis to determine the artery specific pressure gradient-flow relationship. vFAI was then computed based upon the ratio of distal to proximal pressure over the lesions for flows in the range of 0 to 4ml/s. However, vFAI is a function of the geometry of the stenosis and does not take into account the patient specific physiology or the influence of the microvasculature. More recently, the CAAS vFFR workstation has been developed which is a 3D QCA derived model of vFFR. In this model, the pressure drop is calculated by applying the physical laws of Poiseuille and Bernoulli, following the concepts as introduced by Gould

et al (Gould et al., 1982). They include a patient specific aortic pressure and estimate the hyperaemic blood flow empirically from clinical data. Their model does not require full CFD computation and therefore processing times are fast. This model was evaluated in the FAST (Validation of 3D-QCA based software to calculate Fractional Flow Reserve: Fast Assessment of Stenosis Severity) study (Masdjedi et al., 2019). The authors demonstrated good correlation between FFR and vFFR (R=0.89) in a cohort of 100 patients and a diagnostic accuracy of 93%.

1.9.2.4 CathWorks

The CathWorks FFRangio^{TM} system utilises mathematical formulae applied to 3D coronary anatomical reconstructions to produce a virtual FFR. Their method is based upon rapid flow analysis. Following 3D anatomical reconstruction, all stenoses are converted into resistances in a lumped parameter model and scaling laws are used to estimate the microcirculatory bed resistance. The FFR value is then calculated from the ratio of hyperaemic flow rates in the stenosed vessel versus the healthy vessel. This method does not use CFD and produces results within minutes. (Pellicano et al., 2017). The FAST-FFR trial analysed the accuracy of the Cathworks, Ltd model. Investigators studied 319 vessels from 301 patients, demonstrating a per vessel sensitivity of 94% and specificity of 91%. The overall diagnostic accuracy of the model was 92%, which importantly remained high (87%) when only considering FFR values within the grey zone (0.75-0.85). The Bland-Altman limits of agreement were -0.14 to 0.12 (Fearon et al., 2019).

In a large meta-analysis, Collett et al analysed 13 studies comprising 1,842 vessels (Collet et al., 2018). They demonstrated a pooled sensitivity of 89% and specificity of 90% for all angio-vFFR solutions. Meta-regression analysis did not identify differences between the methods used for pressure – drop calculation (CFD versus mathematical formula), type of analysis or software packages. The development of angio-vFFR methods is extremely promising. Angiography derived vFFR will increase the

availability of physiological measurement to a far greater number of patients than at present, being available at the time of original diagnostic angiography, rather than in a minority of interventional procedures. It has added value over CT solutions, as there are no issues of translation of findings and it gives the opportunity for complete diagnostic assessment in one sitting. There are also some advantages of vFFR over measured FFR. vFFR can be calculated anywhere in the coronary tree, including areas where it may be difficult or dangerous to pass a pressure wire. Importantly, it also lends itself to virtual coronary intervention (VCI) whereby different treatment strategies can be trialled 'in-silico' and the predicted physiological outcomes compared.

1.10 Computational modelling applied to coronary stenting

Computational methods are routinely used in designing stents and in predicting their performance using the principles of solid phase mechanics and engineering. They can also be used to model the effect of the stent upon blood flow in a diseased artery at the strut level, where disturbed flow can predispose to thrombosis, restenosis and neo-atherosclerosis. Modelling is particularly applicable to study these phenomena, which are beyond the level of resolution of clinical measurements of flow (Van der Heiden et al., 2013). Modelling can also predict the effects of stenting upon bulk blood flow in the artery. Any desired width or length of stent can be modelled. For this, the details of the stent structure are not required, because details of flow disturbance at the stent/artery interface are not required, reducing the complexity of the modelling. Such a model can not only demonstrate the new appearance of the stented vessel, but also, by being incorporated into one of the systems described above, provide a prediction of the new flow rate and the new vFFR. To an expert in 3D CFD modelling simulating the insertion of a virtual, cylindrical, stented segment into a modelled coronary vessel with recalculation of blood flow is a relatively elementary challenge. This could allow operators to predict the physiological and anatomical response to treatment with stents of different sizes in different locations, to plan the optimal solution before any treatment is delivered. This technique has recently been demonstrated based upon the

Heartflow FFR_{CT} model (Kim et al., 2014). The investigators identified 44 patients with functionally significant lesions who underwent clinically indicated ICA with FFR measurement. CTCA was performed prior to ICA and 3D models of the coronary tree were reconstructed. Data on coronary flow and pressure were simulated using CFD. The pre-stent model was then marked for the location of stent used to treat the patient and a virtual stent was inserted to replicate the *in vivo* procedure. Subsequent vFFR was computed following virtual stent implantation. The diagnostic accuracy to predict ischaemia after PCI was 96% (sensitivity 100%, specificity was 96%, PPV 50%, and NPV 100%). The mean difference between vFFR and measured FFR after PCI was 0.024 (95% level of agreement -0.08-0.13). This tool has been further demonstrated in the study of serial lesions (Ihdayhid et al., 2017). Applying a VCI tool to invasive coronary angiograms will allow treatment planning to occur in the diagnostic cardiac catheterisation laboratory; a major advance. A simple case with an isolated lesion may not require VCI. Interest will be concentrated on complex disease, such as serial lesions, diffuse disease and bifurcations. An important question which VCI can address is to determine the minimum length of stent to provide close to physiological normality. It may be hypothesised that a smaller calibre, shorter stent may provide the same physiological benefit as a longer, larger stent, whilst leaving mild disease uncovered.

1.11 Aims and objectives

The overall aim of this thesis is to develop and validate a VCI tool as an add-on to the existing VIRTUheart^{TM} model of vFFR that can predict the physiological response to various PCI treatment strategies and determine the potential of this tool to impact 'real world' stenting.

My primary hypotheses are:

1.) VCI can predict the physiological response to stenting with a high degree of accuracy.

2.) Combining vFFR and VCI has the potential to influence PCI treatment decisions in the 'real world.'

I will test these hypotheses by completing the following experimental objectives:

1.) Develop a VCI tool as an add-on to the existing VIRTUheart^{TM} workflow.
2.) Validate the novel tool in patients who have undergone PCI guided by invasive FFR measurement.
3.) Determine the ability of VCI to predict the best possible FFR that can be achieved in a cohort of retrospective PCI cases.
4.) Make a comparison between the best possible FFR and actual achieved FFR in these cases to determine the need for treatment planning.
5.) Examine the ability of an all in one diagnosis and treatment planning tool (vFFR and VCI) to impact 'real world' stenting in a retrospective virtual study.
6.) Examine the ability of this all-in-one approach to impact decision making in a virtual clinic setting.

Chapter 2 - Tool development and validation

2.1 Aims and objectives

This chapter describes the development and validation of the computational method of VCI. The aim of the work in this chapter is to develop and validate a VCI tool as an add-on to the existing VIRTUheart™ workflow (Morris et al., 2013).

Objectives:

1.) Develop a VCI tool as an add-on to the VIRTUheart™ system.

2.) Apply the VCI tool to a series of patients who have undergone FFR-guided PCI.

3.) Analyse the ability of the VCI tool to predict the physiological response to stenting.

2.2 The VIRTUheart™ workflow

The VIRTUheart™ workflow can be divided into the following key steps:

1.) Image acquisition

2.) Segmentation

3.) VCI

4.) Mesh preparation

5.) Selection of boundary conditions

6.) CFD analysis.

2.2.1 Image acquisition

The VIRTUheart™ workflow is based upon invasive coronary angiography. Images from standard single plane angiography or rotational angiography can be utilised in the current workflow. Accurate segmentation (3D vessel reconstruction) requires good quality images with adequate views of the region

(vessel) of interest. This requires good contrast opacification and at least two views that demonstrate the region of interest with minimal vessel overlap. Furthermore, it is important to limit the use of magnification and panning across the image.

2.2.2 Segmentation

Segmentation describes the process of generating a 3D reconstruction from the angiographic images. Segmentation based upon coronary angiography has already been described, but remains challenging, largely due to cardiac motion which makes co-registration of images challenging. The segmentation tool incorporated into the VIRTUheart^{TM} workflow has been developed using MATLAB (Mathworks, Massachusetts, US) at the University of Sheffield. It utilises standard, single plane angiographic images, making it universally applicable. First, the DICOM (digital imaging and communications in medicine) images are loaded into the bespoke graphical user interface (GUI) (Figure 2.1). Two views are selected by the user that are at least 30 degrees apart. This can be in either the right anterior oblique (RAO)/ left anterior oblique (LAO) or caudal/cranial direction. The images are imported alongside the ECG trace, allowing the user to identify frames in end-diastole. This phase is chosen because it is when coronary flow is maximal and not impeded by myocardial contraction.

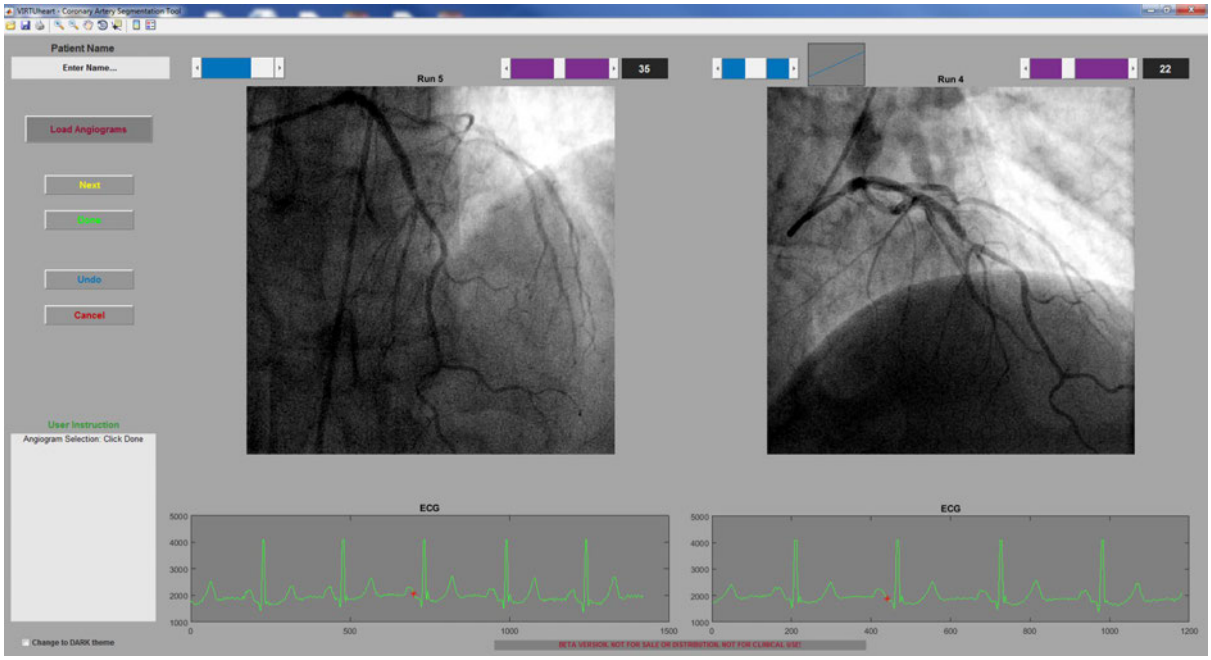


Figure 2.1: The Sheffield segmentation tool graphical user interface (GUI)
The two chosen views are displayed alongside each other with the corresponding ECG trace. The operator can select an appropriate frame using the scroll bar above each image (top right).

Image registration is then required to compensate for any table movement that may have occurred between the two image acquisitions. In the cardiac catheterisation laboratory, the patient is positioned on a table under the x ray C arm. Between image acquisitions, the table is often moved to assist with positioning of the C arm. Accurately registering the two images remains a challenge. Our tool employs a single-point correction method that is based upon the equations of the epipolar lines and is encoded within MATLAB. This method computes the global shift of an object from identification of a single point in the two projections. It assumes that the global z coordinate (representing the table height) and global z translation shift are both known.

To perform the correction, user interaction is required to select a point that can confidently be identified on both images. This is usually a bifurcation point or a section of disease (Figure 2.2). The two images are then co-registered.

Figure 2.2: Image co-registration

A point is selected on the left-hand image. In this example the branch point has been selected (blue cross). The corresponding epipolar line is displayed on the right-hand image and the corresponding point is selected by the user. This branch can be confidently identified in both images allowing accurate registration.

The user then interacts with the GUI to mark the centreline of the vessel of interest on the first image. Once complete, the edges of the vessel are detected automatically by the software. Any errors in edge detection can be corrected manually by the using the manual correction tool (Figure 2.3).

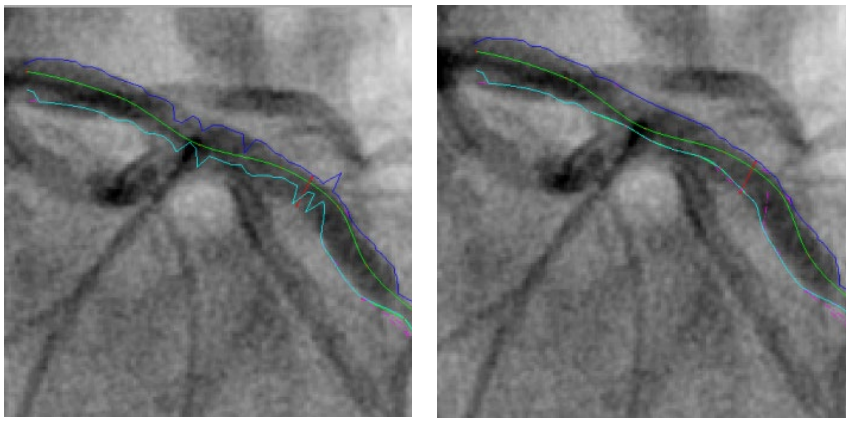


Figure 2.3: Manual correction

Any errors in edge detection can be corrected with the manual correction tool. The user clicks along the edge of the vessel to correct any errors (left image) and the outline is corrected (right image).

This process, from centreline marking to manual correction, is repeated on the second image. Once complete, a surface mesh and centreline of the 3D geometry are generated (Figure 2.4). The surface mesh is exported as a stereolithography (stl) file and the centreline as a visualisation toolkit (vtk) file.

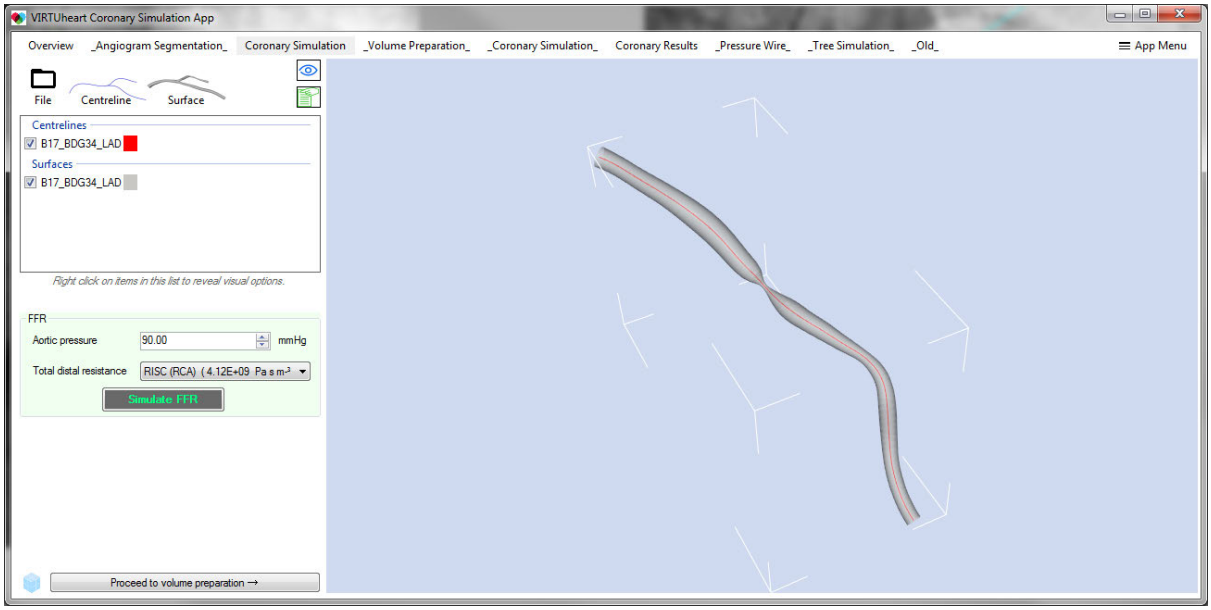


Figure 2.4: The surface mesh
Following completion of segmentation, a surface mesh and centreline (red line) are generated which are imported into the VIRTUheart™ workflow.

2.2.3 VCI 'surface manipulation'

The surface mesh (as either a Virtual Reality Modeling Language (VRML) or STL file) is imported into the VIRTUheart™ system. The centreline of the vessel is selected and the VCI tool can be opened. The VCI tool is a radius correction tool that allows the operator to adjust the radius of the vessel, simulating the effect of inserting a stent. The geometry of the patient vessel is expressed as a set of connected circular cross-sections, following the points that form the centre of the vessel path. Using the dedicated VIRTUheart™ GUI, the operator marks the arterial location of where they wish to deploy a stent (Figure 2.5). The operator then determines the diameter and length of the stent they wish to deploy, just as they would in the cardiac catheter laboratory. Vessel-stent interaction is simulated by smoothing the vessel trajectory using a cubic spline and adjusting the cross-sectional radius. This can be performed by one of

two methods; with or without vessel straightening. In the former, the vessel is straightened between the points where the stent is inserted. In the latter, the radius is adjusted but the vessel curvature remains unchanged. The VIRTUheart^{TM} software then outputs the corrected surface mesh; the virtually stented artery (Figure 2.5). The final vessel geometry is composed of triangle strips connecting each cross-section, each strip containing 128 triangles. This step can be repeated if more than one virtual 'stent' is to be inserted in the same artery. This permits the modelling of multiple stent strategies.

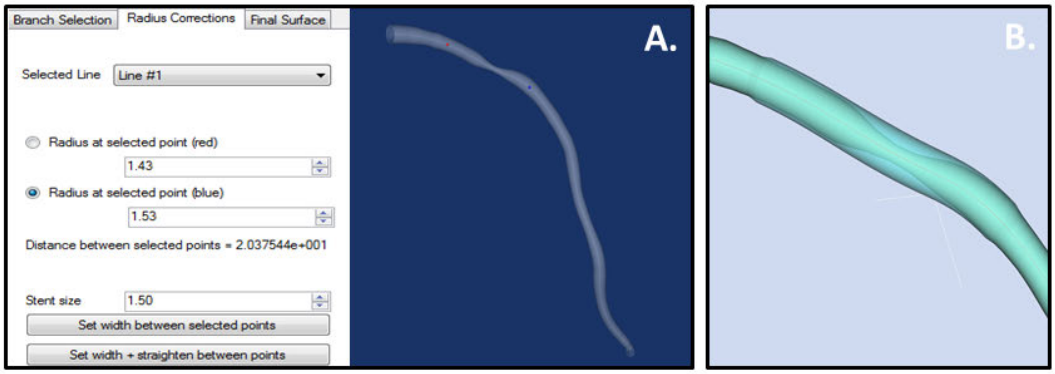


Figure 2.5: The VCI tool

A) The 3-dimensional reconstruction of the artery is displayed on the screen, and the operator marks the arterial location where they wish to deploy a stent identified by the red (proximal) and blue (distal) markers. In the text (left), the vessel radii at both selected points are displayed as well as the distance between them. The operator can adjust the radius of the desired virtual stent in the box below ("stent size"). The length can be altered by moving the position of the red and blue dots. In the example shown, a 3.0mm × 20mm virtual stent has been inserted by the operator. The surface mesh is manipulated to match these stenting criteria. (B) The new surface (the virtually stented artery) is shown overlaying the original vessel (right panel). Reproduced under creative commons license CC BY 4.0 from Gosling et al. Virtual coronary Intervention: A treatment planning tool based upon the angiogram. JACC Cardiovasc Imaging. Mar 9 2018.

2.2.4 Mesh preparation

Once the surface manipulation has been completed, a volumetric mesh is created in a process known as discretisation. The surface is discretised (divided) into millions of tetrahedral cells. The integral forms of the conservation equations are then applied to the control volume defined by the 'cell' to obtain the discrete equations for the cell. This process is completed using ANSYS® ICEM CFD,

which is embedded into the VIRTUheart™ software. An example volume mesh is shown in Figure 2.6.

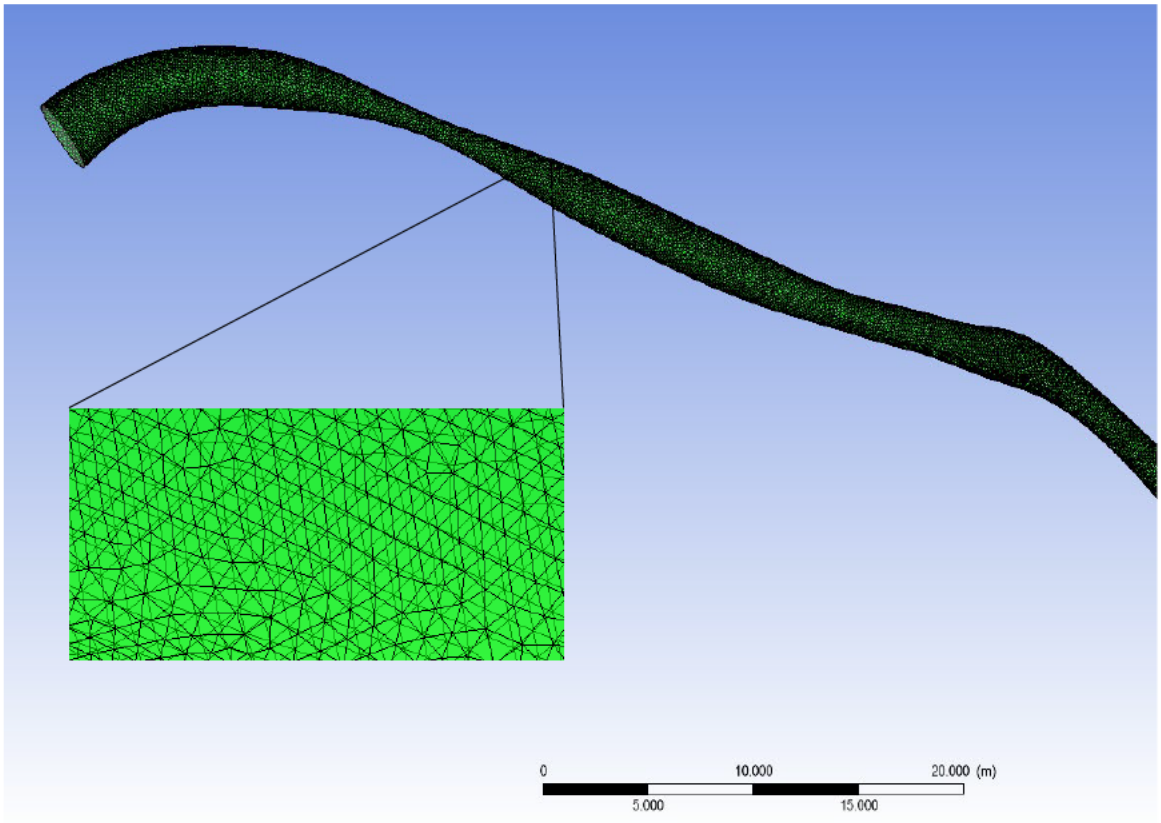


Figure 2.6: The Volumetric Mesh
The surface mesh is discretised into a volumetric mesh. The volumetric mesh is made up of millions of tetrahedral cells allowing the solutions for each 'cell' to be computed by the CFD solver.

2.2.5 Boundary conditions

Before the CFD analysis can be completed, the boundary conditions must be defined. In a coronary artery model, there are three boundaries to be considered; the vessel inlet, the vessel wall and the vessel outlet. This is an important step as poorly defined boundary conditions can significantly affect the reliability of these models. For patients undergoing ICA, the inlet boundary is known (proximal aortic pressure). Therefore, this patient-specific pressure is applied at the inlet. The vessel wall is modelled as a rigid wall. Although this is not physiologically accurate, this method is widely accepted in coronary circulation models (Zeng et al., 2008). The distal (outlet) boundary provides much more of a challenge.

The distal boundary of the coronary artery represents the CMVR. It is known that this varies from patient to patient in health and disease. However, at present, there is no way to accurately predict this value on a patient-specific basis without invasive measurement. Therefore, we can use two approaches. First, if our aim is to compute virtual FFR without the need for invasive pressure measurement, we apply a generic resistance value, derived as an averaged value from a previously studied cohort (CMVR = 8.721e9 Pa/m^3s^{-1}). However, if pressure-wire data is available we can use a personalised distal boundary condition. For this, the patient-specific CMVR is calculated from the Pd (obtained from the pressure wire measurement) and the computed flow. An initial CFD simulation is run using the invasively measured proximal and distal pressures as the respective boundary conditions. From this simulation, coronary flow can be accurately predicted. CMVR is then calculated as:

$$\text{CMVR} = \frac{Pd - Pv}{Q}$$

Pv is assumed to be zero therefore this simplifies to:

$$\text{CMVR} = \frac{Pd}{Q}$$

vFFR is then computed using this personalised patient and vessel-specific CMVR at the distal boundary. In both of these methods, the distal boundary is represented as a single resistance parameter. This method does not permit the production of dynamic data but can provide a single FFR value and is quick (Morris et al., 2017). A more sophisticated approach that has also previously been utilised by our group is to use a Windkessel model. The Windkessel is an electrical analogue of the arterial vasculature, in which the downstream resistance is calculated from the pressure and flow over the heart cycle. Rather than representing the entire coronary circulation within a single compartment, it is possible to discretise into a number of lumped parameters. The three element Windkessel consists of a resistance component, capacitance (elasticity of the arteries) and impedance (ratio of oscillatory pressure and flow when no reflected waves are present) arranged in parallel. In addition, because coronary flow predominates in diastole, further elements must be added to the terminal node to represent the back-pressure. Even more

complex models exist, but the result is only slightly better accuracy with significantly increased user input (Morris et al., 2017).

2.2.6 CFD solver

Once the boundary conditions have been defined, CFD is computed using ANSYS® CFX commercial software. The CFD software solves the steady state equations of fluid flow (Navier-Stokes and continuity) in 3D using the conservation form of the finite volume method. The result is a FFR value for the whole vessel and a pressure map that shows the pressure drop along the vessel (Figure 2.7). In our current workflow, vFFR is computed using a steady state protocol. This allows fast computation, with comparable accuracy to transient solutions, and has significantly reduced computation times (Morris et al., 2017). In the computation of steady state vFFR, the distal parameters of coronary microvascular physiology are reduced to a single time averaged resistance as described above. vFFR can therefore be described as a function of four parameters: mean proximal pressure (Pa), terms Z_1 and Z_2 and total distal resistance. Z_1 and Z_2 represent the linear and quadratic coefficients that describe the relationship between pressure and flow.

The relationship between pressure and flow is described as:

$$dP = (Z_2 \cdot Q_2) + (Z_1 \cdot Q_1) + Z_0$$

where dP = pressure drop, Q is flow and Z_2, Z_1 and Z_0 are dimensional constants.

It is assumed that when flow is zero, pressure drop (dP) is zero, therefore $Z_0 = 0$. At two specified flow rates (Q1 and Q2), the pressure drops are computed as dP_1 and dP_2 respectively. From this Z_1 and Z_2 can be calculated as:

$$Z_1 = \frac{dP_1 Q_2^2 - dP_2 Q_1^2}{(Q_1 Q_2^2 - Q_1^2 Q_2)}$$

$$Z_2 = \frac{(dP_1 Q_2 - dP_2 Q_1)}{(Q_1^2 Q_2 - Q_1 Q_2^2)}$$

Our solver uses flow rates of 1ml/s and 3ml/s. This is based on work by Morris et al (Morris et al., 2017) that determined these as the optimal rates in order to determine the Z_1 and Z_2 parameters.

Once Z_1 and Z_2 are known, the coronary flow, for a given myocardial resistance can be calculated as:

$$Q = \frac{-(Z_1 + R) + \left(\sqrt{(Z_1 + R)^2 + 4Z_2 \cdot Pa}\right)}{2Z_2}$$

vFFR can then be determined as:

$$\text{vFFR} = \frac{Q \cdot R}{P_a}$$

vFFR is then displayed within the VIRTUheart^{TM} workflow as a colour map (Figure 2.7). The vFFR at any point of the vessel can be displayed.

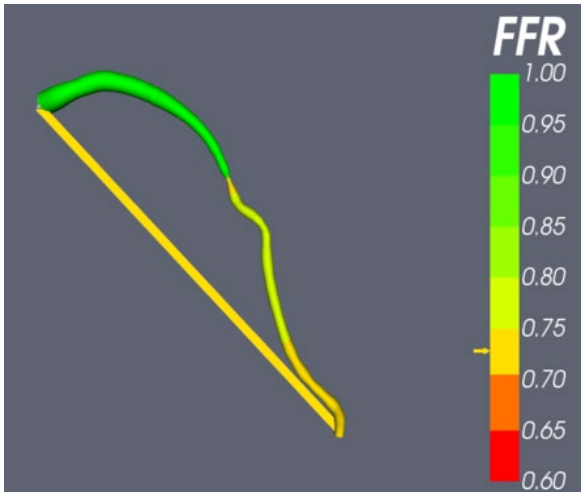


Figure 2.7: Example vFFR result
The simulated vessel is displayed with a corresponding colour map showing the pressure drop down the length of the vessel. The cursor can be moved to reveal the vFFR value at any point along the vessel.

2.3 Tool validation

In order to validate the VCI tool, a cohort of patients who had undergone FFR guided PCI were studied. The aim was to demonstrate the ability of the tool to predict the physiological response to stenting.

Objectives:

1.) Perform VCI on a series of patients who have undergone FFR guided PCI replicating the real-life procedure.
2.) Compare post PCI FFR values with FFR post VCI using both personalised and generic distal resistance values.

The primary aim was to validate the method of virtual stent insertion. The two main factors affecting the accuracy of vFFR are the geometrical reconstruction and the distal boundary conditions (Morris et al., 2017). The method of VCI affects the geometrical reconstruction. Initially, to assess this alone, I use

personalised distal boundary conditions, derived from the invasive pressure wire measurements. This allows us to independently assess the error produced with the VCI tool, i.e. the accuracy is primarily related to the anatomy of the reconstruction and not the boundary conditions. However, as this method requires invasive pressure wire data, its clinical use may be limited as it will be subject to the same problems as invasive FFR assessment. Therefore, I also wanted to test whether, using generic values that do not require invasive pressure wire measurement, it is possible to predict the post treatment FFR with reasonable accuracy. Therefore, in the second step I applied generic boundary conditions. This allows the tool to be used without passing a pressure wire and therefore potentially makes it more clinically usable.

2.3.1 Methods

2.3.1.1 Study design

This was a single site cohort study carried out at the South Yorkshire Cardiothoracic Centre. The study protocol was approved by the local ethics committee (13/YH/0070) (see Appendix).

2.3.1.2 Study population

Data were collected prospectively for patients undergoing elective PCI between January 2014 and June 2016. Patients provided written informed consent and were eligible if they were >18 years of age and had angiographically confirmed disease that was being considered for PCI. Patients were excluded if they had presented acutely within 60 days, had previous CABG surgery, chronic total occlusion(s), or were unable to consent. Clinical, demographic, FFR and angiographic data were collected prospectively for all patients. If patients did not proceed to PCI, either due to a negative FFR or operator judgement, they were not included.

2.3.1.3 Procedure protocol

All patients underwent ICA. All arteries with disease affecting >50% vessel diameter were assessed using a pressure wire (Volcano, Philips, Amsterdam, The Netherlands). Hyperaemia was induced by an intravenous infusion of adenosine at 140μg/kg/min. The FFR was measured during stable hyperaemia. The decision to proceed to PCI was made by the operator utilising the findings from angiographic and invasive FFR assessment. The PCI procedure, including the number and sizes of stent(s), followed standard practice. The number, size and position of stent(s) used was documented. Following PCI, a repeat FFR measurement was taken.

2.3.1.4 Virtual coronary intervention (VCI)

VCI was carried out within the VIRTUheart^{TM} workflow using the methods described above. The dimensions and position of the stent(s) used in the procedure was replicated using the VCI tool, without stent straightening. Two separate analyses were performed. In the first, personalised boundary conditions were applied to the model as described above. In the second, a generic distal resistance value was applied at the distal boundary. This value (8.7231e9 Pa/m^3s^{-1}) was obtained as an average value from a previously studied cohort of patients. Following initial analysis, VCI was repeated in the first 20 cases with stent straightening to determine if there is any significant physiological difference between the two methods.

2.3.1.5 Statistical analysis

Data are presented as mean and standard deviation or as percentages (proportions) unless stated otherwise. Measured (m)FFR and vFFR were compared pre-PCI and post-PCI and post-VCI. The diagnostic accuracy (the ability of VFFR to predict whether mFFR was < or >0.80) was assessed by calculating the sensitivity, specificity, PPV, NPV and overall accuracy. The agreeability between mFFR and vFFR was assessed using a Bland-Altman plot. All statistics were calculated using SPSS version 24

(IBM SPSS Inc., NY). Sample size was determined using a power calculation. It was determined that 58 cases would be required to achieve 90% power to detect a difference of >0.03 (two sided alpha of 5%).

2.3.2 Results

2.3.2.1 Patient and lesion characteristics

I studied 54 patients undergoing elective PCI. Baseline patient and lesion characteristics are shown in Table 2.1

Table 2.1: Baseline patient and lesion characteristics

Patient characteristics	
Mean age (years)	63.2 (±10.7)
Male	45 (83%)
Current smoker	6 (11%)
Hypertension	36 (67%)
Hyperlipidaemia	38 (70%)
Type 2 Diabetes Mellitus	12 (22%)
Previous MI	23 (43%)
Mean BMI (kg/m^2)	29.1 (± 3.9)
Lesion characteristics	
Mean lesion length (mm)	20.6 (±14.4)
Mean % diameter stenosis	58 (±13.1)
Mean stent length (mm)	24.6 (±9.2)
Mean stent width (mm)	3.1 (±0.5)
Bifurcation disease	15 (28%)
Tandem lesions	18 (33%)

Values are mean (±SD) or N(%). MI = Myocardial infarction, BMI = Body mass index.

One patient had no pre-PCI FFR due to an inability to pass the wire, giving 58 paired pre-PCI datasets. In one case, two stents were inserted sequentially with a FFR measurement taken after each, giving 60 paired post-PCI datasets. Of the 59 vessels treated, the number of stents per vessel was 1.1 (±0.3). The stent length and width were 24.6mm (±9.2) and 3.1mm (±0.5) respectively. All patients received second

generation drug eluting stents. CFD solutions were successfully obtained in all vessels. The CFD computational time was approximately two minutes per case (Morris et al., 2017). This time is in addition to the segmentation which is approximately eight minutes per vessel. An example is shown in Figure 2.8.

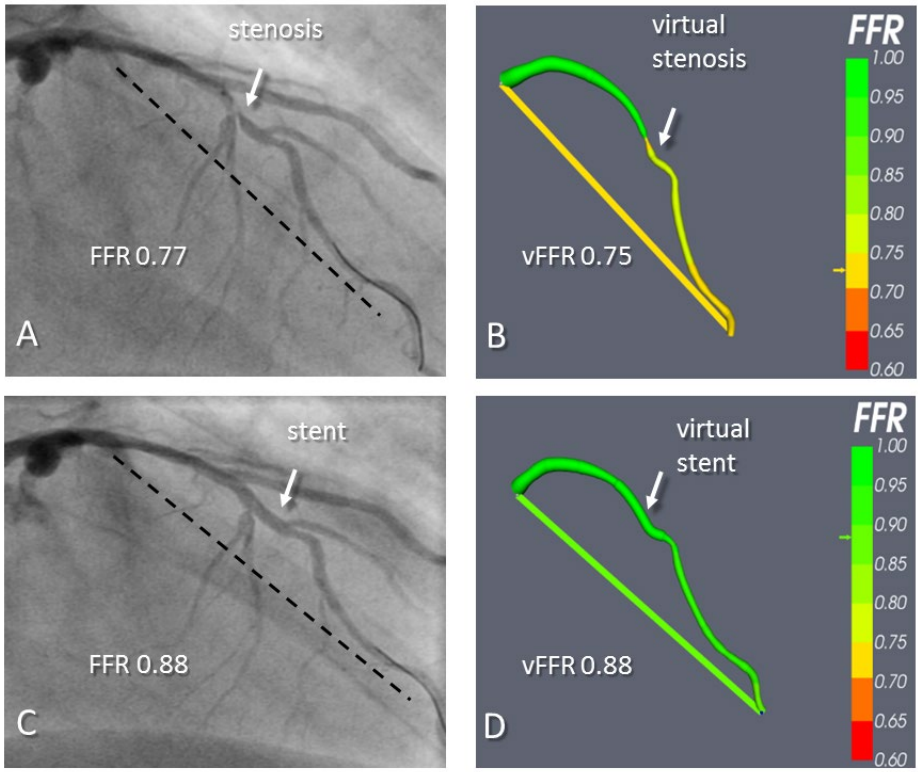


Figure 2.8: Illustrative example of VCI

A) A 66-year-old male presented with symptoms suggestive of stable angina. His LAD had a mid-vessel stenosis (arrow). The measured (m)FFR was 0.77. B) The angiograms were used to model the virtual (v)FFR using the VIRTUheart™ system, which was calculated to be 0.75 over the same segment. C) After implantation of a 2.75mm x18mm stent at the stenosis, the mFFR was 0.88 over the same segment. D) VCI was then used to implant a 'virtual' 2.75mm x18mm stent, and the recalculated vFFR was 0.88. Reproduced under creative commons license CC BY 4.0 from Gosling et al. Virtual coronary Intervention: A treatment planning tool based upon the angiogram. JACC Cardiovasc Imaging. Mar 9 2018.

2.3.2.2 Accuracy to predict vFFR using personalised boundary conditions ($vFFR_{persBC}$)

Prior to PCI, the mean mFFR was 0.66 (±0.14) and the mean $vFFR_{persBC}$ was 0.67 (±0.14). Fifty-six cases were included in this analysis. One patient had no pressure file available meaning the personalised resistance could not be calculated. In another, the transient analysis, by which the CMVR is calculated, failed to converge and therefore there was little confidence in resistance value. The mean difference (bias) between $vFFR_{persBC}$ and mFFR was -0.004 (±0.04). The average error was 0.02 (±0.03). The Bland-Altman plot is shown in Figure 2.9. $vFFR_{persBC}$ and mFFR were closely correlated; R=0.96 (Figure 2.10). The diagnostic accuracy of $vFFR_{persBC}$ to predict ischaemia (invasive FFR ≤0.80) was 91% (PPV 98%, NPV 43%, sensitivity 92%, specificity 75%). After PCI, the mean mFFR was 0.90 (±0.05) and the mean $vFFR_{persBC}$ post VCI was 0.91 (±0.05). The mean difference (bias) between $vFFR_{persBC}$ post VCI and mFFR post PCI was -0.005 (±0.02). The average error was 0.01 (±0.01). The Bland-Altman plot is shown in Figure 2.9. $vFFR_{persBC}$ and mFFR were closely correlated; R=0.88 (Figure 2.10). The diagnostic accuracy to predict residual ischaemia (FFR ≤0.80) was 100% (PPV= 100%, NPV = 100%, sensitivity = 100%, specificity = 100%).

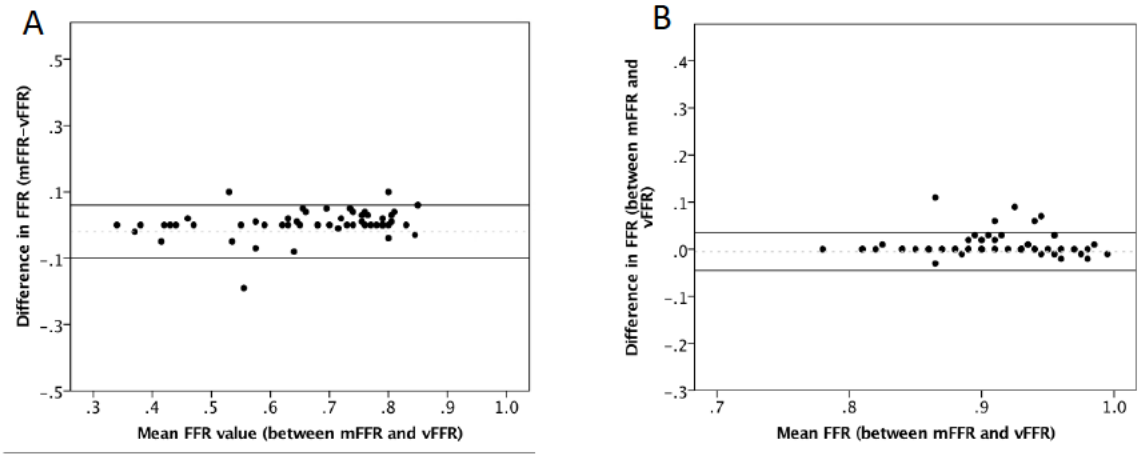


Figure 2.9: Bland Altman plots demonstrating agreement between $vFFR_{persBC}$ and mFFR
The difference between measured (m)FFR and virtual (v)FFR_{persBC} is plotted against the mean value pre-PCI (A) and post-PCI and VCI (B). The two dark lines represent the limits of agreement 2 SD above and below the mean delta.

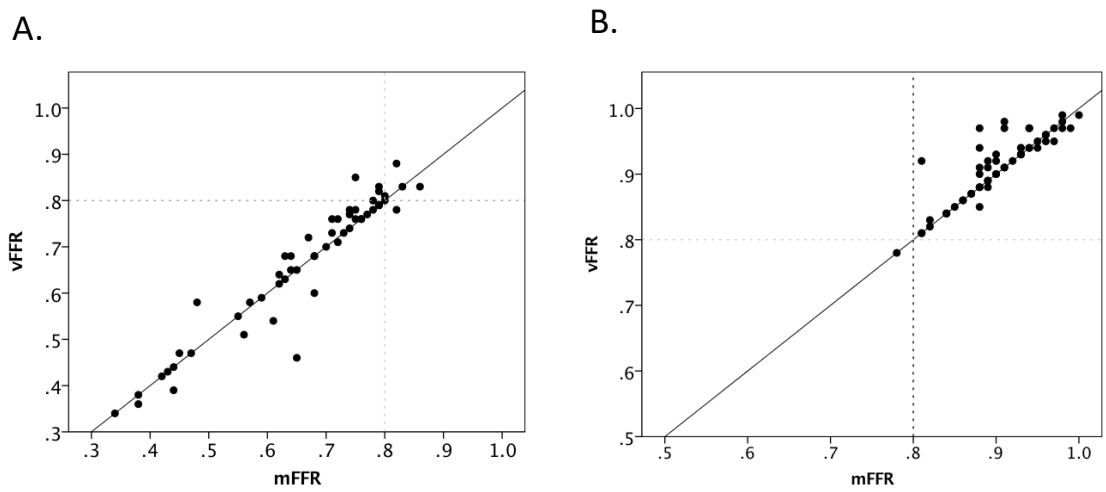


Figure 2.10: Correlation between vFFR and mFFR using personalised boundary conditions
Correlation between $vFFR_{persBC}$ and mFFR pre (A) and post (B) PCI/VCI with a line of best fit passing through the origin. R=0.96 and 0.88 respectively.

2.3.2.3 Accuracy of vFFR using generic boundary conditions ($vFFR_{genericBC}$)

Prior to PCI, the mean mFFR was 0.66 (±0.14) and the mean $vFFR_{genericBC}$ was 0.68 (±0.13). The mean difference (bias) between $vFFR_{genericBC}$ and mFFR was -0.02 (±0.07). The average error was ±0.05 (±0.05). The Bland-Altman plot is shown in Figure 2.11. The $vFFR_{genericBC}$ and mFFR were closely correlated (R=0.87) (Figure 2.12). The diagnostic accuracy of vFFR to predict ischaemia (invasive FFR≤0.80) was 93% (PPV 100%, NPV 64%, sensitivity 92%, specificity 100%). After PCI, the mean mFFR was 0.90 (±0.05) and the mean $vFFR_{genericBC}$ was 0.92 (±0.05). The mean difference between post-VCI $vFFR_{genericBC}$ and post PCI-mFFR was 0.01 (±0.03). The average absolute error was ±0.02 (±0.03). The Bland-Altman plot is shown in Figure 2.11. The $vFFR_{genericBC}$ and mFFR were closely correlated (R=0.80) (Figure 2.12). The diagnostic accuracy to predict residual ischaemia (invasive FFR ≤0.80) was 93% (PPV 100%, NPV 64%, sensitivity 92%, specificity 100%). The diagnostic accuracy per FFR value (combining both pre- and post-VCI cases) is shown in Figure 2.13. All results are shown in Supplemental Table 1 (Appendix).

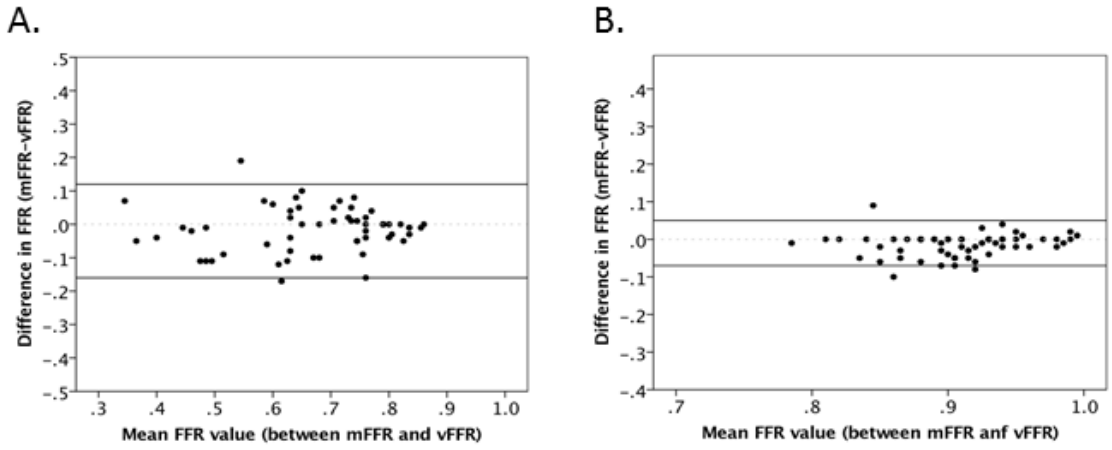


Figure 2.11: Bland-Altman plots demonstrating agreement between $vFFR_{genericBC}$ and mFFR
The difference between measured (m)FFR and $vFFR_{genericBC}$ is plotted against the mean value pre-PCI (A) and post-PCI and VCI (B). The two dark lines represent the limits of agreement 2 SD above and below the mean delta. Reproduced under creative commons license CC BY 4.0 from Gosling et al. Virtual coronary Intervention: A treatment planning tool based upon the angiogram. JACC Cardiovasc Imaging Mar 9 2018.

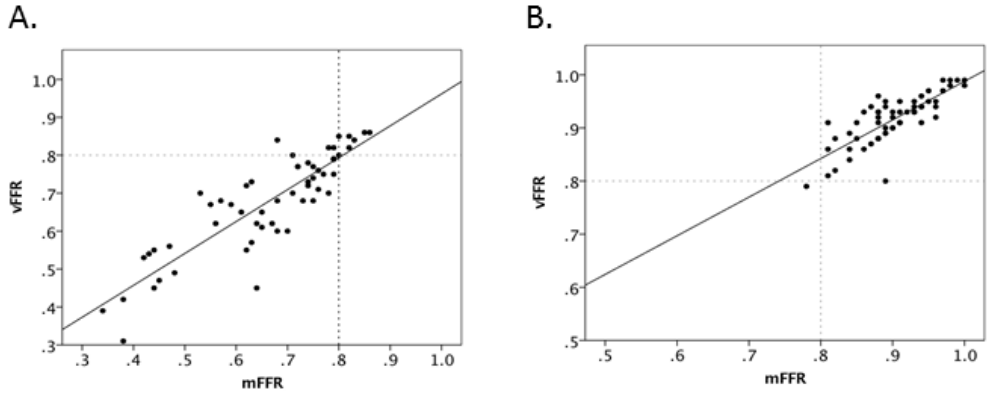


Figure 2.12: Correlation between $vFFR_{genericBC}$ and mFFR before and after VCI
Correlation between virtual (v)$FFR_{genericBC}$ and measured (m)FFR pre PCI (A) and post PCI/VCI (B) with a line of best fit passing through the origin. R= 0.87 and 0.80 respectively. Reproduced under creative commons license CC BY 4.0 from Gosling et al. Virtual coronary Intervention: A treatment planning tool based upon the angiogram. JACC Cardiovasc Imaging Mar 9 2018.

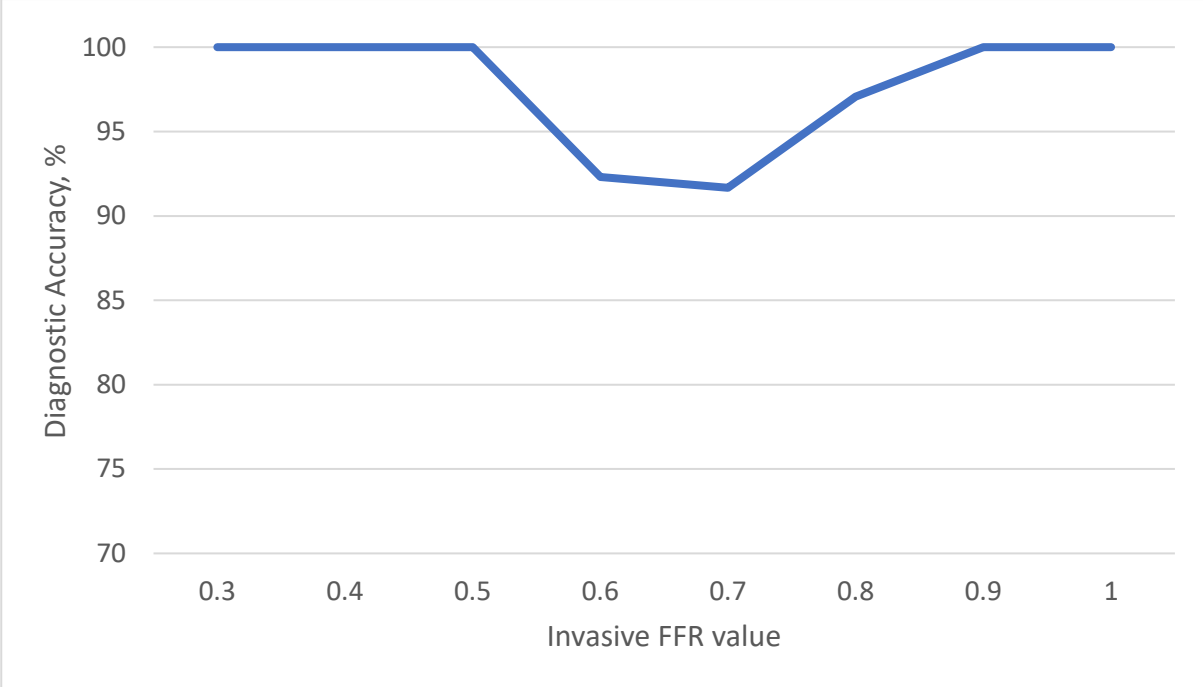


Figure 2.13: Diagnostic accuracy of all cases stratified by invasive FFR value
Diagnostic accuracy is highest in those cases with the lowest and highest FFR values. The closer to the threshold (0.70-0.80) the lower the diagnostic accuracy. This is akin to findings from other studies. However, even around the threshold, diagnostic accuracy remained above 90%.

2.3.2.4 The effect of straightening the vessel upon computed vFFR

For the first 20 cases, VCI was performed twice; with and without stent straightening. An example is shown in Figure 2.14. When VCI was performed without vessel straightening, mean post PCI FFR was 0.91 (±0.05) and mean post VCI vFFR was 0.92 (±0.04). The mean difference (bias) between mFFR and vFFR was -0.010 (±0.019). The average absolute error was 0.01 (±0.02). When VCI was performed with vessel straightening, mean post VCI vFFR was 0.92 (±0.04). The mean difference (bias) between mFFR and vFFR was -0.01 (±0.03). The average absolute error was 0.03 (±0.03). There was no significant difference between the paired FFR values (P=0.58). There was no difference between the absolute error in predicting invasive FFR between the two methods (P=0.22). All results are shown in Supplemental Table 2 (Appendix).

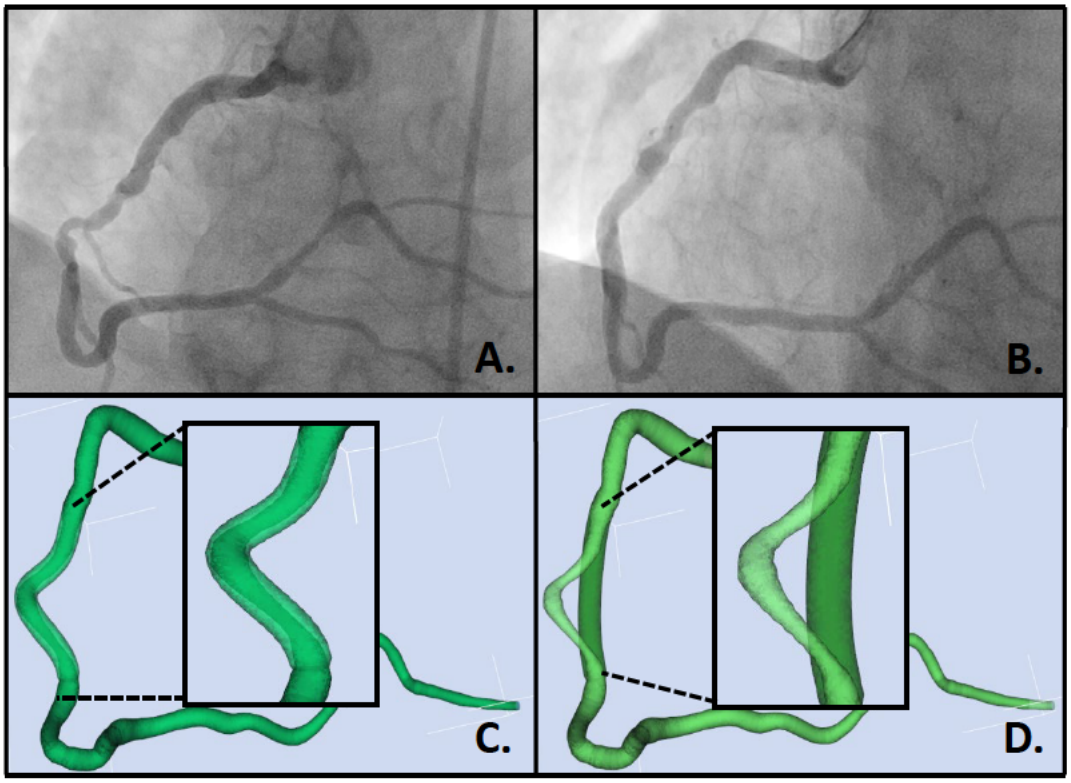


Figure 2.14: Example of the two methods of VCI: with and without stent straightening
Baseline coronary angiography reveals a stenosis in the mid RCA (panel A.). This is treated with PCI with a satisfactory angiographic result (panel B). The PCI procedure is replicated with our VCI tool first without any vessel straightening (Panel C) and then with vessel straightening (Panel D). In the angiographic image, the stent insertion has caused a degree of straightening.

2.3.3 Discussion

In this chapter, I have described the development and validation of a novel VCI tool based upon the angiogram. I have demonstrated the ability of this tool to predict the physiological response to stenting with a high degree of accuracy. Accuracy was improved when personalised boundary conditions were used; however, even with generic boundary conditions, accuracy was within clinically acceptable limits. Therefore, the model could be used with or without baseline pressure wire data. Computational time was approximately two minutes per case making it suitable for use within the cardiac catheterisation laboratory. There were no significant differences in the physiological result whether the vessel was straightened or not, suggesting either method can be used. In most cases, there is no need to straighten

the vessel. However, in particularly torturous vessels, straightening can prevent errors in the meshing stage and therefore is a suitable alternative.

Virtual stenting technology has previously been demonstrated on models derived from CTCA imaging data (Kim et al., 2014), but this is the first time it has been achieved using ICA imaging. This novel imaging-based technique could lead to accurate, patient specific, revascularisation planning. CTCA is still limited by heart rate control and inaccuracy in assessing calcific disease (Hou et al., 2014, Budoff et al., 2008) and the resolution remains inferior to ICA. Furthermore, patients with significant disease will invariably have invasive angiographic images taken prior to PCI. VCI, particularly if available immediately, will therefore permit accurate and objective planning of complex interventions compared with operator-based predictions of the response to a particular stent strategy. This will be particularly useful in patients with complex disease patterns. Whilst iFR has been used to predict the response to stenting (Nijjer et al., 2014), this method still requires passage of a pressure wire, whereas the current method is quick, easy, non-invasive, and can be done either with the patient on the table or offline after the procedure. The latter would permit assessment of angiograms that have been done in hospitals that do not have access to pressure wire technology.

2.3.3.1 VCI for optimisation of PCI

FFR measurement after stenting has been shown to predict adverse events at follow up. Increased rates of MACE at six months and one year have been demonstrated in patients with a post procedural FFR <0.90 (Pijls et al., 2002, Nam et al., 2011). The ability to predict the physiological outcome of a number of alternative stenting strategies would permit the operator to identify the optimal approach prior to intervention. The primary aim of this study was to validate the accuracy of the computed results; a critical first step. This tool permits multiple stenting strategies to be simulated, and the physiological results of each to be compared, thus facilitating the selection of the best PCI strategy before proceeding

with intervention. Currently, each simulation takes approximately two minutes and the cumulative time is dependent upon the number of strategies being compared. However, as the tool is developed further, the aim will be to implement computational methods which significantly accelerate processing time, enabling very rapid CFD results for each strategy, with minimal time cost to the clinician. In addition to prediction of the physiological results associated with virtual PCI, the tool may also facilitate the selection of the ideal stent diameter and length because the GUI reports the diameter along the artery at all points (stenotic and reference segments), and the length between user-specified points. Although this is not the primary aim of this tool, these 3D data, based upon the reconstructed artery prior to VCI, may add supplementary data useful to the operator (see Figure 2.15). For a simple case, such as an isolated severe stenosis with an appropriate clinical background, the use of VCI technology is unnecessary, but in cases with serial lesions (Pijls et al., 2000), diffuse disease or bifurcations, it may have value. This could increase the likelihood of achieving an optimal post-treatment FFR, potentially improving outcomes. Specifically, it will be able to predict the maximum realistically achievable FFR in the context of other disease. It may indeed reveal that localised stenting in a diffusely diseased vessel is of limited benefit. On the other hand, it may show that a modest increase in length or width of stent could provide a substantially improved final FFR. Clinical judgment will always be required, because absolute optimisation of the post-PCI FFR with excessively long and wide stents would be both unrealistic and hazardous in the ‘real world’.

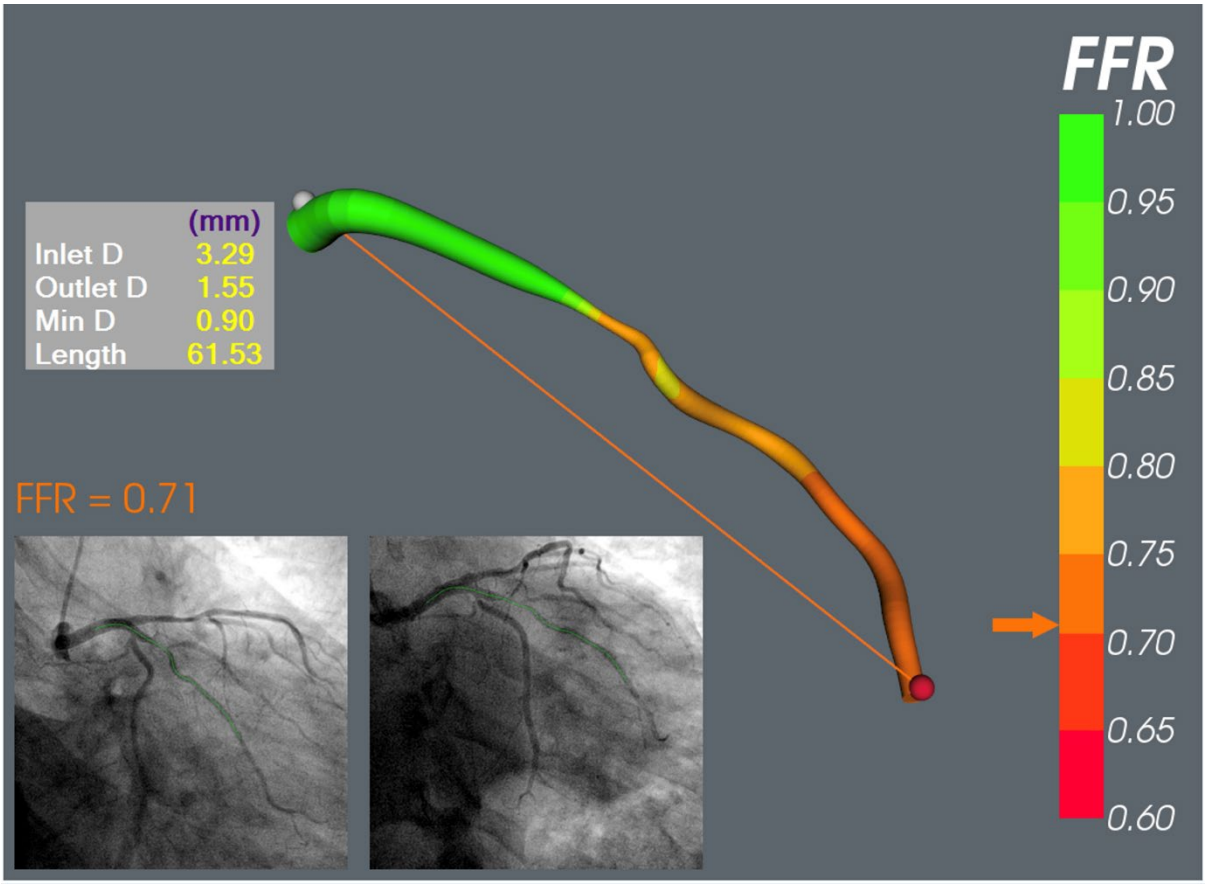


Figure 2.15: vFFR result with diameter data

The vessel reconstruction is displayed along with the corresponding diameter data. The grey and red dots on the reconstruction can be moved along the vessel allowing the dimensions at any chosen point to be checked. The length between the two points is also displayed. This could be useful in stent size selection.

2.3.3.2 VCI to assess tandem lesions

In the presence of tandem or serial lesions, it is impossible to determine accurately the impact of each individual lesion upon coronary blood flow using invasive pressure wire assessment. A distal stenosis provides a fixed resistor which is not amenable to vasodilatation, so assessment of a proximal lesion underestimates its functional significance (Pijls et al., 2000). Only by removing a stenosis (physically or, with our system, virtually) is it possible to increase hyperaemic flow. This is often the strategy employed in FFR-guided PCI, whereby the operator will stent the lesion they believe contributes most to the aggregate FFR, whether based upon a pullback, accepting the limitations, or not. This may lead to the unnecessary stenting of one or other lesion. Some groups have proposed methods of calculating

the ‘true’ FFR from the acquired values. However, many of these require the measurement of the coronary wedge pressure which can only be obtained during balloon coronary occlusion (Pijls et al., 2000). In contrast, by using the current VCI tool, the operator can ‘remove’ each stenosis in turn to assess the true impact of each individual lesion. An example of the VCI tool being used to assess tandem lesions in this way is shown in Figure 2.16. Further outcome studies evaluating this approach are warranted. It remains to be determined whether VCI could help to optimise post PCI FFR values, and in turn patient outcomes. In the next chapters, I aim to explore the potential clinical utility this tool could have in the ‘real world’.

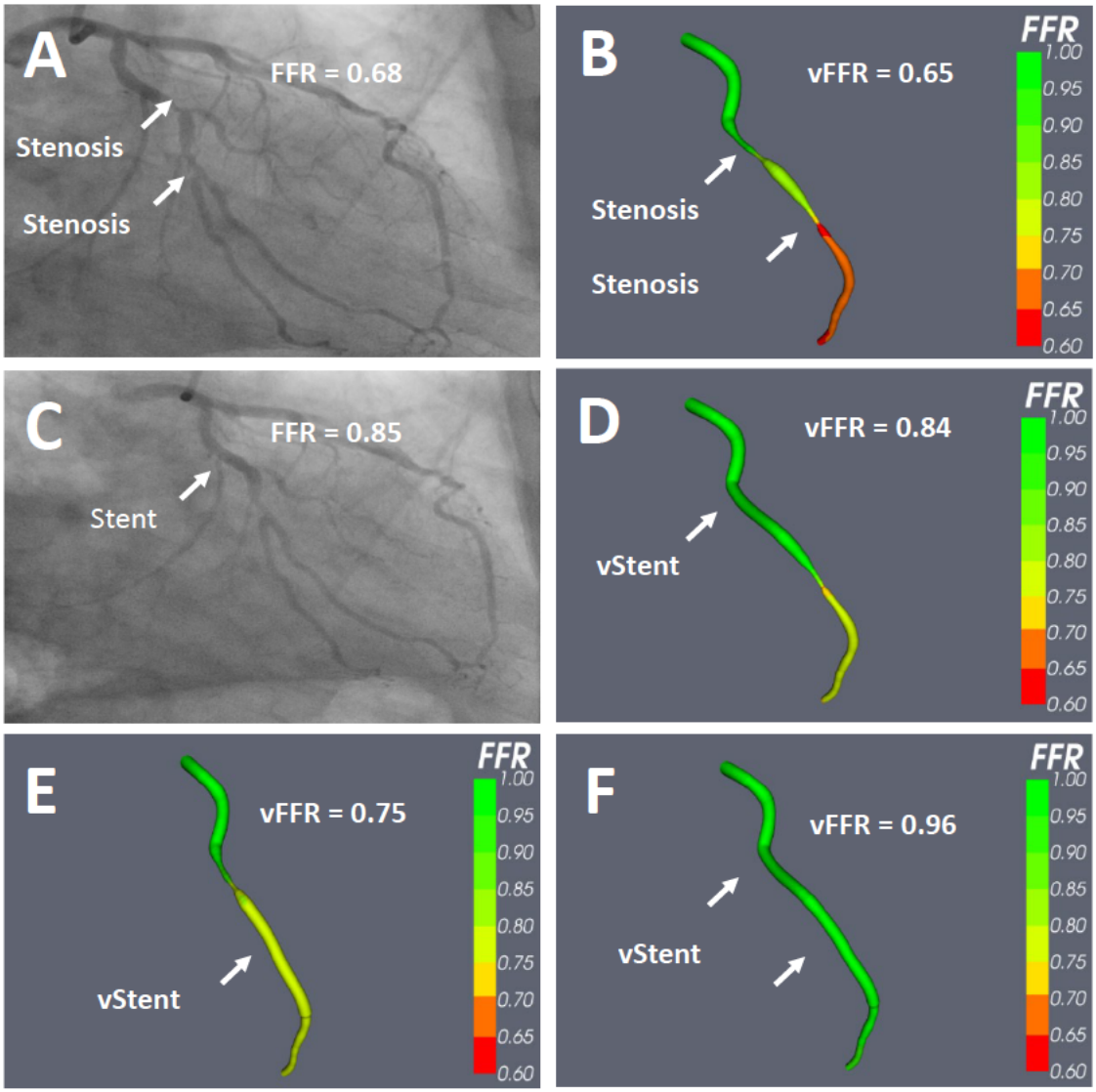


Figure 2.16: The use of VCI to assess Tandem lesions

A 67 year old man presented with symptoms suggestive of stable angina. Angiography revealed the presences of tandem lesions in the left circumflex artery. The measured FFR at the distal vessel was 0.68 (A). The angiogram was used to model the vFFR which was 0.65 over the same segment of artery (B). PCI was undertaken to the proximal lesion with implantation of a 3.5mm x 12mm drug-eluting stent, and the post procedural FFR was 0.85 (C). The distal lesion was left untreated. VCI was used to assess the lesions individually. The proximal stenosis was removed by inserting a 3.5mm x12mm virtual stent. The recalculated vFFR at the distal vessel was 0.84 (D). The distal stenosis was removed by inserting a 2.75x20mm virtual stent and the recalculated vFFR at the distal vessel was 0.75 (E). Following VCI to both stenoses in sequence the vFFR was 0.96 (F). Reproduced under creative commons license CC BY 4.0 from Gosling et al. Virtual coronary Intervention: A treatment planning tool based upon the angiogram. JACC Cardiovasc Imaging Mar 9 2018.

2.3.4 Limitations

The number of cases used in this ‘proof of concept’ work was modest, and performed in ideal circumstances, in elective cases. CFD analysis was based upon a single lumen reconstruction; side branches were not included. This may result in an overestimation of the pressure drop. However, despite this, the model predicted invasive FFR with high accuracy. Also, it was assumed that adequate stent deployment was achieved. Our model of VCI does not model the deployment of the stent or the interaction with the vessel wall. It assumes that the vessel radius is altered to the dimensions of the stent with good stent deployment. This is not always the case in clinical practice, especially in calcific vessels. I also did not take into consideration the degree of inflation of the deployment balloon. Finally, this was a ‘proof of concept’ study and further work is required to demonstrate the potential clinical utility of the VCI tool.

Chapter 3 – Personalised FFR assessment

3.1 Introduction

One of the major limitations of FFR is that it represents a ratio of pressures through a stenosed vessel relative to a hypothetically normal artery. However, PCI seldom achieves a post-treatment FFR of 1.0, even when there is a satisfactory angiographic result. By assuming a FFR of 1.0 is possible, we may be over estimating the potential benefit from PCI. Moreover, it is often not clear whether a sub-optimal post PCI value is a reflection of a poorly optimised procedure (i.e. a better result was possible but not achieved due to procedural factors such as inadequate stent sizing or disease left uncovered) or because that is the best possible FFR in that vessel due to other factors. Our VCI tool could be used to distinguish between these scenarios. Knowing the maximal achievable FFR (FFR_{max}) (the best possible FFR that is achievable with stenting) prior to intervention would be advantageous in planning revascularisation and is possible with VCI technology. The aim of this chapter is to demonstrate the ability of VCI to personalise FFR assessment and to examine the causes of sub-optimal post PCI physiology in a cohort of 'real world' patients.

3.1.1 Objectives:

1.) Use VCI to determine the FFR_{max} on a cohort of 'real world' PCI cases.

2.) Derive a suitable measure for personalised FFR.

3.) Compare personalised FFR with standard FFR as measured in the cardiac catheterisation laboratory.

4.) Demonstrate the potential impact of personalised physiological assessment in a cohort of patients with stable coronary artery disease.

3.2 Methods

3.2.1 Study design

This was an observational cohort study performed between the South Yorkshire Cardiothoracic Centre, Sheffield Teaching Hospitals NHS Foundation Trust, and The University of Sheffield, United Kingdom.

3.2.2 Study population

Data were collected prospectively from patients undergoing coronary angiography and pressure wire assessment between January 2014 and June 2016. Consecutive patients >18 years of age who had angiographically confirmed coronary disease (30-90% stenosis by visual angiographic assessment) were recruited. Patients were excluded if they had presented acutely within the previous 60 days, had prior CABG surgery, chronic total occlusion(s), if passage of a pressure wire would be unsafe, or if the patient was unable or unwilling to consent. All patients provided informed written consent and the study was approved by the regional ethics committee (Appendix). Clinical, demographic and FFR data were collected prospectively. Coronary artery segments were defined according to the American Heart Association (AHA) reporting system (Austen et al., 1975). Diffuse disease and serial lesions were defined according to SYNTAX score definitions (Sianos et al., 2005). Diffuse disease was present if at least 75% of the length of any segment proximal to the lesion, at the site of the lesion or distal to the lesion, had a vessel diameter of <2mm. Serial lesions were defined as sequential lesions in the same vessel, more than three vessel reference diameters apart.

3.2.3 Invasive angiography and measured FFR

Coronary angiography was performed according to standard practice. All diseased arteries were assessed with a pressure wire (Philips Volcano or Abbott Vascular). Hyperaemia was induced by an intravenous infusion of adenosine at 140μg/kg/min. The FFR measurement was taken during maximal stable hyperaemia according to the methods originally described by Pijls et al (Pijls et al., 1993). The decision

to proceed to PCI was made by the operator, guided by angiographic and invasive FFR assessment; not the maximal achievable FFR, which was calculated offline. In patients who underwent PCI, FFR measurement was repeated after treatment.

3.2.4 3D reconstruction and virtual coronary intervention

A 3D reconstruction of the arterial anatomy was created offline after the procedure using methods described in chapter two. To compute the maximal achievable FFR (FFR_{max}), a theoretical ideal intervention was performed in which all discernible stenoses were removed. Personalised proximal and distal boundary conditions were applied on the assumption that the CMVR was not altered by the removal of stenoses (Kanaji et al., 2017, Yong et al., 2012). The result obtained was the 'virtual FFR' of the normalised vessel i.e. the FFR_{max}. The distal boundary was tuned using personalised pressure measurements (Morris et al., 2017). Because the simulation was tuned using the invasive pressure wire data, no assumptions were made about boundary condition selection. As demonstrated in chapter two, this results in increased accuracy in FFR prediction. The purpose of this work was to derive and evaluate a method for personalised FFR assessment and was not a test of virtual FFR accuracy, which is a separate concept. To assess the reproducibility of FFR_{max} computation, ten percent of cases, chosen at random, were re-processed, with the operator blinded to the original results. The focus was on reproducibility of FFR_{max} computation. Therefore, the baseline vessel 3D reconstruction was not repeated. FFR_{max} results were compared and the intra-class correlation coefficient calculated.

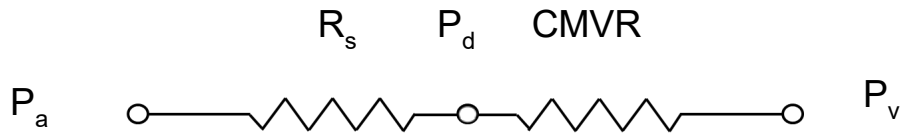
3.2.5 Calculation of personalised FFR

Personalised FFR (FFR_{pers}) was calculated as the invasively measured (m)FFR divided by the FFR_{max} ($\frac{mFFR}{FFR_{max}}$). Therefore, it represents the degree of flow restoration potentially achievable on a vessel-specific basis. It does not attempt to match measured FFR (which is the ratio of flow reduction compared to a

hypothetical normal artery), rather it is an independent index. The mathematical derivation of this index as follows:

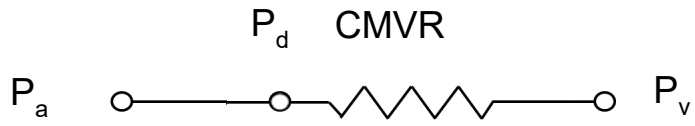
Derivation of 'traditional' FFR is based upon the following electrical analogues.

Pre-intervention



Where P_a = Proximal aortic pressure, R_s = stenosis resistance, P_d = distal aortic pressure, CMVR = microvascular resistance and P_v = venous pressure.

Post-intervention



This model assumes that post intervention (or in the absence of a stenosis) the only resistance is that provided by the CMVR i.e. there is no residual resistance along the epicardial vessel.

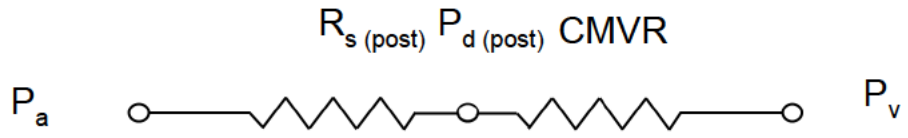
Using this model:

$$\text{FFR} = \frac{Qs}{Qn} \quad \text{where:} \quad \text{Qs} = \frac{Pd}{R} \quad \text{and} \quad \text{Qn} = \frac{Pa}{R}$$

As there is assumed to be no pressure drop along the length of the normalised vessel then P_d=P_a. We can therefore re-arrange the equation such that:

$$\frac{Qs}{Qn} = \frac{Pd}{Pa} = \text{FFR}$$

However, if we adjust this model to accept that a residual epicardial resistance can exist in the absence of a stenosis then our post intervention model is:



In this model

$$\frac{Qs}{Qn} = \frac{Pd}{CMVR} \Big/ \frac{P_{d\,(post)}}{CMVR}$$

therefore,

$$\frac{Qs}{Qn} = \frac{P_d}{CMVR} * \frac{CMVR}{P_{d\,(post)}}$$

Here CMVR cancels out, leaving:

$$\frac{Qs}{Qn} = \frac{P_d}{P_{d\,(post)}}$$

$P_{d\,(post)}$ can be described as FFR_{max} x Pa

Therefore,

$$\frac{Qs}{Qn} = \frac{P_d}{FFR_{max} * P_a} = \frac{mFFR}{FFR_{max}}.$$

3.2.6 Data analysis

Data are described as mean (± SD) and percentage (proportions) unless stated otherwise. FFR_{max} was compared to post-PCI FFR using a paired sample t test and Pearson correlation coefficient. Comparisons of results stratified by vessel or disease category were carried out using one-way ANOVA or independent-samples t test. All statistical analyses were calculated using SPSS version 24 (IBM SPSS Inc., NY, USA).

3.3 Results

3.3.1 Patient, lesion and procedural characteristics

Seventy-one patients with angiographically confirmed disease were studied. The mean age was 65.2 (±9.9), 52 (73%) were male, 15 (21%) had type 2 diabetes mellitus, 46 (65%) had hypertension and 52 (73%) had hyperlipidaemia (Table 3.1). These patients provided one hundred vessels for study; three left main stem (LMS), 52 left anterior descending (LAD), eight diagonal (Dx), four obtuse marginal (OM), 14 left circumflex (LCX), and 19 right coronary arteries (RCA). Twelve (12%) had serial lesions and 25 (25%) had diffuse disease. Average % diameter stenosis, determined by QCA, was 54.1(±12). The mean invasively measured baseline FFR (mFFR) was 0.76 (±0.13). Fifty-two (52%) vessels underwent PCI, and the post-PCI FFR was measured in 50. The average number of stents placed per vessel was 1.1. Mean stent length and diameter were 27.5mm (±10.8) and 3.0mm (±0.5) respectively. All patients received second generation drug-eluting stents. Baseline patient and lesion characteristics are shown in Table 3.1.

Table 3.1: Patient and lesion characteristics

Patient characteristics	
Mean age (years)	65.3 (±9.9)
Sex	
Male	52 (73%)
Female	19 (27%)
Smoking status	
Current	9 (13%)
Ex	41 (58%)
Never	21 (30%)
Prior myocardial infarction	26 (37%)
Hypertension	46 (65%)
Hyperlipidaemia	52 (73%)
Type 2 Diabetes Mellitus	15 (21%)
Vessel specific characteristics	
Vessel studied	
Left main stem	3 (3%)
Left anterior descending	52 (52%)
Left circumflex	14 (14%)
Right coronary artery	19 (19%)
Diagonal artery	8 (8.0%)
Obtuse marginal	4 (4.0%)
PCI treated	52 (52%)
Diffuse disease	25 (25%)
Serial lesions	12 (12%)
QCA average diameter stenosis (%)	54.1(±12.6)
QCA average lesion length (mm)	19.5 (±11.8)

Values are Mean (±SD) or number (%). PCI = Percutaneous Coronary Intervention; QCA = Quantitative Coronary Angiography.

3.3.2 Maximal achievable FFR (FFR_{max})

For all 100 vessels, FFR_{max} was successfully computed in a mean time of 95s. The average FFR_{max} was 0.92 (±0.04) (range = 0.81 - 0.99) (Figure 3.1). A vessel-specific breakdown is shown in Table 3.2. In the 50 cases with a post-PCI FFR measurement, the post-PCI mFFR was 0.89 (±0.05), on average 0.04

(±0.05) lower than the corresponding FFR_{max}; and the range of the difference was 0-0.18 (P<0.001)(Table 3.3). A subgroup analysis of the post-PCI cases in which the FFR_{max} was >0.05 higher than the post-PCI FFR was performed. In 13/14 vessels, this was due to uncovered disease distal to the stented segment (Figure 3.2). In one, there was a residual pressure drop across the stented segment. The average length of 'virtual stent' used to achieve the FFR_{max} was 30.7mm (±9.6) per vessel. The per-vessel virtual stent length was on average 2.8 mm longer than the stent length actually deployed during PCI (P=0.18).

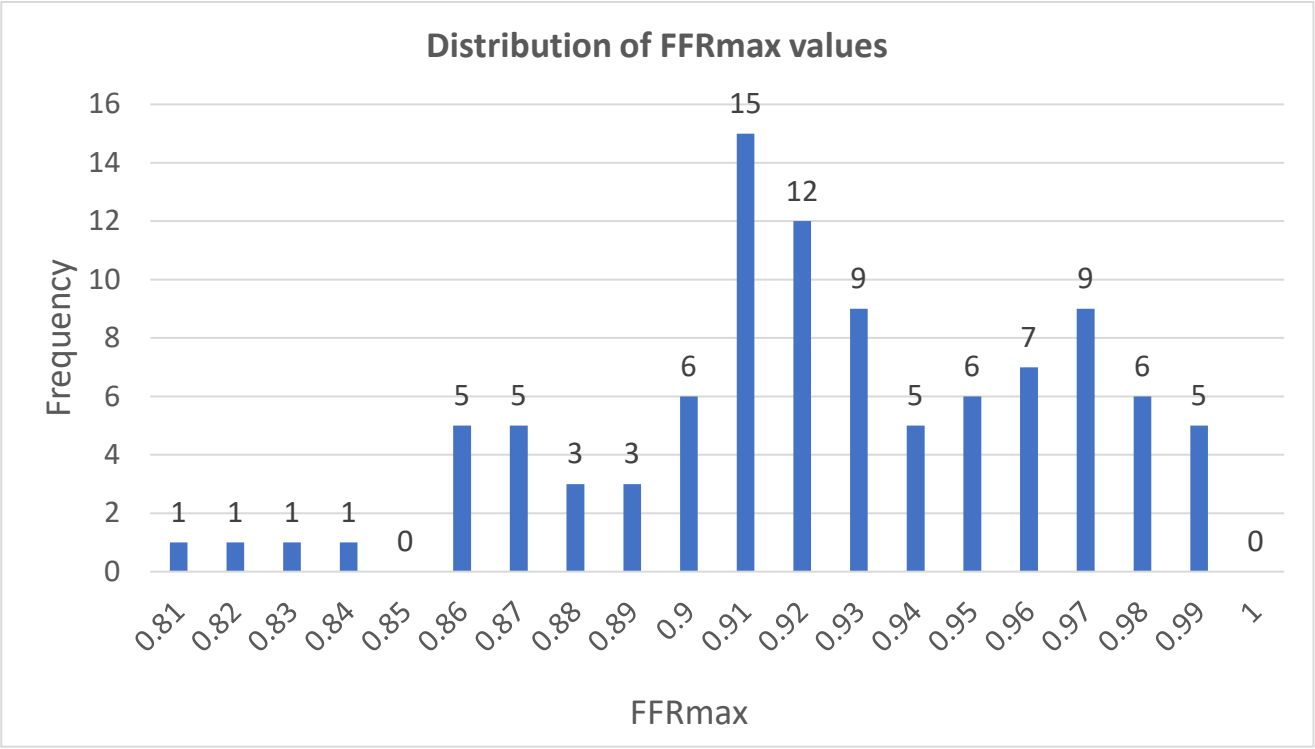


Figure 3.1: Distribution of FFR_{max} values
The FFR_{max} is plotted on the x axis and the frequency on the y axis. The number of cases is indicated above the bar for each value of FFR_{max}.

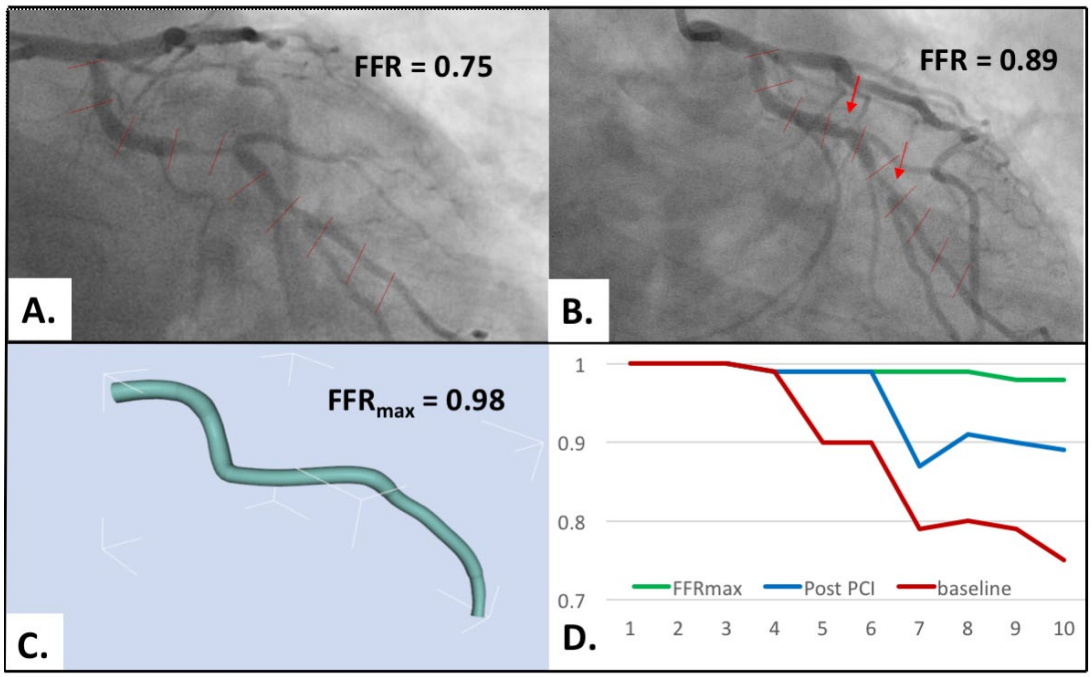


Figure 3.2: Using co-registration to determine the difference between FFR_{max} and post PCI FFR
A 55-year-old with stable angina underwent coronary angiography, revealing a lesion in the left circumflex artery. The invasively measured FFR was 0.75 (Panel A). The patient underwent PCI and measured post PCI FFR was 0.89 (Panel B). The FFR_{max} was calculated as 0.98 (Panel C). This result is significantly higher than the achieved post-PCI FFR suggesting further optimisation may have been possible (there are residual diseased segments distal to the stent, marked in Panel B). By plotting the FFR values along the length of the vessel, a comparison between baseline, post-PCI and FFR_{max} values is made (Panel D). A-J along the x axis represent the 10 vessel segments identified on the angiographic images. This demonstrates a second distal lesion which accounts for the difference between the FFR_{max} and post-PCI FFR. Reprinted from Eurointervention 2019 Oct 20;15 (8), Gosling et al, Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation., pages 707-713, Copyright (2019) with permission from Europa Digital and Publishing (Gosling et al., 2019).

Table 3.2: Mean FFR_{max} stratified by vessel and vessel segment

	N =	FFR_{max}	Average pressure drop (across segment)
Left main stem	68	0.99	0.01
Left anterior descending	54	0.92	0.08
Proximal	54	0.98	0.02
Mid	54	0.94	0.04
Distal	43	0.91	0.04
Left Circumflex	14	0.94	0.06
Proximal	14	0.98	0.02
Distal	14	0.94	0.04
Right coronary artery	19	0.94	0.06
Proximal	19	0.98	0.02
Mid	19	0.96	0.02
Distal	19	0.94	0.02
Diagonal branch	8	0.90	0.10
Obtuse marginal branch	4	0.95	0.05

Table 3.3: Subgroup analysis of PCI treated patients

	N (%)	Baseline FFR (mean)	FFR_{max} (mean)	Post PCI FFR (mean)
All PCI-treated vessels	52	0.68	0.93	0.89
Vessel treated				
Left main stem	1 (2%)	0.57	0.86	0.83
Left anterior descending	31 (60%)	0.69	0.91	0.88
Left circumflex	4 (8%)	0.57	0.96	0.96
Right coronary artery	14 (27%)	0.68	0.94	0.91
Diagonal artery	1 (2%)	0.76	0.96	0.91
Obtuse marginal	1 (2%)	0.64	0.95	0.96

FFR = fractional flow reserve, PCI = percutaneous coronary intervention.

3.3.3 Reproducibility of FFR_{max} computation

The computation of FFR_{max} was highly reproducible. Of the ten cases reprocessed, the average difference was 0.002 (±0.004). The intra-class correlation co-efficient was 0.99 (P<0.001). Reproducibility is shown in Table 3.4.

Table 3.4: Reproducibility of FFR_{max} calculation

FFR_{max} (1)	FFR_{max} (2)	Difference
0.90	0.90	0.00
0.96	0.97	0.01
0.93	0.93	0.00
0.87	0.87	0.00
0.97	0.97	0.00
0.91	0.91	0.00
0.90	0.90	0.00
0.95	0.94	0.01
0.89	0.89	0.00
0.91	0.91	0.00

3.3.4 Subgroup analysis in diffuse disease and serial lesions

Twenty-five patients were prospectively identified as having diffuse disease according to SYNTAX score definitions. Of these, mean FFR_{max} was 0.91 (±0.04). There was no significant difference between cases with and without diffuse disease (FFR_{max} = 0.93 (±0.04), P=0.17). Similarly, there was no significant difference in post-PCI FFR between the two groups (diffuse disease post PCI FFR = 0.89 (±0.06), no diffuse disease post PCI FFR = 0.89 (±0.05), P=0.73). Twelve patients were prospectively identified as having serial lesions according to SYNTAX score definitions. There was no significant difference in the FFR_{max} between vessels with serial lesions and vessels without serial lesions (0.93 (±0.04) versus 0.92 (±0.04), P=0.36). Similarly, there was no significant difference between the post PCI FFR in cases with and without serial lesions (0.89 (±0.06) versus 0.89 (±0.05), P=0.98).

3.3.5 Comparison between measured FFR and personalised FFR (FFR_{pers})

FFR_{pers} was calculated in all vessels. The mean FFR_{pers} was 0.82 (±0.14). The mean difference between FFR_{pers} and measured FFR was 0.06 (±0.04) ($P<0.001$). All measured FFR and corresponding FFR_{pers} results are shown in Figure 3.3.

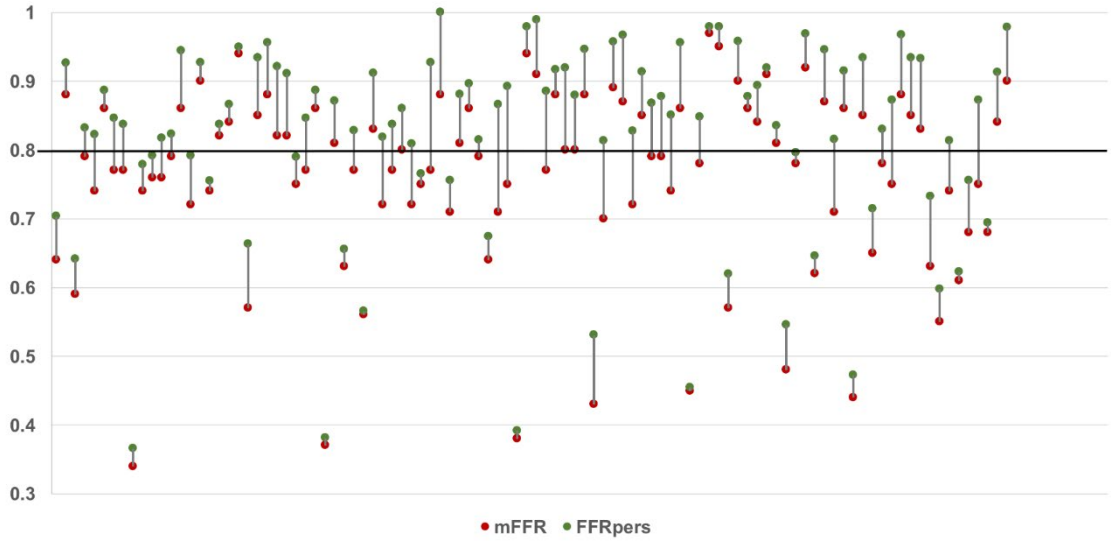


Figure 3.3: Individually plotted mFFR and corresponding FFR_{pers} values for all lesions
The mFFR value is plotted for all 100 lesions studied (red dot). The corresponding FFR_{pers} is plotted (green dot) and joined by a grey line. The black horizontal line represents the 0.80 treatment threshold. Reprinted from Eurointervention 2019 Oct 20;15 (8), Gosling et al, Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation., pages 707-713, Copyright (2019) with permission from Europa Digital and Publishing (Gosling et al., 2019).

3.4 Discussion

In this chapter, I have described a method of determining the maximal achievable FFR (FFR_{max}) prior to intervention based upon the invasive coronary angiogram and standard pressure wire data on a vessel-specific basis. This allowed personalisation of FFR assessment. In a cohort of 'real world' patients with stable coronary artery disease, the mean value of the FFR_{max} was 0.92.

FFR represents the percentage reduction in coronary flow relative to a hypothetically normal artery. However, it does not accurately reflect the potential flow restoration achievable with PCI in a particular patient, because the maximal achievable FFR on a case-by-case basis is not known prior to intervention. As such, it does not always accurately predict which patients will benefit from PCI, and to what degree. Therefore, even with FFR guidance, it may still be challenging to determine which patients will benefit from revascularisation, especially when the measured FFR is close to 0.80 (Al-Lamee et al., 2018). A universal threshold of 0.80 is applied to all patients to determine when revascularisation is likely to provide benefit. Although this threshold is supported by clinical outcome data in large groups as a whole, and is probably satisfactory in most cases, an FFR of 0.78 can describe a number of different physiological situations which may respond differently to PCI. A personalised approach to coronary physiological assessment using FFR_{max} and FFR_{pers} may help identify patients who will gain benefit from targeted PCI (Figure 3.4), patients who are likely to get limited physiological benefit from PCI due to underlying diffuse disease (Figure 3.5) and patients in whom further procedural optimisation may be possible (Figure 3.6).

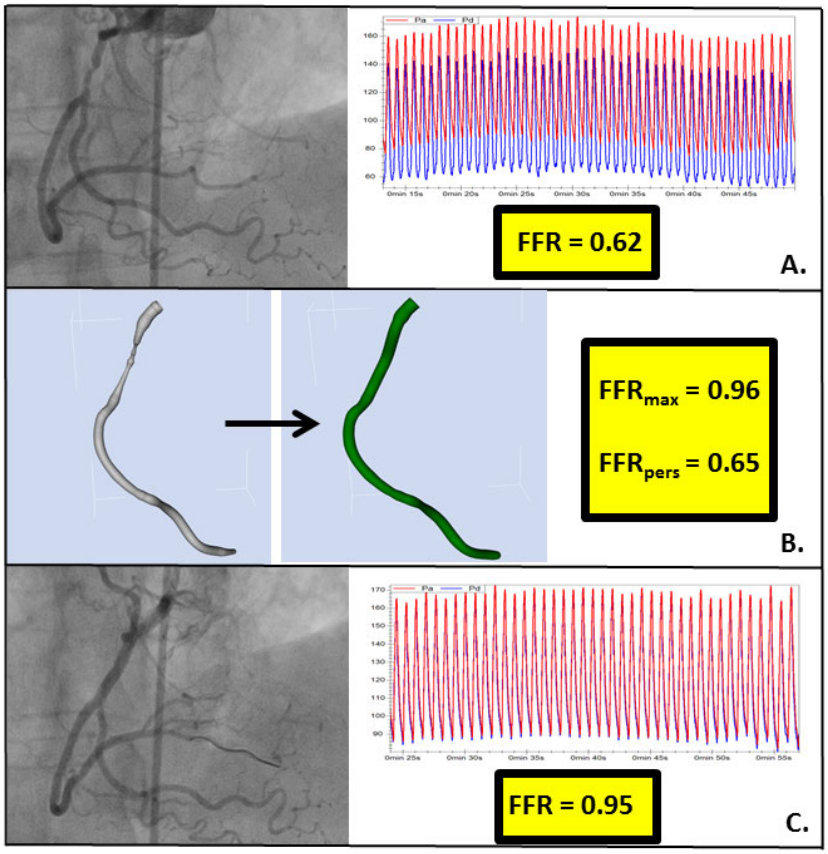


Figure 3.4: Using personalised FFR assessment to identify a focal lesion that is likely to achieve a good physiological result from targeted PCI

An 81-year-old female with stable angina underwent angiography identifying a lesion in the right coronary artery. Invasive pressure wire assessment revealed a FFR of 0.62 (A). Using the VIRTUheart™ software a reconstruction of the arterial geometry was created (Panel B, left image) and the stenoses were virtually removed to reveal the 'normalised' geometry (Panel B, central image). The FFR_{max} and FFR_{pers} were calculated as 0.96 and 0.65 respectively. These results advise the operator that this lesion is likely to get an excellent physiological result from focal PCI. PCI was performed with a good angiographic result (Panel C, left image). Post-PCI measured FFR was 0.95 (Panel C, right image). Reprinted from Eurointervention 2019 Oct 20;15 (8), Gosling et al, Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation., pages 707-713, Copyright (2019) with permission from Europa Digital and Publishing (Gosling et al., 2019).

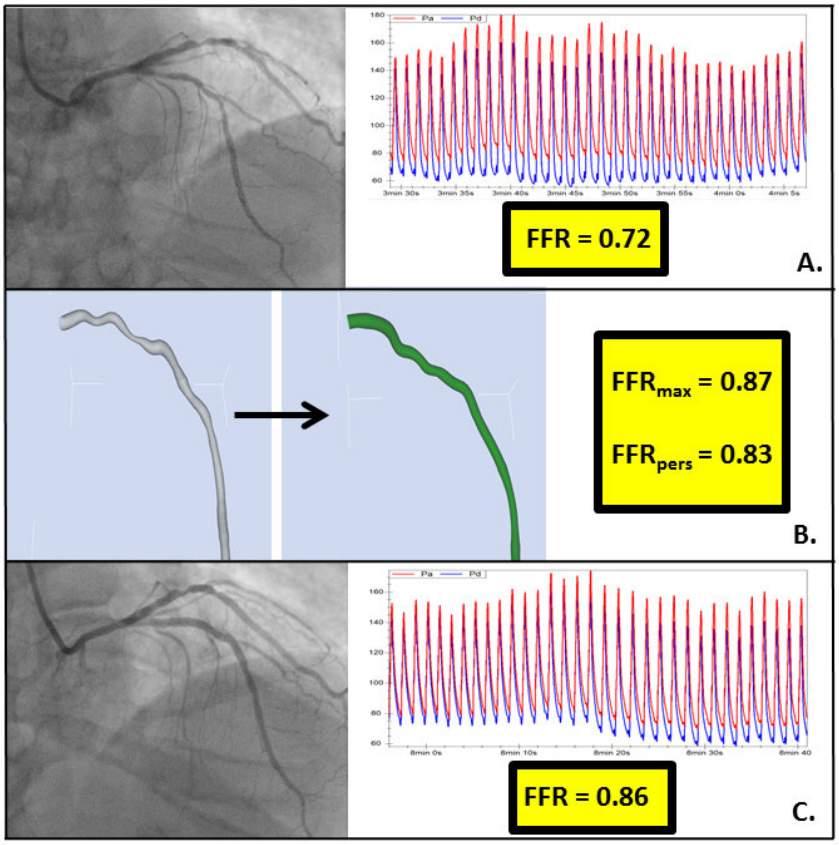


Figure 3.5: Using personalised FFR assessment to identify a lesion that is unlikely to achieve a significant physiological improvement from focal PCI

A 61-year-old male with stable angina underwent coronary angiography revealing a lesion in the LAD. The invasive FFR measurement was 0.72 (A). Using the VIRTUheart™ software a reconstruction of the arterial geometry was created (Panel B, left image) and the stenoses virtually removed to reveal the 'normalised' geometry (Panel B, central image). The FFR_{max} and FFR_{pers} were calculated as 0.87 and 0.83 respectively. These results suggest that only a modest physiological benefit is likely to be achieved from focal PCI. This patient proceeded to PCI with a good angiographic result (Panel C, left image). The post-PCI FFR was 0.86 (Panel C, right image) which is in keeping with the predicted FFR_{max}. Knowing the FFR_{max} in this case could help prevent futile attempts to improve the post PCI FFR with further stent implantation or dilatation. Reprinted from Eurointervention 2019 Oct 20;15 (8), Gosling et al, Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation., pages 707-713, Copyright (2019) with permission from Europa Digital and Publishing (Gosling et al., 2019).

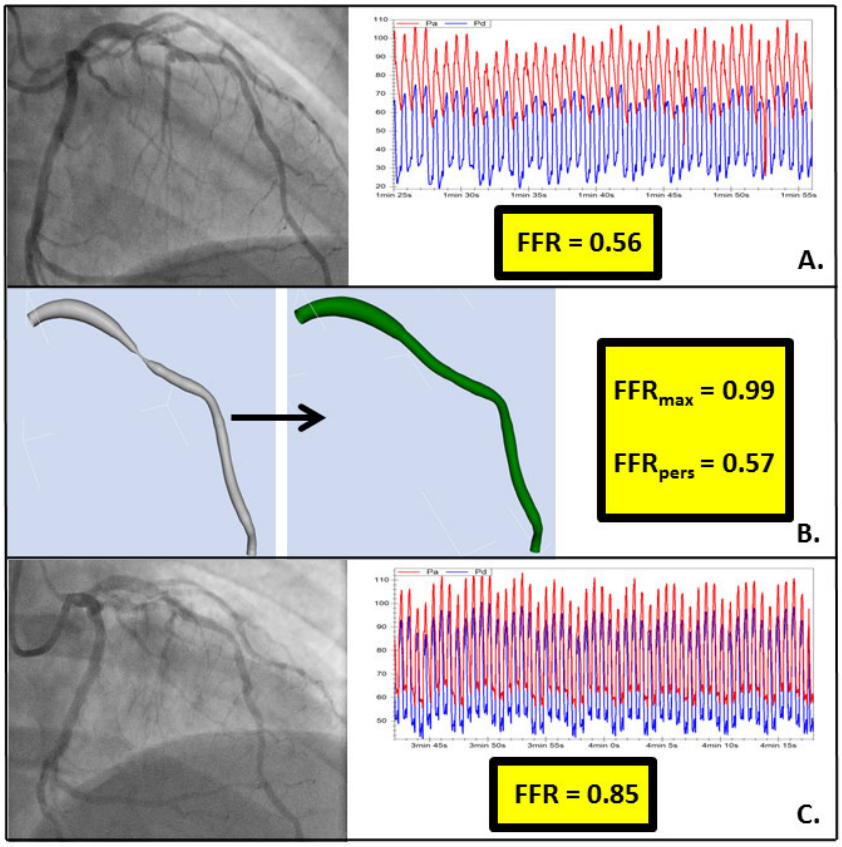


Figure 3.6: Using personalised FFR assessment to identify a lesion that may benefit from further post PCI optimisation

A 55-year-old male with stable angina underwent coronary angiography revealing a lesion in the LAD. The invasively measured FFR was 0.56 (A). Using the VIRTUheart™ software, a reconstruction of the arterial geometry was created (Panel B, left image) and the stenoses virtually removed to reveal the 'normalised' geometry (Panel B, central image). The FFR_{max} and FFR_{pers} were calculated as 0.99 and 0.57 respectively. These results advise the operator that this lesion is likely to get a good physiological result from focal PCI. The patient underwent PCI and the invasively measured post PCI FFR was 0.85 (C). This initial result is significantly lower than the FFR_{max} suggesting that further procedural optimisation may have been possible. Reprinted from Eurointervention 2019 Oct 20;15 (8), Gosling et al, Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation., pages 707-713, Copyright (2019) with permission from Europa Digital and Publishing (Gosling et al., 2019).

3.4.1 Significance of these findings

The degree of flow restoration required in order for the patient to gain symptomatic and/or prognostic benefit remains incompletely understood. Some outcome data suggest that patients with a post-PCI measured FFR >0.90 have reduced rates of MACE following PCI (Pijls et al., 2002). Our method will require outcome studies to determine the value of FFR_{pers} which might more accurately define the threshold for treatment. In this study, 31(31%) cases cross the 0.80 threshold when this method of personalisation is applied as illustrated in figure 3.3. This suggests that for these patients, the benefit of PCI was likely to be less than the operator may have believed at the time of intervention based upon the measured FFR. However, it is important to note that the 0.80 threshold has not been validated using personalised FFR making it difficult to draw any firm conclusions. It is also important to re-iterate that FFR_{pers} does not attempt to replicate measured FFR, but is an independent measure. Any deviation of FFR_{pers} from measured FFR represents an overestimation of measured FFR to predict potential benefit from PCI as opposed to inaccuracy in computational FFR.

Not only was FFR_{max} significantly lower than 1.0, but it varied considerably between cases (range 0.81-0.99). This is consistent with previous work showing that, even in the absence of an angiographic stenosis, there is a pressure drop along the length of the vessel (De Bruyne et al., 2001). In patients with confirmed coronary artery disease elsewhere, the average drop in pressure along an apparently normal vessel was 10 (±8) mmHg under hyperaemic conditions (FFR 0.89 (±0.08), range 0.69–1.00). For eight percent of these patients, the FFR value was below the threshold for treatment (≤0.80). In patients with apparently completely normal arteries, average FFR was 0.97 (±0.02) (range 0.92–1.00). A gradual pressure drop in the presence of diffuse disease can be associated with increased mortality, and it is usually not amenable for intervention (Tonino and Johnson, 2016).

3.5 Causes of a residual pressure gradient

In patients with diffuse disease, an optimal physiological result is seldom achieved following PCI, despite the use of long (>30mm) and ultra-long (>50mm) drug-eluting stents (Baranauskas et al., 2016). In patients with a lesion length > 30mm, less than a third achieved a post PCI FFR of >0.90 with only 11% achieving a FFR value of >0.95. Eight (11%) vessels remained haemodynamically significant (FFR ≤0.80) after PCI. In another study, 17.8% vessels remained ischaemic (FFR<0.80) immediately after treatment, and 9.5% continued to be ischaemic despite further attempts at PCI optimisation. Diffuse disease was a predictor of a post-PCI FFR ≤0.80 (Agarwal et al., 2017). In our study, similar post-PCI FFR results were seen. Eighteen (36%) patients had a post-PCI FFR >0.90 and four (8%) >0.95. Three (6%) remained haemodynamically significant (FFR<0.80). Higher post-PCI FFR results are associated with improved outcomes (Klauss et al., 2005, Nam et al., 2011, Pijls et al., 2002, Agarwal et al., 2016) yet in clinical practice, this is not always achievable. Identifying patients likely to have a suboptimal physiological result to PCI would therefore be advantageous. FFR_{max} could provide this.

In some cases, a suboptimal post-PCI FFR is not due to the presence of untreatable diffuse disease but can be the result of a poorly optimised procedure. The FFR_{max} can help the operator distinguish between these two scenarios either in guiding further optimisation or conversely in preventing further treatment that is futile and potentially harmful. Procedural optimisation with post-dilatation, and in some cases, further stent implantation, has previously been shown to result in modest increases in FFR. In the ILUMIEN 1 trial, a statistically non-significant increase in post-PCI FFR from 0.86 to 0.90 was achieved with OCT driven optimisation (Wijns et al., 2015). In our study, FFR_{max} was on average 0.04 (range 0-0.18) higher that the post-PCI FFR suggesting a similar level of optimisation may have been possible. In 14 (28%) cases, the FFR_{max} was >0.05 higher than the post-PCI FFR. This was most frequently (in 13 out of these 14 cases) due to the presence of uncovered disease distal to the stented segment.

3.6 Limitations

This study was not powered to detect predictors of FFR_{max} or differences between disease subgroups. Further studies including outcome data are warranted. The accuracy of FFR_{max} cannot be fully validated as there is no method of in-vivo measurement available. However, our results are consistent with other studies of *in-vivo* post-PCI results. Furthermore, our model (using personalised proximal and distal boundary conditions) has previously been shown to have high accuracy in predicting FFR (Morris et al., 2017) and we would expect similar accuracy to be extrapolated in the normalised geometries. FFR_{max} is calculated after removing all discernible stenoses. This is currently done by eye by the operator which introduces a degree of subjectivity. Machine learning methods could potentially be utilised to help standardise this process and represented an avenue for further work.

Chapter 4 - Application in the real world

4.1 Introduction

Numerous studies have demonstrated that using FFR assessment to guide PCI is associated with improved clinical outcomes and reduced costs. In the FAME study, FFR guidance reduced the total length of stent per patient from 52mm to 38mm and the number from 2.7 to 1.9 (Tonino et al., 2009). This was associated with a reduction in MACE at follow up (18.3% versus 13.2% at one year). Whether vFFR would have the same impact upon 'real world' stenting remains unknown. The addition of VCI has the potential to further impact 'real world' stenting by providing a predicted response to therapy and more accurate treatment planning. FFR can also impact clinical decision making. In the RIPCORD study, knowledge of FFR results changed the treatment recommendation in 26% of cases, compared to decision making based upon angiography alone (Curzen et al., 2014). This effect was replicated with FFR_{CT} in the FFR-CT RIPCORD study (Curzen et al., 2016). Currently, there is no data available to suggest whether angiography based vFFR would have the same impact. Furthermore, combining vFFR with VCI assessment presents a unique opportunity of an all in one diagnosis and treatment planning tool which could further impact treatment decisions.

In this chapter, I aimed to demonstrate the potential 'real world' impact of adopting an all in one diagnosis and treatment planning approach with vFFR and VCI.

The key objectives were:

1.) To determine the effect of a combined vFFR and VCI approach on PCI recommendations (total number and size of stents) in a retrospective virtual study.

2.) To determine the ability of this approach to alter treatment recommendations in a retrospective virtual study.

These objectives are addressed in two parts of this chapter.

4.2 Part 1 – retrospective virtual study

4.2.1 Methods

4.2.1.1 Study design

This was a retrospective cohort study carried out between the Northern General Hospital, Sheffield, UK which is a tertiary cardiothoracic centre and the University of Sheffield, UK. Clinical and angiographic data were collected prospectively for patients undergoing PCI for either stable angina or NSTEMI. Analysis of data was performed retrospectively.

4.2.1.2 Patient selection

Patients were identified from the Sheffield archive if they had previously undergone PCI without FFR guidance. Patients were excluded if they had presented with STEMI, had previous CABG surgery or CTO(s). Initial angiograms were screened to rule out any that were unsuitable for modelling. Cases were excluded if there was no ECG trace, limited views, or poor quality angiography (see chapter two for requirements of angiography for modelling). Fifty patients were studied based upon a power calculation. In FAME, FFR reduced the recommended number of stents per patient from 2.7 to 1.9. Assuming we would expect to see a similar level of reduction with vFFR and VCI, we would need 47 cases to give to give 90% power (two sided alpha of 0.05).

4.2.1.3 Angiographic procedure

All patients underwent standard single plane coronary angiography. Treatment decisions were made by the operator, at the time of angiography, based upon clinical and angiographic data, as usual. The number, size and position of stent(s) used was recorded prospectively. Patients did not undergo pressure-wire assessment; treatment was guided by the angiography images and clinical history alone.

4.2.1.4 Modelling protocol

The modelling protocol is illustrated in Figure 4.1. For each case, the baseline vessel was reconstructed and the vFFR of the baseline vessel calculated using previously described methods (chapter two). When vFFR was ≤0.80, VCI was performed. Three VCI strategies were modelled. First, the actual PCI procedure was replicated; second, the FFR_{max} was determined (the minimal amount of stenting required to achieve the best possible post treatment FFR); and third, the 'optimal strategy' was determined (the minimal amount of stenting required to achieve a post treatment FFR >0.90.). This value was chosen as it has previously been demonstrated to be associated with improved clinical outcomes. Where a post treatment vFFR of >0.90 was not possible (if the FFR_{max} was lower than this) then the minimal amount of stenting required to achieve the FFR_{max} was also taken as the 'optimal strategy'. Following VCI, volumetric meshing and vFFR computation was completed as previously described (chapter two). Generic boundary conditions were used for all simulations as no invasive pressure wire data were available (Pa = 90mmHg, Distal CMVR= 8.721e9 Pa/m^3s^{-1}).

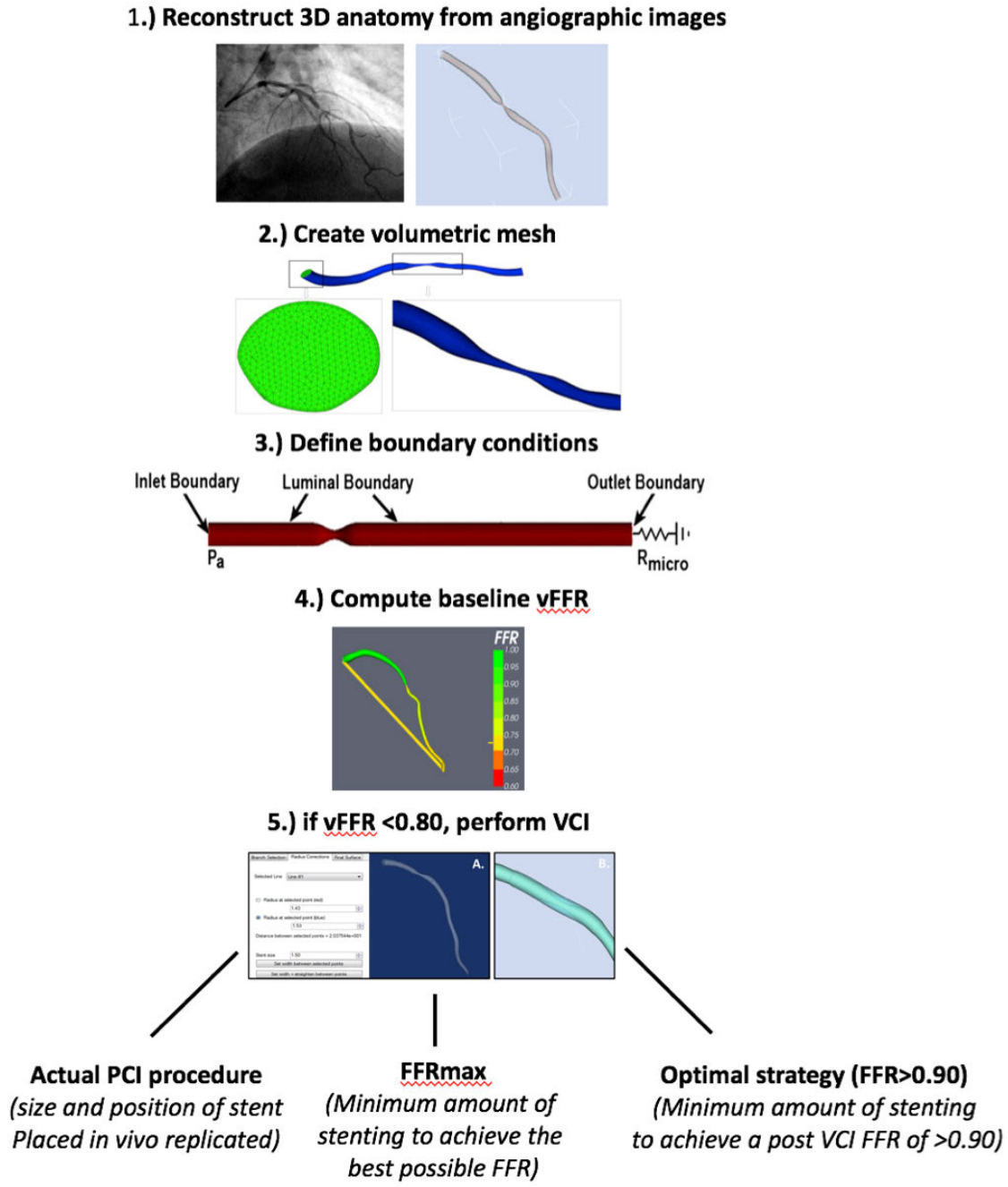


Figure 4.1: The modelling protocol

First, a 3D reconstruction is made from the angiographic imaging. The geometry is then discretised, producing a volume mesh. The boundary conditions of the model are then defined and the baseline vFFR is computed. If vFFR was ≤0.80, VCI was performed. Three stent strategies were computed. First, the actual PCI procedure was replicated. Second, the FFR_{max} was computed (the minimal amount of stent to achieve the best possible post VCI FFR). Third, the optimal strategy was determined; the minimal amount of stenting to produce a post VCI FFR of >0.90.

4.2.1.5 Analysis

Continuous data are presented as mean ±SD unless stated otherwise. Categorical data are presented as percentage (proportions). For each VCI strategy, the total stent length and total number of stents per patient and per vessel were calculated and compared to the actual procedure using paired samples t test. All statistical analysis was performed using SPSS version 24 (IBM, SPSS Inc, New York, US).

4.2.2 Results

4.2.2.1 Patient demographics

Fifty patients (sixty-four vessels) were analysed. Baseline patient and vessel characteristics are shown in Table 4.1. Mean age at presentation was 66 (±11) years. Thirty-six (72%) were male, thirty-three (66%) had hypertension, twelve (24%) had type two diabetes mellitus and twelve (24%) were current smokers. Thirty-three (66%) had presented with NSTEMI and seventeen (34%) had stable angina. Of the 64 vessels analysed, thirty-seven (58%) were LAD arteries, fourteen (22%) were LCX arteries, ten (16%) RCAs, two (3%) OM and one (2%) Dx artery.

Table 4.1: Patient and lesion characteristics

Patient characteristics (N=50)	
Mean age (years)	66 ± 11
Male	36 (72%)
Hypertension	33 (66%)
Hyperlipidaemia	20 (40%)
T2DM	12 (24%)
Current smoker	12 (24%)
Previous MI	6 (12%)
Indication for PCI:	
Stable angina	17 (34%)
NSTEMI	33 (66%)
Vessel characteristics (N=64)	
Vessel	
LAD	37 (58%)
LCX	14 (22%)
RCA	10 (16%)
OM	2 (3%)
Dx	1 (2%)
Baseline vFFR	0.73 ± 0.16
No. of stents	1.1 ± 0.3
Mean stent length (mm)	21.3 ± 7.4
Mean stent width (mm)	3.1 ± 0.4

Values are mean (±SD) and n(%). Dx = Diagonal; LAD = Left Anterior Descending; LCX = Left Circumflex; MI = Myocardial Infarction, NSTEMI = Non ST Elevation Myocardial Infarction; OM = Obtuse Marginal; RCA = Right Coronary Artery; T2DM = Type 2 Diabetes Mellitus; vFFR = Virtual Fractional Flow Reserve

4.2.2.2 Procedural details

Of the 64 vessels treated, the number of stents per vessel was 1.1 (± 0.3) (total 70 stents). Mean stent length and width were 21.3mm (±7.4) and 3.1mm (±0.4) respectively. Total stent length per vessel was 23.4mm (±8.3).

Of the 50 patients treated, the number of stents per patient was 1.4 (±0.6). Total stent length per patient was 29.9mm (±16.1). All patients received second generation drug-eluting stents.

4.2.2.3 Baseline vFFR

Baseline vFFR was successfully computed in all cases. Mean baseline vFFR was 0.73 (±0.16). Twenty-six (41%) vessels had a baseline vFFR >0.80. A break down per vessel is shown in Table 4.2. Eighteen (36%) patients had no vessels with a vFFR <0.80. Baseline vFFR was 0.71 (±0.17) for NSTEMI compared to 0.79 (±0.16) for stable angina, P=0.07. There was a trend for fewer patients with NSTEMI to have a non -significant FFR (>0.80) compared to those presenting with stable angina (34% versus 55%, P=0.17).

Table 4.2: Breakdown of vFFR by vessel

	N=	Baseline vFFR	Post PCI vFFR
LAD	37	0.72 (±0.17)	0.88 (±0.09)
LCX	14	0.72 (±0.20)	0.93 (±0.06)
RCA	10	0.81 (±0.09)	0.94 (±0.05)
OM	2	0.81 (±0.13)	0.92 (±0.08)
Dx	1	0.65	0.88

Values = number or mean (±SD). Dx = Diagonal; LAD = Left anterior descending; LCX =Left circumflex; OM = Obtuse marginal; RCA = Right coronary artery.

4.2.2.4 Virtual coronary intervention – replicating the actual procedure

When the actual procedure was replicated, the mean post PCI vFFR was 0.90 (±0.08). Twenty-five (39%) vessels had a post PCI vFFR of <0.91. When only the 38 vessels with a pre-treatment vFFR of <0.80 were studied, the post PCI FFR was 0.88 (±0.09). Twenty (53%) vessels had a post treatment vFFR of <0.91.

4.2.2.5 Virtual coronary intervention – 'FFR$_{max}$' and 'optimal strategy'

In the 38 vessels with a baseline vFFR <0.80, VCI was performed to achieve the FFR_{max} and the optimal strategy (FFR >0.90). Results are summarised in Table 4.3. Mean FFR_{max} was 0.90 (±0.08). This was on average 0.02 (±0.03) higher than the corresponding post VCI vFFR obtained when the actual procedure was modelled. Thirteen (34%) vessels had a FFR_{max} of <0.91. When the virtual procedure was planned to achieve the FFR_{max}, the number of stents per vessel was significantly less than the actual procedure (0.8 (±0.7) versus 1.1 (±0.3), P<0.001). The total length of stent per vessel was significantly reduced (18.8mm (±17.5) versus 23.3mm (±8.4), P=0.05). The number of stents per patient was significantly less than the actual procedure (1.0 (±1.0) versus 1.4 (±0.6), P=0.001). The total stent length per patient was similar (24.6mm (±27.2) versus 29.8mm (±16.3), P=0.139). Mean stent length and width were 25.1mm (±8.36) and 2.8mm (±0.3) respectively. Mean stent width was significantly less than the actual procedure (2.8mm (±0.3) versus 3.1mm (±0.4), P<0.001). Mean stent length was significantly higher than the actual procedure (25.1mm (±8.4) versus 21.3mm (±7.4), P=0.01).

VCI was also performed to achieve an FFR >0.90 (the 'optimal strategy') in the 38 vessels with a baseline vFFR of ≤0.80. Mean post PCI FFR was 0.89 (±0.08). This was on average 0.01 (±0.03) higher than the corresponding post VCI vFFR obtained when the actual procedure was modelled and 0.007 (±0.01) less than the corresponding FFR_{max}. Thirteen (34%) vessels had a post treatment vFFR <0.91. When the virtual procedure was planned to achieve the 'optimal strategy', the number of stents per vessel were significantly reduced compared to the actual procedure (0.8 (±0.7) versus 1.1 (±0.3), P=0.001). The total length of stent per vessel was significantly reduced compared to the actual procedure (16.4mm (±16.2) versus 23.3mm (±8.4), P=0.003). The number of stents per patient was significantly less than the actual procedure (1.0 (±1.0) versus 1.4 (±0.6), P=0.001). The total length of stent per patient was significantly reduced compared to the actual procedure (20.4mm (±23.6) versus 29.8mm (±16.3), P=0.006). Mean stent length and width were 21.0mm (±8.7) and 2.7mm (±0.3) respectively. Mean stent

width was significantly less than the actual procedure (2.7mm (±0.3) versus 3.1mm (±0.4), P<0.001). There was no difference in mean stent length (21.0mm (±8.7) versus 21.3mm (±7.4), P=0.95). Full results for each patient are shown in Supplemental Table 3 (Appendix).

Table 4.3: Summary of effect of vFFR and VCI on no. of stents and total stent length per patient and per vessel

	Per patient, N = 50		Per vessel, N = 64	
	Average No. of stents	**Total length of stent (mm)**	**Average no. of stents**	**Total length of stent (mm)**
Actual procedure	1.4 (±0.6)	29.8 (±16.3)	1.1 (±0.3)	23.3 (±8.4)
vFFR and VCI (FFR_{max})	1.0 (±1.0)	24.6 (±27.5)	0.8 (±0.7)	18.8 (±17.7)
vFFR and VCI (FFR > 0.90)	1.0 (±1.0)	20.4 (±23.6)	0.8 (±0.7)	16.4 (±16.2)

Values = mean ± SD. vFFR = Virtual Fractional Flow Reserve; VCI = Virtual Coronary Intervention.

4.2.3 Discussion

Using vFFR and VCI to guide treatment was associated with a significant reduction in the total number of stents recommended per patient and per vessel. This effect was seen regardless of whether the procedure was planned to achieve the best possible vFFR (FFR_{max}) or to achieve a FFR of >0.90; the 'optimal strategy'. The total length of stent recommended per patient was significantly reduced when the procedure was planned to achieve 'the optimal strategy' and per vessel regardless of the VCI strategy used. There was a modest increase in the achievable post PCI vFFR with both strategies compared to the actual procedure, suggesting that as well as reducing the amount of stenting, a small improvement in post PCI physiology may be possible when vFFR and VCI are used to guide treatment. Importantly, 41% of vessels studied had a baseline vFFR of >0.80 and 36% of patients had no vessels with a vFFR <0.80, suggesting PCI may have been avoided. This re-emphasises the fact that visual angiographic

assessment tends to overestimate lesion severity. These results are consistent with previously published data. In the FAME study, 37% of lesions selected for PCI based on angiographic assessment had a FFR >0.80. The study design of FAME was such that only patients whom the investigator had already stated that PCI was felt to be indicated were then randomised to angiography or FFR guided treatment. Similarly, in this retrospective study, only patients in whom PCI had been performed based on angiographic assessment were included. Analysis of a large Japanese registry (CVIT-DEFER) similarly revealed anatomical-functional mismatch, where visual estimate determined a stenosis to be >75% yet FFR was >0.80, in 43.4% of lesions (Nakamura et al., 2014). Reverse mismatch (non-significant on visual assessment versus positive FFR) was less frequent (23.2%). I did not analyse reverse mismatch as I only included vessels that were recommended for PCI based upon angiographic assessment.

More recently, there has been increased focus on the post-PCI FFR with a number of studies demonstrating improved outcomes in patients with better physiological results from PCI. In our cohort, when the actual procedure was replicated, 54% of cases had a post PCI FFR of less than 0.91. Using vFFR and VCI to guide treatment reduced this to 34%. This suggests that it is possible to improve physiology and potentially outcomes with VCI. It is important to note that in some cases the post PCI FFR cannot be improved as the FFR_{max} is below this threshold due to other factors. This is discussed in more detail in chapter three.

4.2.3.1 Reduction in stenting

In FAME, patients were identified who had multi-vessel coronary artery disease (defined as >50% stenosis in two or more vessels) in which PCI was indicated in at least one vessel based upon visual angiographic assessment. Patients were then randomised to angiography guided or FFR guided PCI. The authors demonstrated a reduction in the number of stents per patient from 2.7 (±1.2) to 1.9 (±1.3) (P<0.001) and a reduction in the total length of stent per patient from 51.9mm (±24.6) to 37.9mm (±

27.8), (P<0.001). Using FFR to guide treatment was associated with a significant reduction in the composite outcome of death, MI and repeat revascularisation at one year. This was maintained up to two years, but at two to five years the risk for both groups developed similarly (van Nunen et al., 2015). I similarly demonstrated a reduction in both the number and the total length of stent per patient using a physiologically guided approach. This was primarily driven by the cases that no longer required PCI, because the baseline physiology was non-significant. As expected, the number and length of stent(s) to achieve the FFR_{max} was higher than for the 'optimal strategy'. However, the average physiological improvement was small (+0.007). The balance that should be obtained between increased length of stent and improved physiological outcome is currently unknown. In Figure 4.2, an example is shown in which the baseline vFFR was 0.74. In the actual PCI procedure, a 3.0mm x 20mm stent was inserted, and the post-PCI vFFR was 0.91. The FFR_{max} result suggests that with a longer stent (28mm) a better result could have been achieved (vFFR=0.95). Equally, the modelling results demonstrated that with a shorter stent (12mm) an equally good physiological result could have been achieved (vFFR=0.91). There is a trade-off to be made between the extent of stenting and the physiological result. VCI does not take into consideration the practical PCI risks of a short stent; in particular, the risk of disruption if the edge of the stent lands in plaque rather than 'normal' artery. Until now it has not been possible to predict the response to stenting, so there is limited data on this. This will be an important avenue for future work.

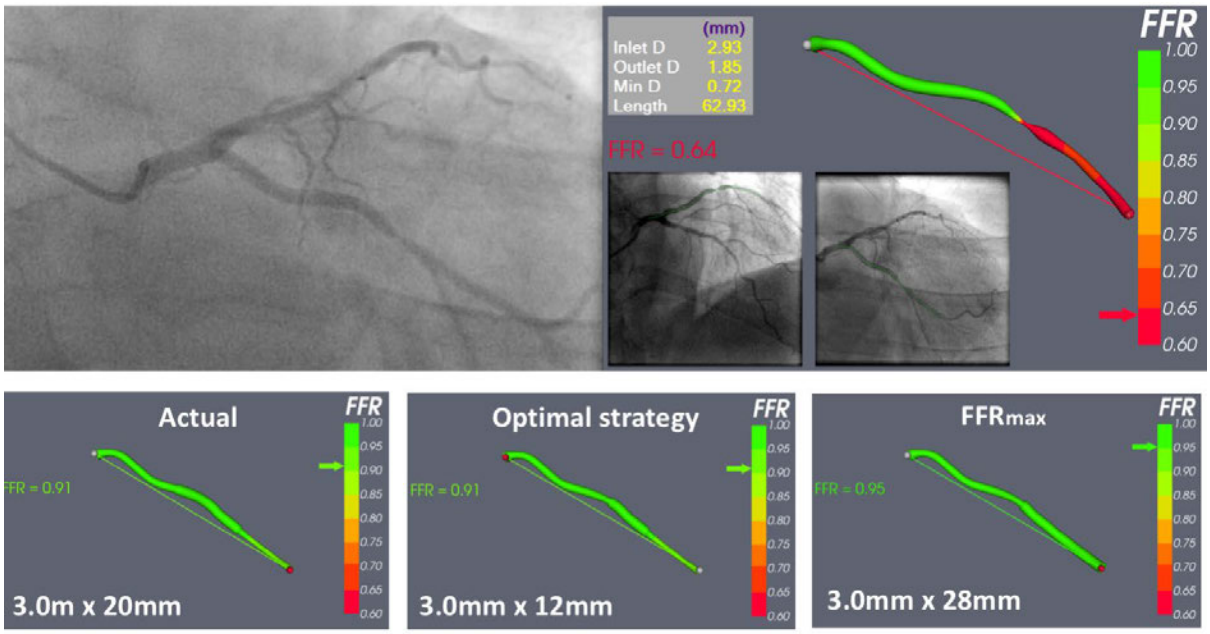


Figure 4.2: Illustrative case example

A 72 year old male presented with shortness of breath on exertion. A coronary angiogram revealed a lesion in the mid left circumflex artery. A 3.0mm x 20 mm stent was inserted by the operator. In the retrospective study, baseline vFFR was calculated as 0.64. Three PCI strategies were modelled. First, the actual procedure was replicated (bottom left), second, the optimal strategy was modelled (bottom middle) and third, the FFR_{max} was determined (bottom right).

4.2.3.2 Stent sizing

Using VCI to guide treatment also led to a significant reduction in the recommended stent width. It is unclear whether this is due to a tendency of the operators in this study to over size based upon angiographic assessment or a limitation of the modelling. Data from IVUS studies suggest angiography is more likely to under-estimate the true vessel diameter(Darmoch et al., 2020). It will be important to further validate our stent sizing tool with the use of intracoronary imaging to examine this further. The tendency to oversize stents has been reported previously. Of 2,931 lesions analysed by Kitahara et al, 82% of lesions with a reference vessel diameter (RVD) of <2.75mm had stent oversizing >10% (defined as (nominal stent diameter- RVD/ RVD)*100) (Kitahara et al., 2017). In vessels with a RVD of >2.75mm, this level of over-sizing was observed in 33%. However, the authors demonstrated a positive impact of stent oversizing on procedural and clinical outcomes, without

increasing rates of edge dissection. Rates of stent thrombosis and target vessel revascularisation were higher in the stents that were not over-sized. This highlights the importance of combining modelling with clinical expertise. The model can report the RVD to the operator, however they may choose to over-size based on their clinical expertise. The model may be more useful in preventing under-sizing. Under-sizing of coronary stents is an independent risk factor for stent thrombosis. In a large registry, it was the second strongest predictor for stent thrombosis (van Werkum et al., 2009). In this study, under-sizing was considered significant if one of the following criteria were met: 1) stent to reference segment diameter < 1; 2) inappropriate alignment of coronary stent within the vessel wall; and 3) mismatch in post deployment stent dimensions in relation to the proximal and distal target vessel. Some studies have suggested rates of under-sizing as high as 20-30% (Cheneau et al., 2003, Uren et al., 2002). Incorrect judgment of coronary vessel size by the operator is likely to be a significant contributing factor. Modelling could assist with this. It is important to note that the model reports size based upon the lumen as seen on angiography. It does not take into consideration the effect of acute vasoconstriction.

4.2.4 Limitations

This was a retrospective study performed on a modest number of cases. Clinical outcomes were not examined. Only cases who had undergone PCI based upon angiographic assessment were included. As a result, I could not examine the impact of vFFR or VCI upon cases initially deemed to not be significant by angiographic assessment. This study design was chosen to allow for direct comparison with FAME, in which only cases where PCI was indicated were included. The chosen PCI strategies for FFR_{max} and optimal strategy were determined based upon modelling alone and did not take into consideration other clinical or procedural factors.

4.2.5 Conclusion

In this cohort, 41% of vessels had a vFFR >0.80 suggesting PCI could have been avoided. Using vFFR and VCI to plan PCI led to a significant reduction in the total number and length of stents recommended per patient. Further work on a larger cohort is required to determine if these findings would translate to improved clinical outcomes.

4.3 Part 2 - Decision making in a virtual clinic setting

4.3.1 Introduction

In the first part of this chapter, I demonstrated the potential for vFFR and VCI to influence 'real world' stenting. However, vFFR and VCI can only be used to guide treatment decisions. They cannot tell the operator exactly what to do. Although they provide an indication of the physiology and predicted response to treatment, this needs to be taken into consideration alongside the clinical history and other anatomical and technical factors that rely upon the clinician's experience and expertise. Moreover, how clinicians make decisions, and how much they are likely to consider physiology in this process, is likely to vary between individuals. The purpose of this study was to determine the potential impact of vFFR and VCI upon 'real world' decision making in the cardiac catheter laboratory and to assess the inter-observer variability in decision making both with and without vFFR and VCI technology.

4.3.2 Methods

4.3.2.1 Patient selection and angiographic procedure

The same 50 patient cases as studied in part 1 of this chapter were analysed in this study. From RIPCORD, we estimated that a change in decision would occur in approximately 25% of patients and anything < 10% would be deemed un-important. The 95% confidence intervals for p are derived from

the formula: $\hat{p} \pm 1.96 \text{ sqrt } (\hat{p}(1-\hat{p})/n)$. A sample size of 50 provides 95% confidence intervals of 12% to 37% for this effect size.

These were all retrospective cases for whom PCI was performed for either stable angina or NSTEMI. The procedures were performed without physiological guidance. Clinical, demographic and procedural data were collected prospectively.

4.3.2.2 Modelling protocol

All vessels with a minimum diameter of 2.25mm and at least mild disease were modelled using previously described methods. VCI was performed as described in chapter two. Multiple VCI strategies were performed to determine the FFR_{max} and optimal strategy as well as simulating realistic choices, taking into consideration the angiographic and baseline vFFR appearances. A selection of up to four VCI strategies were then presented for each case.

4.3.2.3 MDT protocol

All 50 cases were presented to two experienced interventional cardiologists independently (cardiologist A and cardiologist B). The protocol and data collection form that were used are shown in the Appendix. The cardiologists were initially presented with the clinical history, ECG, and baseline angiographic images. Based upon these conventional data sources, they were asked to give their recommendation for treatment. They were asked to specify whether they would recommend OMT, PCI, CABG or 'more information required'. If they selected PCI, they were asked to specify the vessel(s) for revascularisation and the number and size of stent(s) they would recommend. If they selected CABG, they were asked to specify the vessel(s) to be grafted. If they selected 'more information required', they were asked to specify what information they would request. This could be a pressure wire examination or any other investigation or data they felt would be helpful in their decision making. They were encouraged to answer based upon their real clinical practice. They were also asked to state the reasons for their

decisions. At each stage, they were asked to rate their confidence in their decision on a scale of 1-10 (10 being high). After they had made their initial recommendations, they were shown the results of the baseline vFFR modelling along with the stent sizing information (Figure 4.3). They were then asked the same questions regarding their treatment plan and their confidence level in their decision. They were also asked to specify why their plan had or had not changed. Finally, they were shown the VCI results. They were presented with a series of treatment strategies along with the predicted FFR values (see Figure 4.4 for an example case). Once more, they were asked to state their treatment plan and their confidence level in the decision. They were again asked why their treatment plan had or had not changed. Importantly, it was at the cardiologists' discretion as to whether, and to what degree, they took into consideration the modelling results. The purpose of this was to determine the potential effect of this model system upon decision making. The cardiologists were expected to utilise the modelling in combination with their own clinical judgment to make decisions. A diagrammatic representation of the study protocol is shown in Figure 4.5.

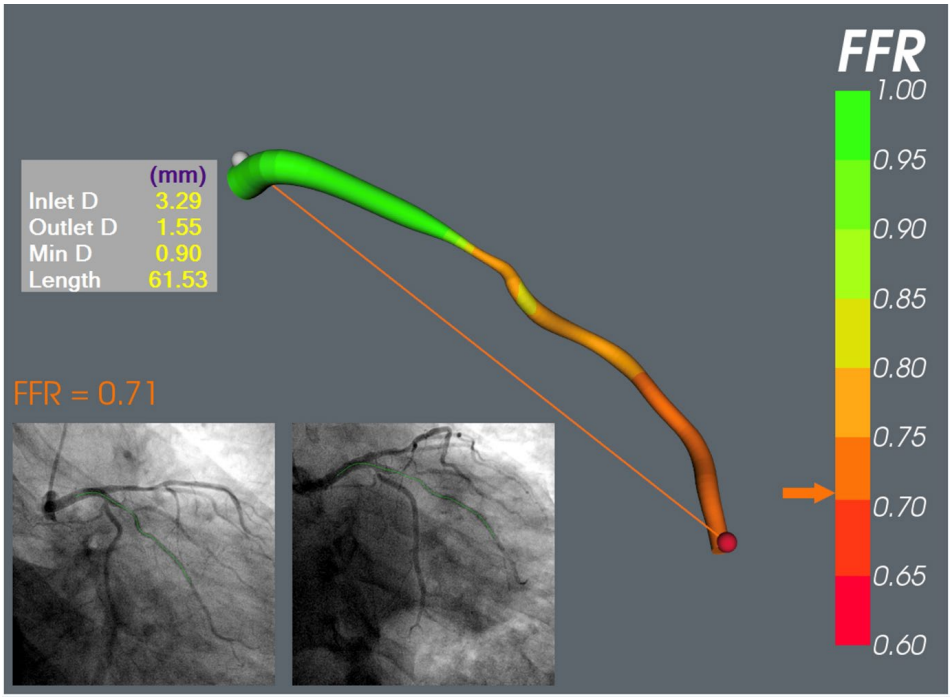


Figure 4.3: Example vFFR result as demonstrated in the study

The reconstructed vessel is demonstrated alongside the angiographic images. The vFFR for the studied region is displayed on the screen (orange). The stent sizing tool displays the diameter data corresponding to the selected points (grey and red dots). The grey and red dots on the reconstruction can be moved along the vessel allowing the dimensions at any chosen point to be determined. The length between the two points is also displayed.

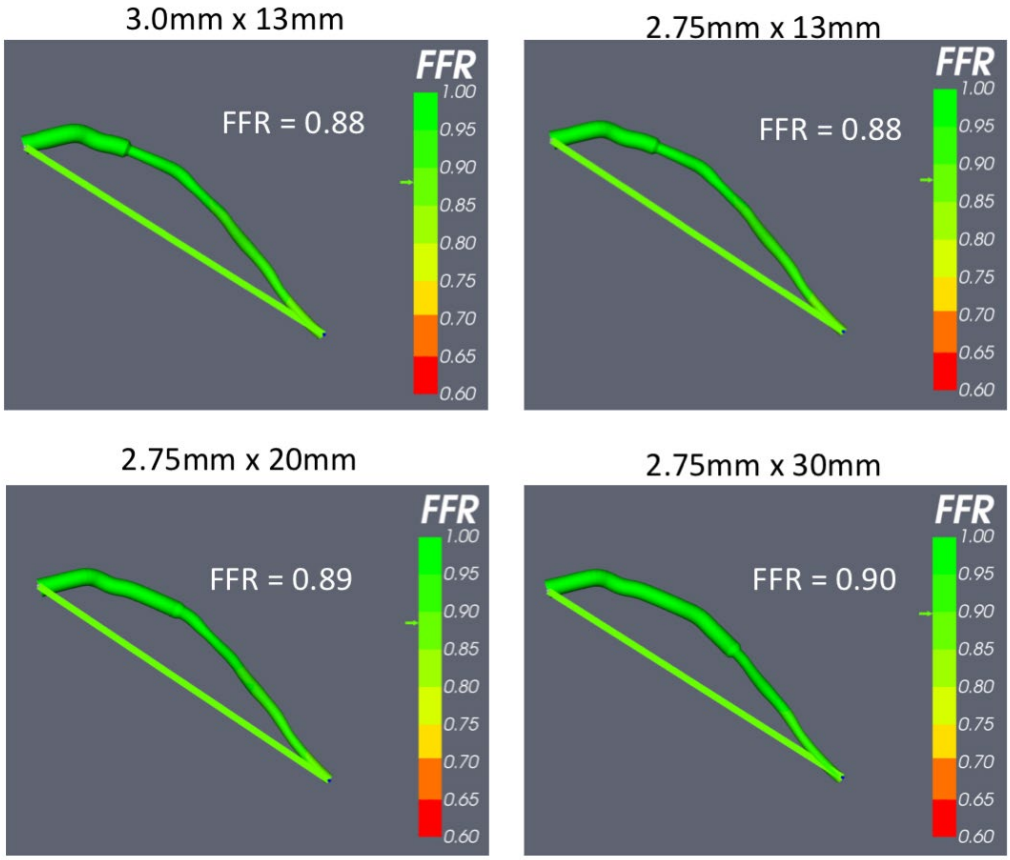


Figure 4.4: Example VCI result demonstrated in the study

Four VCI strategies are demonstrated for review. For each, the size of virtual stent is stated top centre and the post VCI FFR in white.

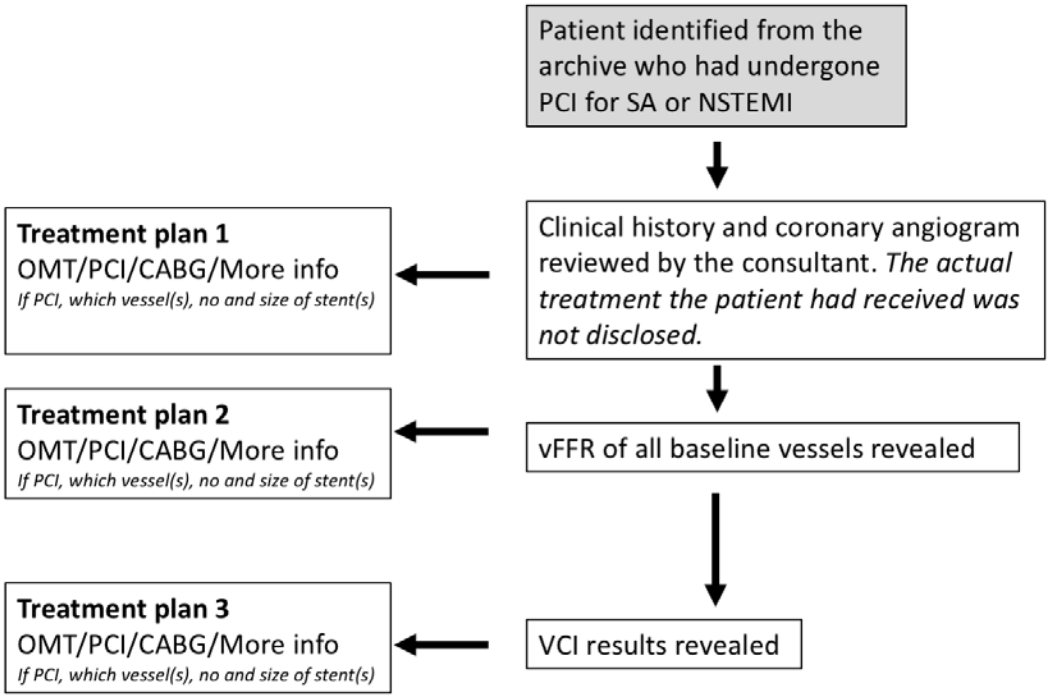


Figure 4.5: Diagrammatic representation of case-analysis protocol
The cardiologists were shown retrospective cases. Three treatment plans were made, the first based upon clinical history and angiographic assessment alone, the second with vFFR in addition to the above and the third with VCI as well. OMT = optimal medical therapy, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery. vFFR = virtual fractional flow reserve, VCI = virtual coronary intervention.

4.3.2.4 Assessment of inter-operator variability

A subset of 12 cases were then shown to six further interventional cardiologists (providing eight datasets in total) to assess the inter-operator variability in decision making. These 12 were selected at random from the original 50, using a random number generator. The cases were presented in the same way as above. These assessments were carried out independently of each other. The cardiologists were not aware of the answers provided by their colleagues or the actual treatment each patient had received.

4.3.2.5 Analysis

Continuous data are presented as mean (±SD) unless stated otherwise. Categorical data are presented as percentages (proportions). For all 50 cases, the patient-level treatment strategies based upon angiographic assessment, vFFR assessment and VCI assessment were compared. The primary outcome was the number/percentage of cases whereby the treatment recommendation changed following the availability of the virtual physiology results. Cardiologist A's recommendations were also compared to that of cardiologist B. Agreeability between the two cardiologists was assessed using Cohen's kappa coefficient and confidence intervals were calculated. Stent size recommendations based upon angiographic assessment, vFFR assessment and VCI assessment were also compared. The number of occasions in which the stent size recommendation was altered based upon vFFR or VCI was calculated. The number of stents and total stent length were calculated for all patients with a definitive management plan (OMT, PCI or CABG) and compared using paired sample t-test or repeated measures ANOVA. The confidence scores at each stage (angiographic, vFFR and VCI) were compared using repeated measures ANOVA. For the subset of 12 patients, all eight treatment strategies were compared along with the percentage of treatment plans that were changed based upon vFFR and VCI assessment between operators. Agreement between the management plans, both pre- and post-physiological assessment, for all eight cardiologists, was assessed using Cohen's kappa coefficient and confidence intervals were calculated. All statistical analysis was performed using SPSS version 24 (SPSS Inc, New York, US).

4.3.3 Results

Fifty patient cases were included for analysis. Baseline characteristics are summarised in Table 4.1. Mean age at presentation was 66±11 years. Thirty-six (72%) were male, thirty-three (66%) had hypertension, twelve (24%) had type two diabetes mellitus and twelve (24%) were current smokers. Thirty-three (66%) had presented with NSTEMI and seventeen (34%) had stable angina. Eighty-six vessels with a diameter >2.25mm and with at least mild disease on eyeball assessment were identified.

In eight (9%), vFFR modelling was not possible due to unsuitability of the angiographic images (see chapter two for requirements of angiography for modelling). Seventy-eight vessels remained in which baseline vFFR was successfully computed and VCI was performed; 43 LAD arteries, 17 LCX arteries, 13 RCA arteries, three Dx arteries and two OM arteries. The mean baseline vFFR was 0.73 (±0.17). All 50 cases were reviewed by two interventional cardiologists independently (cardiologist A and cardiologist B).

4.3.3.1 Angiography based management plans

After reviewing the coronary angiogram, cardiologist A initially recommended OMT in four (8%), PCI in 30 (60%), CABG in 0 (0%) and 'more information required' in 16 (32%) patients. The 'more information' requested was pressure wire assessment in 15/16 (94%) cases and further diagnostic angiography images in one (6%) case. Of the 30 patients in whom PCI was recommended, this was single-vessel in 22 (73%) and multi-vessel in 8 (27%). In total, PCI was recommended in 46 vessels with 48 stents. Mean recommended stent length and width were 23.5mm (±6.9) and 3.0mm (±0.4) respectively. An average of 1.2 (±0.7) stents were recommended per patient. The total recommended stent length per patient was 27.1mm (±18.3). Cardiologist A's recommendation agreed with the actual management plan in 30 (60%) patients. For the actual procedure, an average of 1.4 (±0.6) stents were recommended per patient. The total recommended stent length per patient was 29.9mm (±16.3).

Cardiologist B initially recommended OMT in 0 (0%), PCI in 36 (72%), CABG in 0 (0%) and 'more information required' in 14 (28%) patients. The more information requested was pressure wire assessment in all of these cases. Of the 36 patients in whom PCI was recommended, this was single-vessel in 27 (75%) and multi-vessel in 9 (25%). In total, PCI was recommended in 52 vessels with 55 stents. Mean stent length and width were 22.5mm (±9.5) and 2.9mm (±0.3) respectively. An average of 1.4 (±0.9) stents were recommended per patient. The total recommended stent length per patient was

31.6mm (±24.3). Cardiologist B's recommendation agreed with the actual management plan in 36 (72%) of cases. A summary of all of cardiologist A and B's recommendations are shown in Supplemental Table 4 (Appendix).

4.3.3.2 vFFR based management plans

After reviewing the baseline vFFR results, cardiologist A recommended OMT in 7 (14%), PCI in 33 (66%), CABG in 0 (0%) and 'more information required' in 10 (20%) patients. The 'more information' requested was a pressure wire in nine cases (90%) and better angiographic images in one case (10%). Of the 33 patients in whom PCI was recommended, this was single vessel in 26 (79%) and multi-vessel in 7 (21%). In total, PCI was recommended in 47 vessels with 49 stents. Mean stent width and length were 2.9mm (±0.3) and 24.3mm (±7.0) respectively. An average of 1.1 (±0.7) stents were recommended per patient. The total recommended stent length per patient was 24.7mm (±18.0).

After reviewing the vFFR results, cardiologist A changed the patient-level management plan in 10 cases (20%, 95% confidence interval; 11.2% to 33.0%). A detailed breakdown showing the nature of the changes is shown in Table 4.4. Of the 10 patients initially allotted to the 'more information required' category, three (30%) were reallocated to OMT and five (50%) to PCI. Of the 33 patients initially allotted to PCI, two (6%) were reallocated to more information required. In both of these cases, the vFFR was negative, although close to the borderline. This placed enough doubt in the cardiologist's mind for them to wish to have an invasive FFR before proceeding to PCI. There was a trend towards the treatment plan being more commonly changed in patients with stable angina (5/16, 31%) compared to those with ACS (5/34, 15%), although this was statistically non-significant (P=0.16).

In 22 (44%) cases, after vFFR was revealed, the recommended treatment plan contradicted that which was recommended solely by vFFR. In 11 of these cases (50%), this was because the model was not

believed to be accurate, and the operator was more confident in his angiographic assessment, so PCI was still recommended despite a vFFR above the 0.80 threshold. In five cases (23%), the vFFR was borderline and the operator did not have complete confidence, therefore an invasive pressure wire was recommended. In a further five cases (23%), the vFFR was positive (<0.80) but PCI was not recommended for other clinical or technical reasons. Finally, in one case, the vFFR was felt to be irrelevant as the vessel was recommended for PCI as part of a bifurcation treatment therefore the reason was to protect the branch and not for physiological improvement.

After reviewing the baseline vFFR results, cardiologist B recommended OMT in one (2%), PCI in 43 (86%), CABG in zero (0%) and 'more information required' in six (12%) patients. The 'more information' requested was a pressure wire examination in all six of these cases. Of the 43 patients in whom PCI was recommended, this was single vessel in 27 (63%) and multi-vessel in 16 (37%). In total, PCI was recommended in 62 vessels with 68 stents. Mean stent width and length were 2.8mm (±0.3) and 24.1mm (±9.7) respectively. An average of 1.5 (±0.9) stents was recommended per patient. The total recommended stent length per patient was 36.0mm (±23.5). After reviewing the vFFR results, cardiologist B changed the patient-level management plan in 12 cases (24%, 95% confidence intervals; 14.3% to 37.4%). A detailed breakdown showing the nature of the changes is shown in Table 4.5. Of the 14 patients initially allotted to 'more information required', nine (64%) were reallocated to PCI and one (7%) to OMT. Of the 36 patients initially allotted to PCI, two (6%) were reallocated to 'more information required'. In both of these cases, the vFFR was negative, although close to the borderline. This placed enough doubt in the cardiologist's mind to recommend an invasive FFR before proceeding to PCI. The number and location of vessel(s) for PCI was changed in a further five cases (10%), so the total number of cases in which management was changed was 17 (34%, 95% confidence intervals; 22.4% to 47.9%). There was a trend towards the treatment plan being more commonly changed in patients with

stable angina (7/16, 44%) compared to those with ACS (10/34, 29%) although this was statistically non-significant (P=0.25).

In 17 cases (34%), after vFFR was revealed, the recommended treatment plan contradicted that which was recommended by vFFR alone. In eight cases, this was because the clinical history was suggestive of acute plaque rupture, and although the vFFR was negative, PCI was recommended on the basis of it being the suspected culprit lesion. In four cases in which the vFFR was negative (>0.80), the cardiologist did not believe the model captured the severity of the stenosis, and recommended PCI anyway, based upon their angiographic assessment. In another four cases, the vFFR was borderline negative but with a convincing clinical history. The cardiologist therefore requested an invasive pressure wire to clarify. In one case, the FFR was positive, but PCI was not recommended, because a CMR had already shown that region to be non-viable.

Table 4.4: Patient level treatment plans made by cardiologist A based upon angiographic and vFFR assessment.

	vFFR based management plan				
Angiography based management plan	OMT	PCI	CABG	More info	Total
OMT	4	-	-	-	4
PCI	-	28	-	2	30
CABG	-	-	-	-	-
More info	3	5	-	8	16
Total	7	32	-	11	50

A change in patient-level management was observed in 20% of cases (95% confidence interval 11.2–33.0%), highlighted in yellow. CABG = coronary artery bypass graft; OMT = Optimal medical therapy; PCI = percutaneous coronary intervention; vFFR = virtual fractional flow reserve.

Table 4.5: Patient level treatment plans made by cardiologist B based upon angiographic and vFFR assessment.

	vFFR based management plan				
Angiography based management plan	OMT	PCI	CABG	More info	Total
OMT	-	-	-	-	0
PCI	-	34	-	2	36
CABG	-	-	-	-	-
More info	1	10	-	3	14
Total	1	44	-	6	50

A change in patient-level management was observed in 24% of cases (95% confidence interval 14.3% to 37.4%), highlighted in yellow. CABG = coronary artery bypass graft; OMT = Optimal medical therapy; PCI = percutaneous coronary intervention; vFFR = virtual fractional flow reserve.

4.3.3.3 VCI based management plan

After reviewing the VCI results, cardiologist A recommended OMT in seven (14%), PCI in 33 (66%), CABG in 0 (0%) and 'more information required' in 10 (20%) patients. VCI did not lead to a further change in patient level management (beyond that seen with vFFR) in any cases. After reviewing the VCI results, cardiologist B recommended OMT in one (2%), PCI in 44 (88%), CABG in 0 (0%) and 'more information required; in five (10%) of cases. Patient-level management was changed in one (2%) case compared to the vFFR treatment plan. In this case, the vFFR was borderline which led the cardiologist to recommend an invasive pressure wire. However, VCI showed an excellent result with minimal stenting therefore this was enough to convince him to proceed with PCI without the need for an invasive pressure wire.

4.3.3.4 Stent sizing

After reviewing the vFFR and baseline vessel dimension data, the cardiologists were asked to state their recommended stent size for any vessel where PCI was the chosen strategy. This was then compared to the initial stent size selected based on the angiographic images alone. For cardiologist A, of the 28 cases where PCI was recommended on both occasions, the recommended stent size changed in five cases (18%). In three cases, this was a reduction in stent length, in one a reduction in stent diameter and in one an increase in stent diameter. After VCI results were made available, the cardiologists were then given the opportunity to further adjust their recommended stent size. After VCI, cardiologist A further changed his recommendation in four out of 33 (12%) cases. In two cases, this was a decrease in stent length, in one an increase in stent length and in one a reduction in stent diameter. In total, cardiologist A changed his recommendation with either vFFR or VCI, 18% of the time. For cardiologist B, after reviewing the baseline vFFR and vessel dimension data, of the 34 patients in whom PCI was recommended on both occasions, the recommended stent size changed in 26 cases (77%). In 15 cases, this was an increase in stent length, in seven a reduction in stent length, in nine a reduction in stent diameter and in two an

increase in stent diameter. After reviewing the VCI results, Cardiologist B further changed the recommendation in 23 out of 43 (53%) cases. In 11 cases, this was an increase in stent length, in six a reduction in stent length, in five a reduction in stent diameter and in one an increase in stent diameter. In total, cardiologist B changed his recommendation with either vFFR or VCI, 77% of the time.

4.3.3.5 Comparison between cardiologist A and B

Based upon angiographic assessment, cardiologist B's patient-level recommendation differed from that of cardiologist A in 19 (38%) of cases. In a further four cases for whom PCI was selected by both operators, the vessel(s) for revascularisation differed. Therefore, combined, the management plan between cardiologist A and B differed in 23 (46%) of cases. Using Cohens kappa analysis, there was minimal agreement between the two operators' management plans, (k=0.23, 95% CI -0.02 to 0.48, P=0.06). There was no significant difference in the total number of stents recommended per patient (1.4 versus 1.2, P=0.28) nor the total length of stent recommended per patient (31.6mm versus 27.1mm, P=0.40).

After vFFR assessment, cardiologist B's management plan differed from cardiologist A's in 16 (32%) cases. Additionally, the vessel(s) for PCI differed in four cases. Therefore, combined the management plan between cardiologist A and cardiologist B differed in 20 cases (40%). Using Cohen's kappa analysis, there was minimal agreement between the two operators' management plans, (k= 0.21, 95% CI 0.02 to 0.40 P=0.03). There was no significant difference in the likelihood of changing management based upon vFFR between the operators (20% versus 34%, P=0.12). Following vFFR assessment, cardiologist B recommended significantly more stents per patient and greater total length stent per patient compared to cardiologist A (1.5 versus 1.1, P=0.01 and 36.0mm versus 24.7mm, P=0.02).

Cardiologist B was significantly more likely to change stent size recommendation based upon baseline vFFR and sizing data (77% versus 18%, P<0.001). Similarly, cardiologist B was significantly more likely to change the stent size recommendation based upon the VCI results (53% versus 12%, P<0.001).

4.3.3.6 Confidence in management plan

Mean confidence scores from cardiologist A and cardiologist B combined in their angiography based patient-level management, vessel-level management and stent sizing were 8.1 (±1.5), 8.4 (±1.5) and 6.9 (±1.0) respectively. After baseline vFFR results were made available, the confidence level in patient-level management increased by 0.5 (P<0.001), vessel-level by 0.5 (P<0.001) and stent sizing by 1.0 (P<0.001). After reviewing the VCI results, the confidence level in patient-level management increased by 0.1 (P=0.03), vessel-level by 0.1 (P=0.31) and stent sizing by 0.7 (P<0.001) further beyond that with vFFR alone. Summarised data are shown in Table 4.6. There was no relationship between the operator's confidence in the angiography based management plan and the likelihood to change management based upon vFFR (8.2 versus 7.8, P=0.32). However, initial confidence in stent size was significantly lower in those cases where the stent size recommendation was subsequently changed (7.2 versus 6.6, P=0.02).

Table 4.6: Confidence scores in patient-level management, vessel-level management and stent sizing following angiographic assessment, vFFR assessment and VCI (scale 1-10).

	Angio	vFFR	VCI	P value
Cardiologist A				
Patient level	8.7±1.4	8.8±1.3	8.9±1.3	0.04
Vessel level	9.2±1.0	9.2±1.0	9.3±0.9	0.52
Stent size	7.3±1.0	7.9±0.9	8.6±0.9	<0.001
Cardiologist B				
Patient level	7.6±1.4	8.2±1.2	8.4±0.9	<0.001
Vessel level	7.6±1.5	8.3±1.2	8.4±1.0	<0.001
Stent size	6.6±0.7	7.7±1.0	8.4±0.8	<0.001
Combined				
Patient level	8.1±1.5	8.5±1.3	8.6±1.2	<0.001
Vessel level	8.4±1.5	8.7±1.2	8.8±1.1	<0.001
Stent size	6.9±1.0	7.8±0.9	8.5±0.9	<0.001

Values = Mean ± SD. vFFR = Virtual Fractional Flow Reserve; VCI = Virtual Coronary Intervention. P value shown for significance of change in confidence level after vFFR and VCI assessment (repeated measures ANOVA).

4.3.3.7 Assessment of inter-observer variability

A subset of twelve cases from the original 50 were selected at random to be reviewed independently by eight interventional cardiologists. Baseline patient and vessel characteristics are shown in Table 4.7. Mean age at presentation was 63.5 (±10.3) years. Eight (67%) were male, seven (58%) had hypertension, one (8%) had T2DM and four (33%) were current smokers. Eight (67%) presented with NSTEMI and four (33%) had symptoms suggestive of stable angina. These 12 cases contributed 20 vessels for vFFR and VCI assessment; nine LAD arteries, six LCX arteries and five RCAs. Mean vFFR was 0.73 (±0.15).

Table 4.7: Baseline patient and vessel characteristics

Patient characteristics (N=12)	
Mean age (years)	64 (±10)
Male	8(67%)
Hypertension	7 (58%)
Hyperlipidaemia	5 (42%)
T2DM	1 (8%)
Current smoker	4 (33%)
Previous MI	2 (17%)
Indication for PCI:	
Stable angina	4 (33%)
NSTEMI	8 (67%)
Vessel characteristics (N=20)	
Vessel	
LAD	9 (45%)
LCX	6 (30%)
RCA	5 (25%)
Baseline vFFR	0.73 (±0.15)

Values are mean ± SD or number (%). LAD = Left Anterior Descending; LCX = Left Circumflex; MI = Myocardial Infarction; NSTEMI = Non-ST-segment Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; RCA = Right Coronary Artery; T2DM = Type 2 Diabetes Mellitus; vFFR = Virtual Fractional Flow Reserve.

After angiographic assessment, PCI was recommended in a median of five patients (range; three to seven) and 5.5 vessels (range; three to nine). OMT was recommended in a median of 0.5 patients (range; zero to three) and 'more information required' in a median of six patients (range; four to nine). Of the 48 times this was requested, the modality was a pressure wire assessment in 45, better angiographic views in two and a CMR to assess for myocardial viability in one. The number of patients and vessels recommended for revascularisation per operator is shown in Table 4.8. After angiographic assessment, all cardiologists agreed on the patient-level management plan in two cases. Seven out of eight agreed in two cases, six out of eight in four cases, five out of eight in two cases, four out of eight in one case and

three out of eight in one case. A detailed breakdown by patient is shown in. At Cohen's kappa analysis, there was minimal agreement between the cardiologists' management plans (k=0.30, 95% CI 0.21-0.39, P<0.001). In four cases in which PCI was selected, the target vessel(s) differed between cardiologist. After angiographic assessment, an average of 1.0 stent was recommended per patient, with significant variation between operators (range; 0.6 to 1.4, P=0.03). Average total stent length per patient was 21.7mm (±12.9) (range; 12.7mm to 30.6mm, P=0.12) (Table 4.9).

Table 4.8: No. of patients and vessels where revascularisation was recommended by each cardiologist based upon angiographic assessment and vFFR assessment

	Angiographic assessment		vFFR assessment	
	No. of patients	No. of vessels	No. of patients	No. of vessels
Cardiologist A	4	4	4	4
Cardiologist B	7	9	9	12
Cardiologist C	7	7	7	7
Cardiologist D	5	7	7	9
Cardiologist E	4	4	8	9
Cardiologist F	6	6	6	6
Cardiologist G	3	3	7	9
Cardiologist H	5	5	5	5

After vFFR assessment, PCI was recommended in a median of seven patients (range; four to nine) and eight vessels (range; four to 12). OMT was recommended in a median of three patients (range; zero to five) and 'more information required' in a median of three patients (range; one to six). Of the 23 times, 'more information' was requested, this was pressure wire assessment in 18 cases, better angiographic images in one case, a CMR to assess for viability in one case and OCT imaging in three cases to determine the presence of acute thrombus. All cardiologists agreed on the patient-level management plan in two cases, seven out of eight in three cases, six out of eight in three cases, five out of eight in three cases and four out of eight in one case. There was minimal agreement between the cardiologist's

management plans (k=0.39, 95% CI 0.31-0.47, P<0.001). This was slightly increased compared to the agreement between the angiography derived plans (k= 0.30, 95% CI 0.21-0.39). The percentage of cases in which patient-level management changed based upon vFFR, ranged from 8% to 50% (average of 33%). Patient-level treatment recommendations for all cases are summarised in Figure 4.6. In five cases, where PCI was selected by more than one cardiologist, the target vessel (s) varied between the operators. After vFFR, an average of 0.9 (±0.7) stents was recommended per patient with significant variation between cardiologists (range; 0.4 to 1.7, P=0.008). Average total stent length per patient was 21.9mm (±17.6) with significant variation between cardiologists (range; 8.8mm to 40.6mm, P=0.02) (Table 4.9).

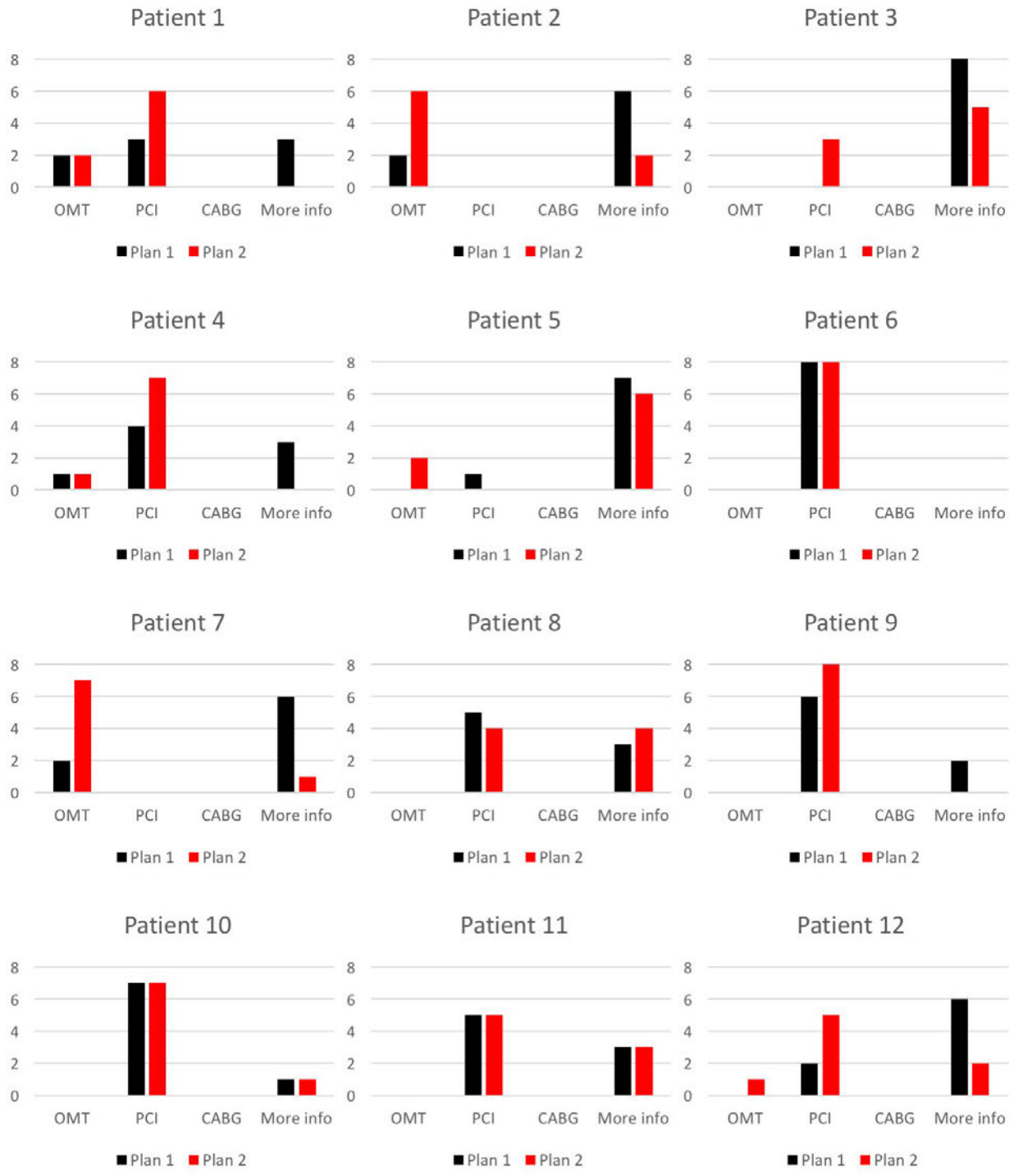


Figure 4.6: A breakdown of management plans is shown for all 12 cases

For each case, angiography-based plans are shown in black and vFFR based plans are shown in red. There was limited agreement between plans based upon angiography (k= 0.30, 95% CI 0.21-0.39, P<0.001) with only slight improvement based upon vFFR (k=0.39, 95% CI 0.31-0.47, P<0.001).

Table 4.9: Mean number of stents and total length of stent recommended per patient by each cardiologist after angiographic assessment, vFFR assessment and VCI assessment

	No. of stents per patient				Total length of stent per patient (mm)			
	Angio	**vFFR**	**VCI**	**P value**	**Angio**	**vFFR**	**VCI**	**P value**
Cardiologist A	0.8 (±0.4)	0.8 (±0.6)	0.8 (±0.6)	1.0	19.2 (±10.4)	21.5 (±15.7)	21.1 (±15.7)	0.95
Cardiologist B	0.9 (±0.4)	0.7 (±0.5)	0.7 (±0.5)	0.67	27.0 (±14.0)	19.6 (±16.3)	19.1 (±15.8)	0.51
Cardiologist C	1.4 (±0.6)	1.0 (±0.7)	0.9 (±0.6)	0.36	30.6 (±15.2)	24.6 (±17.1)	20.9 (±16.2)	0.71
Cardiologist D	0.6 (±0.5)	0.4 (±0.5)	0.4 (±0.5)	0.87	12.7 (±13.0)	8.8 (±10.7)	8.8 (±10.7)	0.74
Cardiologist E	1.4 (±0.8)	1.7 (±0.9)	1.6 (±0.8)	0.85	27.3 (±12.6)	40.6 (±22.2)	39.2 (±22.5)	0.39
Cardiologist F	0.8 (±0.5)	0.7 (±0.5)	0.7 (±0.5)	0.92	15.4 (±9.8)	15.9 (±10.4)	13.9 (±10.4)	0.91
Cardiologist G	1.0 (±0.0)	1.0 (±0.7)	1.1 (±0.6)	0.91	22.3 (±10.2)	24.4 (±22.6)	31.9 (±20.5)	0.91
Cardiologist H	1.0 (±0.0)	0.8 (±0.4)	0.9 (±0.4)	0.67	23.2 (±8.7)	22.7 (±13.3)	21.3 (±11.6)	0.96
Average	1.0 (±0.6)	0.9 (±0.7)	0.9 (±0.7)	0.74	21.7 (±12.9)	21.9 (±17.6)	21.0 (±17.2)	0.95
P value	0.03	0.008	0.005		0.12	0.02	0.004	

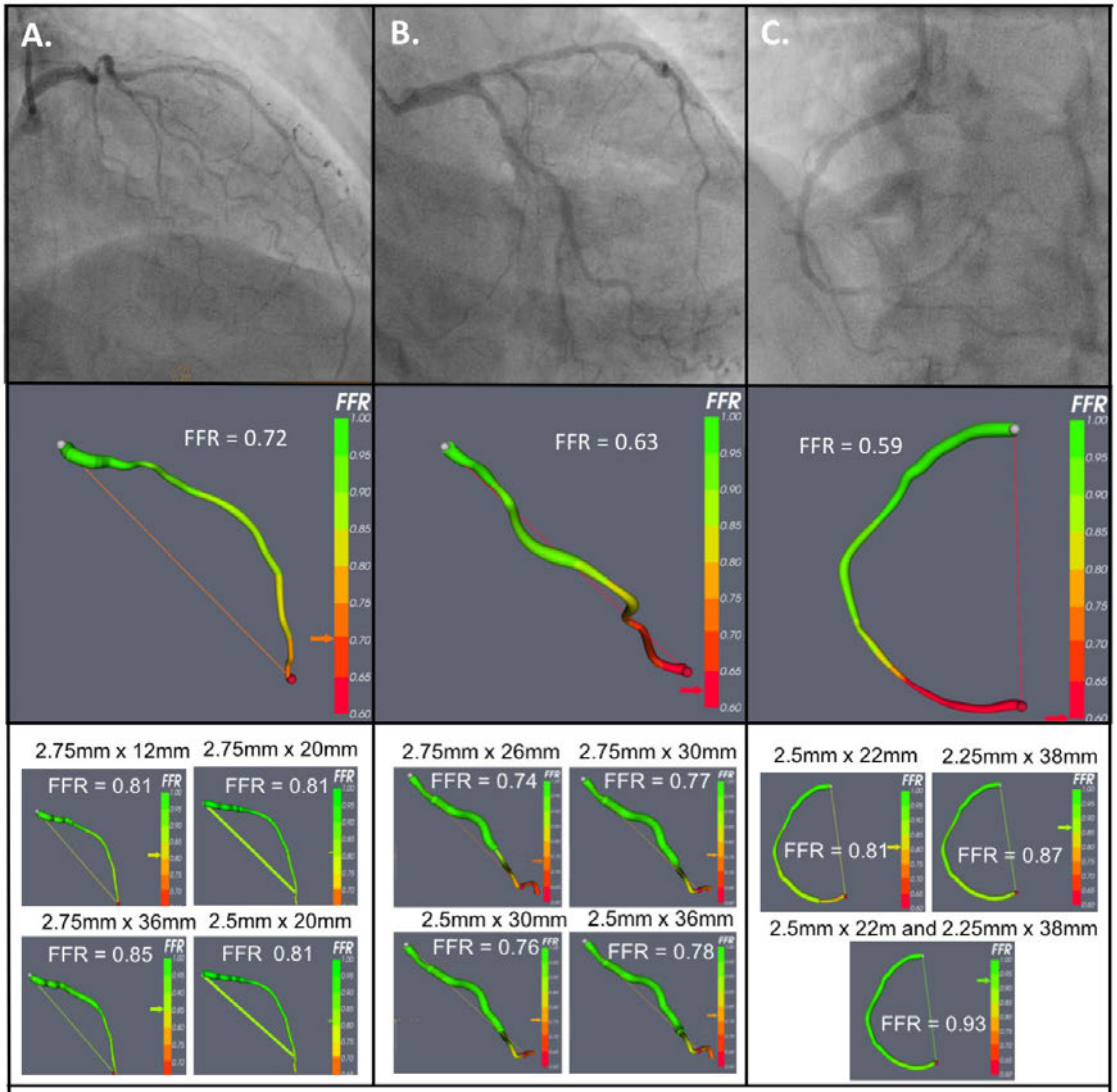
Values = mean (±SD). vFFR = Virtual Fractional Flow Reserve, VCI = Virtual Coronary Intervention.

Combining all eight cardiologist's responses, on 36 (38%) occasions, after reviewing vFFR results, the chosen management plan contradicted the vFFR result. Per cardiologist this varied from 25% to 75% of cases. On 19 occasions, this was where the vFFR was positive (<0.8) but PCI was not recommended for other clinical or technical reasons including the presence of diffuse disease (11) and previous imaging demonstrating non-viable myocardium (7). On six occasions, the vFFR was positive but near the borderline with a less convincing clinical history. Therefore, the cardiologist wished to confirm the presence of ischaemia with an invasive pressure wire before proceeding to PCI. On six occasions, the vFFR was negative but near the borderline. Therefore, the cardiologist requested an invasive pressure wire as he wanted to ensure it was non-significant before deferring PCI. On four occasions, the vFFR was negative but PCI was recommended on the basis that it was an acute lesion in the setting of a NSTEMI.

After VCI results were revealed, PCI was recommended in a median of seven patients (range; four to 10) and eight vessels (range; four to 13). OMT was recommended in a median of three patients (range; zero to five) and 'more information required' in a median of three patients (range; one to six). All cardiologists agreed on the patient-level management plan in two cases, seven out of eight in three cases, six out of eight in three cases, five out of eight in three cases and four out of eight in one case. The patient-level management plan was further changed (compared to the plan made after reviewing the vFFR result) on just one occasion. This was a case in which, after vFFR, the cardiologist had still requested an invasive pressure wire as it was a borderline result. However, VCI showed an excellent result with minimal stenting therefore this was enough to convince him to proceed with PCI without the need for an invasive pressure wire. After VCI, an average of 0.9 (±0.7) stents was recommended per patient with significant variation between operators (range; 0.4 to 1.6, P=0.005). The average total stent length per patient was 21.0mm (±17.2) with significant variation between cardiologists (range; 8.8mm to 31.9mm, P=0.004) (Table 4.9).

4.3.3.8 Stent sizing

After baseline vFFR results were made available, the stent size recommendation changed in an average of 17% of cases (range; 0% – 64%). In 62% of cases this was an increase in stent length, in 8% a decrease in stent length, in 15% an increase in stent diameter and in 15% a decrease in stent diameter. After the VCI results were made available, stent size recommendation changed, on average, in a further 16% of cases (range; 0-33%). In 20% this was an increase in stent length, in 60% a decrease in stent length and in 20% a decrease in stent diameter. Stent size recommendation changed, in length or width, either with vFFR or VCI, in an average of 29% of cases (range; 0% to 69%). Stent sizing varied significantly between cardiologists. An example case is shown in Figure 4.7.



	Angiographic		vFFR		VCI	
Cardiologist	Plan	PCI details	Plan	PCI details	Plan	PCI details
A	OMT	-	OMT	-	OMT	-
B	PCI RCA	2.25 x 28 mm	PCI RCA and LCX	RCA: 2.25 x 32mm, 2.75 x 32 mm LCX: 2.5 x 28mm	PCI RCA and LCX	RCA: 2.25 x 32mm, 2.75 x 32 mm LCX: 2.5 x 28mm
C	PCI RCA	3.0 x 48mm	PCI RCA	3.0 x 48mm	PCI RCA	3.0 x 48mm
D	PCI RCA and PW LCX	2.5mm x 30mm	PCI RCA	2.5 x 38mm	PCI RCA	2.5 x 38mm
E	PW LAD, if +ve surgical referral	-	PCI RCA	2.75 x 30mm	PCI RCA	2.75 x 30mm
F	OMT	-	OMT	-	OMT	-
G	PW LAD, if +ve surgical referral	-	PCI LCX	2.5 x 23mm	PCI LCX	2.5 x 26mm
H	PCI RCA	3.0 x 38mm	PCI RCA	3.0 x 38mm	PCI RCA	3.0 x 38mm

Figure 4.7: Illustrative case example

A 78 yr old female with a background of T2DM and hypertension attended A&E with severe chest tightness, lasting for 90 minutes. Her troponin had raised from 12 to 140. There were no localising features on ECG. Baseline angiographic images of the LAD, LCX and RCA are shown in top panel A, B and C respectively. vFFR and then VCI results are shown below. The cardiologist's management plans based upon angiographic, vFFR and VCI assessment are shown in the table.

4.3.3.9 Confidence scores

Based upon angiographic assessment, mean confidence scores in patient level management, vessel level management and stent sizing were 8.2 (±1.3), 8.1 (±1.4) and 7.3 (±1.1) respectively. After baseline vFFR results were made available, the confidence level in patient level management increased by 0.5 (±0.9) (P<0.001), vessel level management by 0.6 (±0.9) (P<0.001) and stent sizing by 1.0 (±1.1) (P<0.001). After VCI results were made available, the confidence in patient level management increased by 0.1 (±0.5) (P=0.22), vessel level management remained unchanged (0.0 (±0.6) (P=1.0)) and stent sizing increased by 0.6 (±0.8) (P<0.001) further beyond that with vFFR alone.

4.3.4 Discussion

In this study, I have analysed the potential of both vFFR and VCI to alter patient management in a virtual study. When 50 'real world' patient cases were reviewed, knowledge of the baseline physiology (vFFR) led to a change in patient management in an average of 27% of cases. Moreover, VCI, along with the stent sizing feature, led to a change in recommended stent size in an average of 48% of cases. Interestingly, when multiple cardiologists reviewed the same cases, the number of cases in which management was changed based upon the physiology varied significantly between cardiologists (range = 8-50%) and there were significant discrepancies between the management plans. Both vFFR and VCI significantly improved the cardiologist's confidence in their management plans.

4.3.4.1 Impact of vFFR upon patient management

When baseline vFFR results were revealed, a change in the proposed management plan occurred in an average of 27% of cases (20% for cardiologist A and 34% for cardiologist B.). Interestingly, when multiple cardiologists reviewed the subset of 12 cases, this varied from 0-50% (mean= 33%). The effect of coronary physiology upon decision making has previously been examined in the RIPCORD and FFR_{CT} RIPCORD trials (Curzen et al., 2014, Curzen et al., 2016). In RIPCORD, 200 patients with

symptoms suggestive of stable CAD underwent coronary angiography for clinical indications. Following the coronary angiogram, the cardiologist was asked to state the management plan consistent with their routine clinical practice. As in the current study, the options were OMT, PCI, CABG or 'more information required'. The cardiologist was also asked to specify which vessel(s) were recommended for revascularisation. All vessels were then assessed with an invasive pressure wire. The FFR data were then disclosed to the cardiologist who was invited to consider and document a revised management plan using the same options as above. The authors reported a change in the patient-specific management plan in 26% of cases, a similar level observed in the current study. Additionally, in 32% of cases, the number of vessels considered as significant changed after FFR data were revealed. The current study differed from RIPCORD in a number of ways. First, I included patients with ACS as well as stable angina. In fact, two thirds of the patients included had presented with NSTEMI. This proportion is akin to the typical case mix seen in the cardiac catheter laboratory in the UK (BCIS, 2016). Second, this was a virtual study using retrospective cases that had already received their treatment. Third, only patients that had initially been selected for PCI were included. This was because, as well as examining the impact of vFFR, I also wanted to examine the impact of VCI on treatment planning. Finally, RIPCORD is based upon invasive FFR, the gold standard method for the physiological assessment of lesion significance. Our model of vFFR, although able to predict invasive FFR with a high degree of accuracy, is not the gold standard and therefore its interpretation by clinicians, and therefore ability to alter management, may be expected to differ from that of FFR itself.

In a similar study design to RIPCORD, the FFR_{CT} RIPCORD study recruited 200 patients undergoing CTCA for the assessment of stable CAD. Three cardiologists assessed the CTCA and agreed a management plan by consensus. FFR_{CT} was then revealed and a second management plan was made. The authors reported a change in management in 36% of cases. The biggest change observed was from patients initially selected for 'more information required' (an invasive pressure wire) that were then re-

stratified to either OMT (28) or PCI (10). This constituted 53% of the cases where a change in management was observed. I similarly observed this to be the biggest change; in our study in 70% of the cases where a change in management was observed, this was removal of the need for a pressure wire. In our study, an invasive pressure wire was initially selected in 30% of cases. This is much higher than the observed 5-10% reported in the 'real world' (Dattilo et al., 2012). In the FFR_{CT} RIPCORD study, this figure was 19%. Although operators were encouraged to state what they felt they would actually do, as this was a virtual study and the operators did not have to carry out their management plans, there was no way to control for such a potential bias. Moreover, this study was carried out in a tertiary cardiology centre where perhaps invasive pressure wire use is higher than the national average.

The majority of the early FFR trials focused on its use in patients with stable angina. However, acute cases contribute to approximately two thirds of the typical case mix in a UK cardiac catheter laboratory (BCIS, 2016). These patients had initially been excluded from many of the earlier trials due to concerns over the applicability of FFR in this setting, due to FFRs reliance on minimising microvascular resistance. The FAMOUS-NSTEMI trial specifically assessed the role of FFR in NSTEMI patients (Layland et al., 2015). In this study, patients who attended the cardiac catheter laboratory with NSTEMI were randomised to angiography or FFR guided management. FFR was measured in both groups, but only disclosed to the operator in the FFR guided group. The proportion of patients treated with medical therapy was significantly higher in the FFR group (22.7% versus 13.2%). Furthermore, in the FFR group, FFR disclosure led to a change in the proposed treatment plan in 21.6% of cases. In our study, this was 22% in the NSTEMI subgroup. There were no significant differences in MACE at 12 month follow up, however the rate of revascularisation was lower in the FFR group (21.0% versus 13.2%, P=0.05). The design of this study was such that in the FFR group, the FFR was always followed, i.e. all vessels with a FFR $\leq$0.80 were treated and all vessels with a FFR >0.80 were not. Conversely, in our study, the operator had the option to choose to ignore the vFFR and select an alternative management plan. In the

acute setting, there is a trade-off between physiology and biology. It is possible that plaque with rupture prone biology may be non-flow limiting (FFR >0.80). Whether it is safe to leave these lesions uncovered is unclear. In our study, the operators frequently chose to proceed to revascularisation in these cases.

4.3.4.2 Inter-observer variability

Unlike RIPCORD and FFR_{CT} RIPCORD, I also sought to examine the variation in decision making between operators. When the same 12 patient cases were reviewed by eight cardiologists independently, the percentage of cases in which patient-level management was changed based upon vFFR varied from 8-50% (mean = 33%). I also observed significant variation between the management plans chosen with only a slight increase in agreement in the plans made following vFFR disclosure (Figure 4.6). Inter-observer variability in assessing coronary angiograms has been reported previously. A number of studies have demonstrated that differences between operator's assessments of the severity of disease occurs in 15 - 45% of cases (Detre et al., 1975, Zir et al., 1976, Herrman et al., 1996, DeRouen et al., 1977, Fisher et al., 1982). Most of these studies focused on the assessment of lesion severity by percentage stenosis estimation. However, the impact of these discrepancies upon treatment decisions in the 'real world' has been less well examined. I found that when management plans were made based upon coronary angiographic assessment, the kappa value was 0.30, indicating minimal agreement between operators. Only in two out of twelve cases did all of the cardiologists agree on the management plan. Even with the introduction of a more objective method of assessment (vFFR), there was only a slight improvement in agreement between the cardiologist's management plans (kappa=0.39) suggesting there is still considerable variation in the interpretation of these results and other factors in the decision-making process. In Figure 4.7, an example case is demonstrated where significant discrepancies between the cardiologist's chosen management plans was observed. In this case, in the setting of a NSTEMI, baseline physiology was positive (vFFR<0.80) in all three vessels (LAD, LCX and RCA). However, some cardiologists felt that the disease was not amenable to PCI (as the disease was predominantly distal) so

recommended OMT. Others felt that one or another vessel was more likely to be the culprit so proceeded with single vessel PCI. Even after VCI had revealed that only a limited physiological result was achievable with PCI to the LAD and LCX arteries, some cardiologists still chose to proceed to PCI in these vessels. The predominant reason for this was that they were keen to treat what they felt was likely to be the culprit lesion and therefore felt physiology was less relevant. Even where cardiologists agreed on the vessel for PCI, the chosen stent sizes varied significantly between cardiologists. This case highlights the importance of other clinical factors in decision making, but also highlights the subjectivity that remains in these decisions even when objective measures such as vFFR are available. In the current study, another factor that varied between cardiologists was the likelihood of that particular cardiologist to believe and trust the vFFR especially when it went against their angiographic assessment. Despite several studies demonstrating disagreement between visual and physiological assessment, many operators often still believe angiography to be superior. The ERIS study analysed the use of physiological assessment across 76 Italian cardiac catheter laboratories (Tebaldi et al., 2018). The authors reported that invasive physiology was used in accordance to national guidelines in only half of cases and a large proportion of patients with a class one indication for physiological assessment did not receive it. Interestingly, the predominant reason for not performing physiological assessment was that the operator was confident in the management plan based upon the history and angiography alone. In only a small number of cases were other factors such as procedural time, the requirement for adenosine or other technical factors given as reasons for avoiding pressure wire assessment. Interestingly, I found the cardiologist's initial confidence in their management plan was unrelated to both the likelihood of their plan to accord with physiology or the likelihood they would then change their plan. This suggests that being confident in angiographic assessment is not a good reason to refrain from physiological assesment.

In the current study, cardiologists were presented with measures of coronary physiology whether they would have requested it or not. Yet in a considerable number of cases, they disregarded the result, because they were more confident in their angiographic assessment than they were of the new technology. Combining all responses, I found that in an average of 38% of cases, after vFFR was made available, the management plan still contradicted what would be recommended by vFFR alone. The most common reason for this (33%) was the presence of other clinical or technical factors that precluded PCI, such as diffuse disease, distal disease, or non-invasive imaging confirming non-viability. However, in 22% of these cases, the operator stated that they were more convinced by their angiographic assesment than the vFFR.

4.3.4.3 Impact of VCI on treatment planning

In this study, as well as examining the effect of physiological assessment with vFFR upon decision making, I also explored the ability of the novel VCI tool to influence treatment planning decisions. Although disclosure of the VCI results had little impact on patient-level management, above and beyond that achieved with vFFR alone, the procedural details (size of stent) changed in 33% of cases based upon VCI alone, and 48% when combined with the stent sizing feature. An example is shown in Figure 4.8, in which VCI allowed the cardiologist to adjust their strategy. This was a case in which there were two sequential lesions in the LCX artery. The cardiologist initially chose to insert two stents covering both lesions. However, VCI revealed minimal benefit from stenting the proximal lesion which led the cardiologist to refine their strategy. VCI is intended to be a treatment planning tool, so its main use is in cases in which the operator has already decided that PCI is warranted, based upon either angiographic or physiological assessment. VCI then allows the operator to plan the procedure accurately. In this study, I have demonstrated, for the first time, that this approach has the potential to significantly impact treatment decisions. This would not only allow patients to achieve maximal physiological benefit from PCI which could translate to improved outcomes, but could also reduce the risks of stent over- and

under-sizing and complications associated with excessive stenting. This would need to be further explored in a large prospective study.

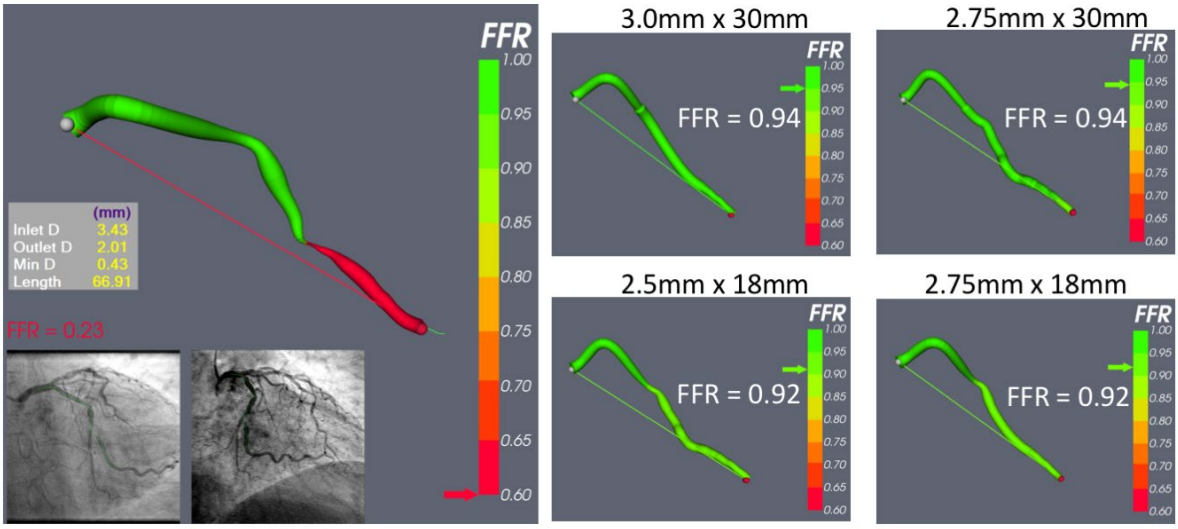


Figure 4.8: Using VCI to alter treatment recommendations

A 69 year old male with hypertension, hyperlipidaemia and a positive family history attended A&E with chest pain occurring at rest. His troponin was significantly elevated. Coronary angiography revealed a tight lesion in the OM branch. vFFR was strongly positive (left image). Based upon angiography and vFFR assessment, Cardiologist B recommended PCI to the OM with a 3.0mm x 18mm stent proximally and a second 2.75mm x 22mm stent distally. VCI results revealed a good physiological result with a short stent covering the distal lesion, with minimal benefit from a longer stent covering the proximal lesion (right image). After reviewing this, cardiologist B changed his recommendation to a single 2.75mm x 18mm stent covering the distal OM lesion.

4.3.4.4 Confidence in management

I observed a consistent increase in the cardiologist's confidence in the management plan after both vFFR and VCI results were made available. This was irrespective of whether the physiology changed the plan. Interestingly, there was no relationship between the initial level of confidence and the likelihood to alter the patient-level management plan, suggesting that the operator's perception of the accuracy of their angiographic assessment is not reliable. Conversely, confidence in the stent size was related to the likelihood to change the stent size based upon VCI. This suggests that although there is still perhaps a

lack of awareness of a mismatch between angiographic and physiological assessment, there is better awareness of the limitations of stent sizing. Moreover, if the cardiologist was not happy with the initial stent choice, they would be more likely to seek out other sources (stent sizing and VCI) to guide them.

4.3.5 Limitations

First, this was a retrospective analysis of prospectively collected data. Second, as the focus was on VCI based treatment planning, only patients undergoing PCI were studied. Therefore, I could not assess the potential impact upon patients who were initially declined PCI, but who may have warranted PCI. Third, the sample size was modest and did not allow for reliable comparison between subgroups. Fourth, stent sizing decisions were made without the aid of a balloon, or other cues, which would normally be available to assist the operator with sizing during the invasive procedure. As this was a virtual study, this was not possible. Fifth, because invasive pressure wire data were not available, no comparison between vFFR and FFR could be made. Sixth, vFFR was computed using generic boundary conditions, although previous work has demonstrated acceptable accuracy with this method. All cardiologists were advised of the accuracy of the tools before they began their assessment. Seventh, in a virtual study with modest numbers I cannot report on complications or outcomes. Eighth, cardiologists were encouraged to state their treatment recommendations based upon their real-life practice; but as this was a virtual study, it was not possible to control for potential bias.

4.3.6 Conclusion

Disclosure of vFFR led to a change in patient management in an average of 27% of cases compared to angiography based assessment. Additionally, combining our novel stent sizing tool with VCI resulted in a change to stent sizing recommendations in 48% of cases. However, the likelihood to alter management, as well as the management plan itself, varied significantly between cardiologists.

Chapter 5 – Conclusions and further work

5.1 Summary of current stage of work

In this thesis, I have described the development and validation of a novel VCI tool that can be applied to coronary angiography to predict the physiological response to interventional PCI strategies. I have then demonstrated its potential utility as a treatment planning tool in the 'real world'. In chapter two, I demonstrated the ability of the tool to predict the response to stenting (post-procedural FFR) within ±0.01 using personalised boundary conditions or ±0.02 with generic (averaged) boundary conditions. The former requires the passage of an invasive pressure wire to obtain the distal boundary condition whereas the latter can be performed in the absence of any invasive instrumentation. This is the first time that VCI based upon the coronary angiogram has been described. An angiography-based tool permits treatment planning to occur on the same images on which the PCI procedure will be based, potentially allowing for better translation than CTCA derived models. With increased focus on the prognostic value of the post procedural FFR value, this tool is even more relevant, because not only can it predict this value, but it can also allow the operator to adjust the procedure to achieve the best possible result before committing to intervention in the patient. It is frequently observed in clinical practice that post PCI physiology seldom returns to 1.0 (physiological normality), particularly in the context of diffuse disease. However, until now, it was not possible to determine if this was due to a poorly optimised procedure or if that was the maximal achievable FFR for that vessel. In chapter three, I explored this concept further by using VCI to predict the maximal achievable FFR of 100 vessels and comparing this to the post PCI FFR values. The mean FFR_{max} was 0.92. This was on average 0.04 higher than the corresponding post PCI FFR value. Using VCI to predict the FFR_{max} allows us to calculate a personalised assessment of what PCI can achieve, allowing better informed decision making regarding whether to, and how to, treat coronary artery lesions. Knowing the FFR_{max} can also prevent operators from attempting to improve

what they consider to be a suboptimal physiological PCI result with further intervention that may be futile. Conversely, in cases where improvement can be achieved, this can specifically be targeted. It is important that FFR_{max} is interpreted in line with its limitations. As discussed in Chapter 3, there is an element of subjectivity in its calculation and it cannot be fully validated as there is no comparable *in vivo* measure. Its purpose is to provide the operator with a guide as to the extent the vessel based FFR could be improved with PCI, if the perfect PCI result was achieved. Utilising the VCI tool to examine and compare the post treatment FFR values of specific PCI strategies is likely to be more clinically relevant and as such was the focus of chapter four. In chapter four, I sought to determine the potential impact of an all in one vFFR and VCI diagnosis and treatment planning approach on 'real world' stenting by performing a retrospective virtual study. Adopting a vFFR and VCI guided approach led to a significant reduction in the total number and length of stent recommended per vessel compared to the actual procedure. This finding was consistent whether the procedure was planned to achieve the best possible FFR (FFR_{max}) or the optimal strategy (the minimum amount of stenting required to achieve a post PCI FFR of >0.90). In 41% of the vessels studied, the baseline vFFR was >0.80 suggesting PCI could have been avoided. However, as vFFR and VCI are only designed to assist decision making alongside the clinical history and operator experience, I also wanted to determine the potential effect of our tool on 'real world' treatment decisions. In the second part of chapter four, 50 patient cases were shown to two interventional cardiologists independently. There were asked to state their management plan based upon conventional methods (the clinical history and coronary angiogram) and then again after reviewing the vFFR and VCI results. Knowledge of vFFR led to a change in management in an average of 27% of cases. VCI and the novel stent sizing tool led to a change in recommended stent size in an average of 48% of cases. I also examined the inter-operator variability in a small subset of these patients. Interestingly, not only was there significant variation in the plans between operators but also in the likelihood to change management based upon vFFR and VCI. In summary, throughout this thesis I have developed and validated a novel VCI tool and demonstrated its potential to impact treatment in the

'real world'. However, there are key areas of future work to be completed as well as significant challenges to be overcome, before this tool could fully enter the clinical domain.

5.2 Further work and challenges

5.2.1 Improved accuracy

One of the key determinants of the accuracy of this model is the accuracy of the boundary conditions employed in its set up. In this thesis, I describe two methods of vFFR computation with different boundary condition settings. The first uses data from an invasive pressure wire to calculate a personalised value of distal microvascular resistance. This value is then applied at the distal boundary. This method produces highly accurate results but can only be used in patients that have already had invasive FFR assessment. For baseline vFFR computation, this is illogical. With the addition of VCI, there is still a potential role of using the model in these circumstances as it provides information above and beyond what the pressure wire can achieve (the predicted response to invasive strategies). However, in reality it is likely that the majority of patients will not have invasive pressure wire measurements. In these patients, we currently use generic boundary conditions. For this method, a generic value of microvascular resistance (identified as the average value from a previously studied cohort) is applied to the distal boundary in a 'one size fits all' approach. This approach produces a reasonable result, but is significantly less accurate than when personalised boundary conditions are used. An ideal solution would be a method that is capable of personalising the resistance value without the need for invasive instrumentation. It seems logical that a number of patient and clinical factors may be predictive of microvascular resistance. Ongoing work is looking into this using a database of patients with extensive clinical data to determine the ability to predict microvascular resistance using statistical and machine learning methods and personalise this without the need for invasive instrumentation.

5.2.2 Practical improvements to the VCI tool

A second area of further work will be dedicated to making practical improvements to the VCI tool itself. The current VCI tool has been developed within MATLAB® (Mathworks LTD, Massachusetts, US) by our in-house software developers. It has a simple GUI and is relatively user friendly. However, there are a few important adaptations that would be desired before it is deployed in the clinical realm. First, it would be beneficial to develop a stent library. Currently, to select the size of virtual stent to insert, the operator manually enters a width and selects two points on the artery to determine the length (Figure 5.1). For clinical deployment, it would be preferable to select the position on the artery and then to select a stent from the stent library to insert. The available options can be created to match commonly sized stents that are available commercially. Second, the current interface for VCI does not include the angiographic images. The stent is inserted into the reconstructed artery. It would be beneficial, and could greatly assist with stent positioning, if the angiogram was also displayed and marked to match the position selected on the reconstruction (Figure 5.1). Third, it would be beneficial to be able to model a tapering stent. Currently, the tool only models a cylindrical shape with the proximal and distal radii being equal. In clinical practice, it is common to post dilate the proximal stent to a greater size than the distal stent. We cannot currently capture this in our model. Finally, another current limitation of the tool is the inability to model bifurcations accurately. This is challenging because of the anatomical detail required to accurately reconstruct a coronary artery bifurcation. Others have achieved this by combining angiography with either OCT or IVUS and this could be avenue for future work. However, currently our model is not ideal for planning bifurcation stenting.

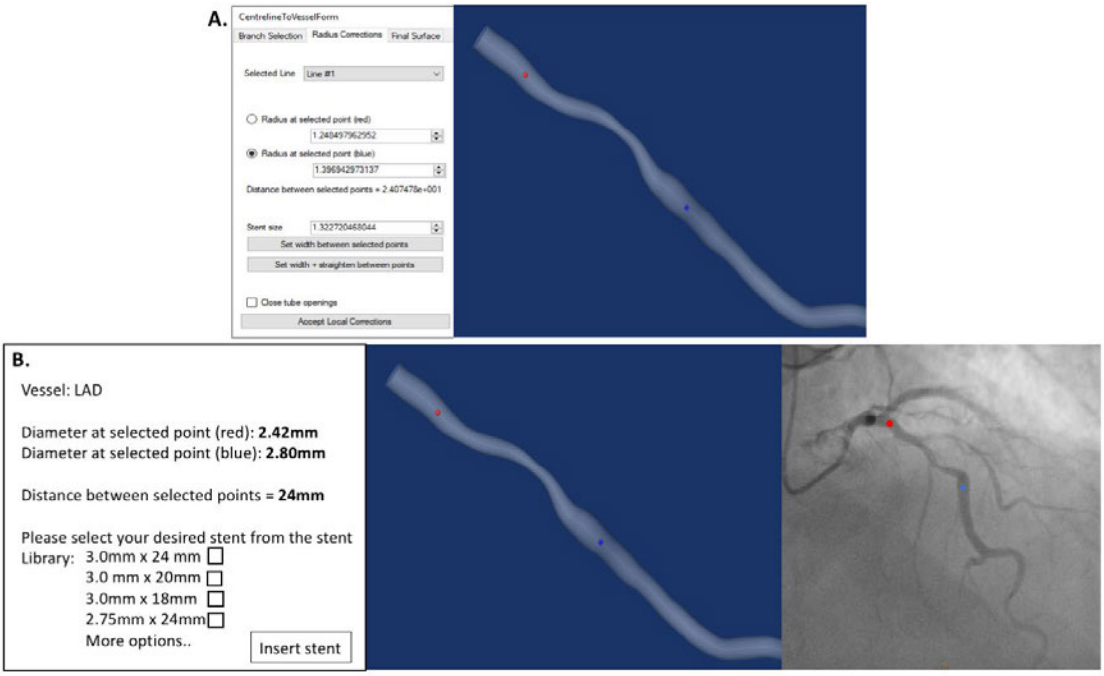


Figure 5.1: VCI tool improvements

The current VCI tool is shown in panel A. The tool reports the radii at the two selected points (red and blue dots). The length between the dots is also shown. The operator must then enter the desired radius of the stent to be inserted into the box labelled stent size. The box 'set width between selected points' is then selected to insert the virtual stent. The length can not be chosen but is matched to the exact distance between the two chosen points. In Panel B, the proposed improvements are shown. The vessel reconstruction is shown in the same way and the operator can select the proximal and distal points (red and blue dots). The angiogram is displayed alongside and the corresponding points are shown. The tool informs the operator of the diameter at each point and the distance between the two. The operator can then select an appropriate stent size from the stent library.

5.2.3 Improved processing times

Currently, to produce a vFFR or simulated VCI result from segmentation to results takes approximately 10 minutes per case. This is a significant improvement from early vFFR studies in which computational time was >24 hours. However, if an operator wishes to trial a number of VCI strategies, it becomes unrealistic to perform with the patient on the table. It would be desirable to have instantaneous results, especially with VCI. Our current methodology uses ANSYS® CFX (ANSYS Inc, Pennsylvania, US) simulation software. More recently, a newer package; ANSYS® Discovery Live has become available. This technology allows CFD solutions to be obtained instantaneously. This could permit a live read out of predicted physiology as the virtual stent is inserted and then repositioned. Current work is focused on

implementing this into our current workflow and assessing the accuracy. It will be important to determine whether the increased speed is associated with a reduction in accuracy below a clinically acceptable level. Another alternative option is to introduce a reduced order model (ROM). ROMs allow for simplification of larger more complex mathematical models to reduce computer burden. The complexity is reduced to give an approximation of the original model. Our group has some experience in this area and this will continue to be a focus of further work. Again, it will be crucially important to examine the impact on accuracy as there is often a trade-off between speed and accuracy.

5.2.4 Clinical data required

As well as the improvements to the model described above, further clinical data are required and, perhaps most importantly, this will include outcome data. It will be important to demonstrate improved clinical outcomes associated with the use of a vFFR and VCI guided approach. This will require a large prospective trial comparing our method to an angiography-guided approach. The work completed in this thesis provides important pilot data that will support this. The aim would be to determine if the beneficial effects of FFR (as demonstrated in the FAME trial) can be replicated or even improved upon with vFFR and VCI. It is important to note that vFFR and VCI does not necessarily have to be 'as good' as invasive FFR. The important comparison is between vFFR and VCI and angiography alone as this is what most patients have in reality. Invasive FFR could still be utilised in patients who have borderline or inconclusive results with vFFR and VCI. A cost-effectiveness analysis would also be of interest. Extrapolating from the results of FAME, and the results of the virtual study presented in this thesis, one may predict that using vFFR and VCI would result in a reduction in stent use. Moreover, software is unlikely to be costly and will be significantly cheaper than the equipment required for invasive pressure wire assessment. The above data will be a crucial step towards commercialisation and regulatory approval. There remain other research areas that this work leads on to.

5.2.5 Determining the target FFR

The main benefit of VCI is the ability to predict, before committing to intervention, the post-procedural FFR value and thus prospectively optimise the procedure based upon this. However, it is not entirely clear what post treatment FFR value we should be trying to achieve. A number of small studies have suggested that achieving a post treatment FFR of >0.90 is associated with improved clinical outcomes (Rimac et al., 2017). However, there are limited data on whether there is a specific value that correlates with an improvement in patient symptoms, or whether it is the magnitude in improvement in FFR that is more important than the overall post PCI value. Indeed, when performing PCI in patients with stable angina, the primary goal is to improve symptoms, therefore, this is an important question. It is conceivable that this 'target FFR' varies from patient to patient as there is significant heterogeneity in patients' anatomical, physiological and lifestyle factors. A patient who is minimally active may not require the same FFR as an athlete to be symptom free. With an increase in the use of activity monitors in healthcare, this could be an interesting avenue for future research.

5.2.6 Moving beyond FFR

The focus of this thesis has been on describing the ability of VCI to predict the physiological response to stenting in terms of vFFR. It would, however, be possible to use the same technology allied to other physiological indices such as absolute coronary flow. FFR is currently the gold standard physiological measure used in clinical practice, as it is supported by the most outcome data. However, it is coronary flow that determines ischaemia not FFR. Due to limitations associated with the invasive measurement of coronary flow, FFR has continued to be used as a surrogate. With computational modelling technologies, absolute flow can be predicted with a reasonable degree of accuracy, and this has been achieved by our group (Morris et al., 2019). Being able to predict the response to PCI in terms of absolute coronary flow may be more relevant than FFR. However, significant further work will be required to examine this in more detail. Additionally, although FFR or even flow computation can

inform on the local conditions in that vessel, it cannot currently inform how this contributes to the total myocardial ischaemic burden. The total ischaemic burden is related to the amount of disease in all of the epicardial arteries and the microvasculature. How each lesion contributes is likely to be related to the position of the lesion in the coronary tree and the territory supplied by that individual vessel. A lesion in a larger artery supplying a bigger area of myocardium is likely to have a bigger contribution to global ischaemic burden than a lesion in an artery supplying only a small amount of myocardium. Currently there is no accurate method to determine how one particular lesion will contribute to total ischaemia; the primary factor in determining the patient's symptoms and prognosis. Equally, there is no way to assess the degree to which stenting of one lesion, in the setting of multi-vessel disease, will relieve ischaemia. This is especially relevant as we are treating an increasing number of patients with complex, multi-vessel disease. CMR imaging can be used to assess rest and stress perfusion and is a highly sensitive and specific test for myocardial ischaemia. Combining CMR imaging with computational modelling presents a unique opportunity to determine how individual lesions can contribute to total ischaemic burden. This could allow more effective treatment planning, particularly in patients with multi-vessel disease.

5.3 The future of VCI

As well as the further work discussed, there are a number of challenges to be faced before clinical adoption can be achieved.

5.3.1 Regulatory approval

The first, and perhaps most significant challenge, is achieving regulatory approval. There are significant commercial considerations regarding the accuracy and reliability of validation of such tools. The US FDA is addressing this through a benchmarking initiative that aims to advance the application of CFD technologies within the regulatory context. They have identified "developing computer modelling

technologies" as a regulatory science priority. Furthermore, the American society of mechanical engineering has produced standards for the verification and validation of CFD models. To allow widespread adoption, these or similar need to be extended to Europe.

5.3.2 The human factor

One of the most striking findings of my work was the variability in decision-making observed between operators, even between operators in a single centre. This was probably expected in the study in which I recorded decisions based upon the angiogram; but the introduction of physiology, even though it was 'virtual', might have been expected to introduce a little standardisation. In fact, this was not the case. Possible explanations include a lack of trust in modelling techniques, an over confidence in the operators own angiographic assessment and inherent differences in how individuals make decisions. I found that even after virtual physiology was available, the management plan contradicted the vFFR in 38% of cases. In 22% of these cases, this was because the operator felt more confident in their own angiographic assessment. This varied between operators, with some more likely to alter their management based upon vFFR than others. More work will be required to convince cardiologists that a virtual physiology guided approach is superior to an angiography guided approach. Data from outcome studies and the possible introduction into national guidelines will assist with this. My findings also possibly relate to the complexity of decision making in 'real world' clinical practice that goes above and beyond physiology alone. In 'real world' cases there are many factors to be considered alongside the coronary physiology, such as the patient history, age, frailty, clinical presentation and data from other imaging or laboratory tests. The way in which the operators prioritise these data sources and assimilate the information to reach a decision varies between individuals. Thus, even if increased acceptance can be achieved, there is likely to remain a degree of variation in clinical decision making between operators.

5.4 Final conclusion

In this thesis, I have developed and validated a VCI tool based upon the VIRTUheart^{TM} model of angiography derived vFFR. I have shown that this tool can predict the physiological effect of stenting with a high degree of accuracy. In the latter chapters I have demonstrated the potential ability of this tool to be used in the 'real world'. This can be used to predict the FFR_{max} (the best possible physiological result that can be achieved), define the 'optimal strategy' (the minimal amount of stenting that is required to achieve a target FFR) and to impact clinical decision making. Clinical trials are required to demonstrate the efficacy of this tool in the clinic and the ability to impact patient outcomes.

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XI. Appendix

5.5 Supplemental tables

Supplemental Table 1: Table of all results using both generic and personalised boundary conditions pre-and post-PCI

Case	Vessel	Pre-PCI mFFR	Pre-PCI $vFFR_{gen}$	Pre-PCI $vFFR_{pers}$	Post-PCI mFFR	Post-PCI $vFFR_{gen}$	Post-PCI $vFFR_{pers}$
V001	LAD	0.64	0.62	0.68	0.93	0.93	0.93
V002	RCA	0.44	0.45	0.39	0.98	0.98	0.98
V003	LAD	0.62	0.72	0.64	0.84	0.84	0.84
	LCX	0.67	0.62	0.72	0.93	0.93	0.94
V004	RCA	0.79	0.79	0.83	0.99	0.99	0.97
V005	RCA	0.86	0.86	0.83	0.98	0.96	0.99
V008	LAD	0.80	0.85	0.81	0.91	0.91	0.91
V009	LAD	0.34	0.39	0.34	0.93	0.93	0.93
V010	LAD	0.74	0.78	0.74	0.90	0.93	0.92
	Dx	0.76	0.71	0.76	0.91	0.91	0.91
V011	LAD	0.79	0.79	0.79	0.86	0.86	0.86
	RCA	0.76	0.76	0.76	0.89	0.89	0.89
V012	LAD	0.72	0.77	0.76	0.84	0.86	0.84
V013	LAD	0.74	0.72	0.78	0.94	0.96	0.97
V015	RCA	0.38	0.42	0.38	0.88	0.93	0.90
V019	LAD	0.82	0.85	0.78	0.88	0.91	0.85
V020	LAD	0.75	0.74	0.85	0.90	0.90	0.90
V021	LCX	0.42	0.53	0.42	0.98	0.99	0.97
V023	RCA	0.63	0.57	0.68	0.81	0.86	0.92
V025	LAD	0.56	0.62	0.51	0.85	0.91	-
V026	LAD	0.59	0.67	0.59	0.95	0.95	0.95
V028	LCX	0.44	0.55	0.44	0.88	0.93	0.88
V029	LAD	0.77	0.75	0.77	0.88	0.88	0.91
V030	RCA	0.79	0.79	0.79	0.94	0.91	0.94
V037	LCX	0.75	0.68	0.76	0.89	0.80	0.89
	RCA	0.65	0.65	0.65	0.93	0.93	0.93
V038	LAD	0.83	0.84	0.83	0.88	0.88	0.88
V049	RCA	0.79	0.79	0.79	0.89	0.89	0.92
	OM	0.64	0.45	0.65	0.96	0.92	0.96
V051	LAD	0.75	0.77	0.78	0.82	0.88	0.83
	RCA	0.47	0.56	0.47	0.90	0.92	0.90

V054	LCX	0.38	0.31	0.36	0.97	0.97	0.97
V055	LAD	0.71	0.70	0.76	0.89	0.95	0.91
V056	LAD	0.43	0.54	0.43	0.81	0.91	0.81
V057	LAD	0.70	0.60	0.70	0.84	0.89	0.84
V061	RCA	-	-	0.89	-	0.94	-
V062	LAD	0.72	0.77	0.71	0.86	0.93	0.86
V064	RCA	0.85	0.86	-	1	0.98	-
V065	RCA	0.79	0.75	0.82	0.93	0.94	0.94
V068	LCX	0.45	0.47	0.47	1	0.99	0.99
V069	LAD	0.53	0.70	-	0.91	0.93	0.97
	LAD	-	-	-	0.94	0.94	0.97
V073	RCA	0.57	0.68	0.58	0.92	0.93	0.92
V077	LAD	0.80	0.80	0.80	0.93	0.95	0.93
V078	RCA	0.48	0.49	0.58	0.88	0.88	0.94
V079	RCA	0.78	0.82	0.78	0.97	0.99	0.95
V082	LAD	0.82	0.82	0.88	0.89	0.90	0.88
V083	RCA	0.62	0.55	0.62	0.96	0.94	0.96
V084	LAD	0.68	0.84	0.60	0.95	0.97	0.94
V085	LAD	0.71	0.80	0.73	0.87	0.94	0.87
V087	RCA	0.73	0.68	0.73	0.96	0.95	0.95
V092	LAD	0.65	0.61	0.46	0.78	0.79	0.78
V093	LAD	0.79	0.82	0.79	0.94	0.94	0.94
V099	LAD	0.63	0.73	0.63	0.81	0.81	0.81
V100	LAD	0.55	0.67	0.55	0.87	0.87	0.87
V101	LAD	0.74	0.73	0.77	0.82	0.82	0.82
V103	RCA	0.61	0.65	0.54	0.88	0.92	0.97
V104	RCA	0.68	0.68	0.68	0.85	0.88	0.85
V106	LAD	0.68	0.60	0.68	0.91	0.95	0.98
V114	RCA	0.78	0.70	0.80	0.90	0.90	0.93

Dx = Diagonal; LAD = Left Anterior Descending Artery; LCX = Left Circumflex Artery; OM = Obtuse Marginal; RCA = Right Coronary Artery.

Supplemental Table 2: Comparison of post VCI vFFR with and without stent straightening method

Case no.	Vessel	Post PCI FFR	Post VCI FFR (no straightening)	Post VCI FFR (straightening)	Difference between straightening and no straightening
1	LAD	0.93	0.93	0.97	0.04
2	RCA	0.98	0.98	0.98	0
3	LAD	0.84	0.84	0.84	0
4	LCX	0.93	0.93	0.93	0
5	RCA	0.99	0.99	0.96	-0.03
6	RCA	0.98	0.96	0.96	0
7	LAD	0.91	0.91	0.91	0
8	LAD	0.93	0.93	0.93	0
9	LAD	0.90	0.93	0.93	0
10	Dx	0.91	0.91	0.91	0
11	LAD	0.86	0.86	0.91	0.05
12	RCA	0.89	0.89	0.89	0
13	LAD	0.84	0.86	0.84	-0.02
14	LAD	0.94	0.96	0.95	-0.01
15	LAD	0.88	0.91	0.89	-0.02
16	LAD	0.90	0.90	0.90	0
17	LCX	0.98	0.99	0.98	-0.01
18	RCA	0.81	0.86	0.90	0.04
19	LAD	0.85	0.91	0.92	0.01
20	LAD	0.95	0.95	0.95	0

Dx = Diagonal; LAD = Left Anterior Descending; LCX = Left Circumflex; RCA = Right Coronary Artery.

Supplemental Table 3: Using VFFR and VCI to guide PCI; table of all results.

		Actual			FFR_{max}			Optimal strategy		
Vessel	vFFR	No. of stents	Total stent length (mm)	Post VCI vFFR	No. of stents	Total Stent length (mm)	Post VCI vFFR	No. of stents	Total stent length (mm)	Post VCI vFFR
LAD	0.72	1	16	0.87	2	46	0.93	2	46	0.93
LAD	0.85	2	31	0.94	0	0	-	0	0	-
LCX	0.82	1	38	0.95	0	0	-	0	0	-
LCX	0.23	1	30	0.95	1	30	0.95	1	18	0.91
LAD	0.75	1	18	0.86	2	46	0.90	2	46	0.90
OM	0.90	1	14	0.96	0	0	-	0	0	-
LAD	0.90	1	12	0.95	0	0	-	0	0	-
RCA	0.91	1	28	0.96	0	0	-	0	0	-
LAD	0.67	1	19	0.97	1	12	0.97	1	12	0.97
LAD	0.76	1	13	0.86	2	23	0.87	2	23	0.87
RCA	0.59	1	22	0.80	2	66	0.92	2	66	0.92
LCX	0.71	1	26	0.74	1	36	0.81	1	36	0.81
LAD	0.74	1	12	0.81	1	36	0.85	1	36	0.85
LAD	0.80	1	16	0.89	2	30	0.91	2	30	0.91
LCX	0.74	1	38	0.96	1	38	0.96	1	36	0.96
LAD	0.64	1	24	0.70	1	34	0.71	1	34	0.71
LCX	0.85	1	18	0.90	0	0	-	0	0	-
LAD	0.81	1	36	0.94	0	0	-	0	0	-
LAD	0.45	1	14	0.90	1	24	0.91	1	24	0.91
LAD	0.83	1	20	0.96	0	0	-	0	0	-
LAD	0.80	1	18	0.88	2	36	0.92	2	36	0.92
OM	0.71	1	16	0.87	1	25	0.89	1	25	0.89
LAD	0.86	1	23	0.91	0	0	-	0	0	-
LAD	0.60	2	40	0.88	2	40	0.88	2	40	0.88
RCA	0.79	1	32	0.95	1	32	0.95	1	19	0.91
LAD	0.88	1	16	0.94	0	0	-	0	0	-

LAD	0.42	1	18	0.51	2	48	0.61	2	48	0.61
LCX	0.47	1	18	0.89	1	34	0.91	1	34	0.91
LCX	0.93	1	20	0.97	0	0	-	0	0	-
LAD	0.89	1	24	0.95	0	0	-	0	0	-
LCX	0.96	2	37	0.98	0	0	-	0	0	-
RCA	0.77	1	22	0.93	1	32	0.94	1	14	0.93
LCX	0.52	1	18	0.93	1	15	0.93	1	15	0.93
RCA	0.87	1	28	0.97	0	0	-	0	0	-
LAD	0.81	1	16	0.90	0	0	-	0	0	-
LAD	0.11	1	20	0.88	1	27	0.90	1	27	0.90
LAD	0.81	1	20	0.90	0	0	-	0	0	-
LCX	0.83	1	28	0.94	0	0	-	0	0	-
RCA	0.77	1	38	0.96	1	38	0.96	1	22	0.95
LAD	0.64	1	26	0.96	1	26	0.96	1	20	0.95
LCX	0.73	1	30	0.94	1	40	0.95	1	26	0.93
LAD	0.77	1	38	0.91	1	38	0.91	1	38	0.91
LAD	0.73	1	30	0.80	2	32	0.81	2	32	0.81
LAD	0.87	2	36	0.96	0	0	-	0	0	-
LCX	0.76	1	18	0.97	1	18	0.97	1	16	0.96
LAD	0.82	1	20	0.85	0	0	-	0	0	-
Dx	0.65	1	20	0.88	1	28	0.93	1	28	0.93
LAD	0.80	1	18	0.92	1	18	0.92	1	15	0.91
LAD	0.71	1	16	0.79	1	24	0.81	1	24	0.81
RCA	0.82	1	32	0.97	0	0	-	0	0	-
LCX	0.86	1	20	0.96	0	0	-	0	0	-
LAD	0.81	1	18	0.92	0	0	-	0	0	-
LAD	0.74	1	26	0.93	1	26	0.93	1	26	0.93
LAD	0.49	2	20	0.93	1	26	0.94	2	20	0.93
RCA	0.89	1	13	0.92	0	0	-	0	0	-
LAD	0.66	1	16	0.94	1	16	0.94	1	16	0.94
LAD	0.83	2	40	0.86	0	0	-	0	0	-

LAD	0.53	2	48	0.95	2	48	0.95	1	22	0.92
RCA	0.85	1	32	0.92	0	0	-	0	0	-
RCA	0.79	1	28	0.97	1	25	0.97	1	15	0.95
LCX	0.64	1	20	0.91	1	28	0.95	1	12	0.91
LAD	0.71	2	32	0.83	1	30	0.86	1	30	0.86
LAD	0.50	1	26	0.71	1	34	0.72	1	34	0.72
LAD	0.88	1	12	0.94	0	0	-	0	0	-

Dx = Diagonal; LAD = Left Anterior Descending; LCX = Left Circumflex; OM = Obtuse Marginal; RCA = Right Coronary Artery.

Supplemental Table 4: Patient level management plans provided by cardiologist A and cardiologist B based upon angiographic, vFFR and VCI guidance

Patient	Cardiologist A			Cardiologist B		
	Angio	vFFR	VCI	Angio	vFFR	VCI
1	PCI	PCI	PCI	PCI	PCI	PCI
2	PCI	PCI	PCI	More info	PCI	PCI
3	PCI	PCI	PCI	More info	PCI	PCI
4	More info	More info	More info	More info	OMT	OMT
5	PCI	More info	More info	More info	More info	More info
6	PCI	PCI	PCI	PCI	PCI	PCI
7	PCI	PCI	PCI	PCI	PCI	PCI
8	More info	More info	More info	PCI	PCI	PCI
9	OMT	OMT	OMT	PCI	PCI	PCI
10	PCI	PCI	PCI	PCI	PCI	PCI
11	PCI	PCI	PCI	PCI	PCI	PCI
12	PCI	PCI	PCI	PCI	PCI	PCI
13	OMT	OMT	OMT	More info	More info	More info
14	PCI	PCI	PCI	PCI	PCI	PCI
15	PCI	PCI	PCI	PCI	PCI	PCI
16	PCI	PCI	PCI	PCI	PCI	PCI
17	PCI	PCI	PCI	PCI	PCI	PCI
18	OMT	OMT	OMT	PCI	PCI	PCI
19	PCI	PCI	PCI	PCI	PCI	PCI
20	More info	More info	More info	More info	PCI	PCI
21	More info	More info	More info	PCI	PCI	PCI
22	OMT	OMT	OMT	PCI	PCI	PCI
23	More info	More info	More info	PCI	More info	More info
24	More info	OMT	OMT	PCI	More info	More info
25	More info	More info	More info	More info	PCI	PCI

26	PCI	PCI	PCI	PCI	PCI	PCI
27	More info	PCI	PCI	More info	PCI	PCI
28	More info	OMT	OMT	More info	More info	PCI
29	PCI	PCI	PCI	PCI	PCI	PCI
30	PCI	PCI	PCI	PCI	PCI	PCI
31	PCI	PCI	PCI	More info	PCI	PCI
32	More info	PCI	PCI	PCI	PCI	PCI
33	More info	PCI	PCI	PCI	PCI	PCI
34	PCI	PCI	PCI	PCI	PCI	PCI
35	More info	PCI	PCI	PCI	PCI	PCI
36	PCI	PCI	PCI	PCI	PCI	PCI
37	PCI	PCI	PCI	PCI	PCI	PCI
38	PCI	PCI	PCI	PCI	PCI	PCI
39	More info	More info	More info	PCI	PCI	PCI
40	PCI	PCI	PCI	PCI	PCI	PCI
41	PCI	PCI	PCI	PCI	PCI	PCI
42	PCI	PCI	PCI	More info	PCI	PCI
43	PCI	PCI	PCI	PCI	PCI	PCI
44	More info	More info	More info	More info	PCI	PCI
45	PCI	More info	More info	More info	PCI	PCI
46	PCI	PCI	PCI	PCI	PCI	PCI
47	More info	PCI	PCI	More info	More info	More info
48	More info	OMT	OMT	PCI	PCI	PCI
49	PCI	PCI	PCI	PCI	PCI	PCI
50	PCI	PCI	PCI	PCI	PCI	PCI

Angio = Angiography; More info = More information required; OMT = Optimal medical therapy; PCI = Percutaneous coronary intervention; VCI = Virtual coronary intervention; vFFR = virtual fractional flow reserve.

5.6 MDT standard operating procedure

1.) Display clinical history
    a. Presentation
    b. Cardiovascular risk factors
    c. Other PMH
    d. Relevant Investigations
2.) Display ECG where available
3.) Display diagnostic angiogram
4.) Ask cardiologist:
    a. What treatment do you recommend for this patient?
        i. OMT
        ii. PCI
        iii. CABG
        iv. More information required (please specify)
    b. How confident are you in your treatment recommendation? (Scale 1-10)
    c. If PCI or CABG, which vessels?
    d. How confident are you in your treatment recommendation? (Scale 1-10)
    e. If PCI, no. of and size of stent(s) to be used.
    f. How confident are you in your treatment recommendation? (Scale 1-10)
5.) Display vFFR result for baseline vessels
6.) Ask cardiologist:
    a. What treatment do you recommend for this patient?
        i. OMT
        ii. PCI
        iii. CABG
        iv. More information required (please specify)
    b. How confident are you in your treatment recommendation? (Scale 1-10)
    c. If PCI or CABG, which vessels?
    d. How confident are you in your treatment recommendation? (Scale 1-10)
    e. If PCI, no. of and size of stent(s) to be used.
    f. How confident are you in your treatment recommendation? (Scale 1-10)
    g. Why has your management plan changed/not changed?
7.) Display a series of VCI options with predicted post VCI FFRs for all relevant vessels
8.) Ask cardiologist:
    a. What treatment do you recommend for this patient?
        i. OMT
        ii. PCI
        iii. CABG
        iv. More information required (please specify)
    b. How confident are you in your treatment recommendation? (Scale 1-10)
    c. If PCI or CABG, which vessels?
    d. How confident are you in your treatment recommendation? (Scale 1-10)
    e. If PCI, no. of and size of stent(s) to be used.
    f. How confident are you in your treatment recommendation? (Scale 1-10)
    g. Why has your management plan changed/not changed?

5.7 MDT data collection sheet

Patient no: Consultant:

Angiography based treatment plan

OMT *PCI* *CABG* *More info*

Further comments:

Confidence: 1 2 3 4 5 6 7 8 9 10

Vessel(s) for revascularisation:

LAD *LCX* *RCA* *OM* *Dx* *Int*

Confidence: 1 2 3 4 5 6 7 8 9 10

Proposed PCI details:

Vessel	No.of stents	Stent width	Stent length	Further comments

Confidence: 1 2 3 4 5 6 7 8 9 10

vFFR based treatment plan

OMT *PCI* *CABG* *More info*

Further comments:

Confidence: 1 2 3 4 5 6 7 8 9 10

Vessel(s) for revascularisation:

LAD *LCX* *RCA* *OM* *Dx* *Int*

Confidence: 1 2 3 4 5 6 7 8 9 10

Proposed PCI details:

Vessel	No.of stents	Stent width	Stent length	Further comments

Confidence: 1 2 3 4 5 6 7 8 9 10

Change in management decision: *Yes* *No*

Why?/Why not?:

VCI based treatment plan

OMT *PCI* *CABG* *More info*

Further comments:

Confidence: 1 2 3 4 5 6 7 8 9 10

Vessel(s) for revascularisation:

LAD *LCX* *RCA* *OM* *Dx* *Int*

Confidence: 1 2 3 4 5 6 7 8 9 10

Proposed PCI details:

Vessel	No.of stents	Stent width	Stent length	Further comments

Confidence: 1 2 3 4 5 6 7 8 9 10

Change in management decision: *Yes* *No*

Why?/Why not?:

5.8 Ethics approvals

Downloaded: 13/10/2017
Approved: 30/05/2017

Rebecca Gosling
Cardiovascular Science

Dear Rebecca

PROJECT TITLE: Virtual coronary intervention: a novel treatment planning tool in complex coronary artery disease
APPLICATION: Reference Number 013378

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 30/05/2017 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 013378 (dated 16/05/2017).

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Yours sincerely

Jean Lazenby
Ethics Administrator
Medical School

East REC Centre Unit
002, TEDCO Business Centre

Dr Julian Gunn
Senior Lecturer / Honorary Consultant Cardiologist
University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust Department of Cardiovascular Science
Medical School
University of
Sheffield Beech Hill
Road Sheffield
S10 2RX

Dear Dr Gunn

Study title: Virtual coronary physiology: An angiogram is all you need

REC reference:	**13/YH/0070**
Protocol number:	**STH16467**
IRAS project ID:	**108461**

The Research Ethics Committee reviewed the above application at the meeting held on 28 February 2013. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so.
Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Miss Sarah Grimshaw, nrescommittee.yorkandhumber-southyorks@nhs.net.

Ethical opinion

The Chair, Ms Susan Hampshaw, welcomed you and thanked you for attending.

The REC informed you that your application was well-written and thanked you for this.

Members noted that in the response to question A13 of the IRAS form it was stated that some participants may undergo an extra cardiac magnetic imaging before and after PC1, but questioned what the risks were, which patients would undergo the MRI scan and why a second test would be performed as it was not the standard technique used to look at coronary arteries.

You responded that this had been added to the IRAS form by mistake; the research team are currently applying for funding to do this extra test and if successful would apply to the committee to amend the study to be able to do so.

The Committee noted that the researchers would reimburse participants the cost of the taxi fare to the hospital, but queried why this would be so as the participants would only be attending at routine visits.

You replied that the appointment could be on an awkward day for participants to attend. You went on to clarify that patients would take part at the routine pre-admission visit and would be seen by a research nurse as opposed to a clinical nurse, who would explain both the research and normal clinical care to participants.

Members felt that the reimbursement of a taxi fare could serve as an incentive to participate because patients would not normally receive this as standard care, and suggested that you could instead offer to pay for any extra parking charges incurred by taking part in the study.

The Committee questioned whether participants would know that the standard care was the cardiac catheter, and that the research would be to include a pressure gradient measurement.

You confirmed that that would be the case.

Members therefore questioned why only 5% of patients would receive the pressure measurement and that if this was the case whether the clinical care team would be trained and have enough skill and expertise to complete the procedure effectively.

You clarified that you would perform the pressure measurement procedure, of which you had done approximately 300. You went on to say that you had done 3000 angioplasties.

You explained that patients who could receive the intervention would be drawn from the current angioplasty waiting lists. You would review the angiogram which would be on a CD from the patients' diagnostic visit and would decide if the patient would need a stent, as in standard practice. If patients were borderline, they would receive the pressure wire, whereas patients whose arteries were too thin would not have the procedure as this would not be safe for them. Therefore some will receive the wire, and some will not.

You went on to clarify that the use of this procedure is limited by cost, not time, because each wire is £300-400.

You left the room.

The Committee discussed the responses.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Additional Conditions Specified by the Committee

1. Confirmation that a second MRI scan will not be performed on participants. (If funding is secured for a second MRI scan then the researcher needs to submit as an amendment after approval)

2. Confirmation that participants will not be given expenses for taxis as this could be considered an incentive to participate. The Committee suggests that participants are reimbursed instead for parking charges above what would normally be paid at a routine visit.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		31 January 2013
GP/Consultant Information Sheets	2.2	15 January 2013
Investigator CV		
Letter of invitation to participant	2.2	15 January 2013
Other: Data collection sheet	1.1	14 January 2013
Participant Consent Form	1.0	14 March 2012
Participant Information Sheet	2.4	29 January 2013
Protocol	1.8	30 January 2013
REC application	1.0	31 January 2013

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- **Notifying substantial**
- **amendments Adding new sites**
- **and investigators**
- **Notification of serious breaches of the**
- **protocol Progress and safety reports**
  Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/YH/0070	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp Ms Susan Hampshaw Chair

Email: nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers" SL-AR2

Copy to: *Mrs Jennifer Boston, Sheffield Teaching Hospitals NHS Foundation Trust*

NRES Committee Yorkshire & The Humber - South Yorkshire Attendance at Committee meeting on 28 February 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Ms Jo Abbott	Consultant in Public Health	No	
Dr A H Abdelhafiz	Consultant Physician, Elderly Medicine	Yes	
Reverend Joan Ashton	Co-ordinator of Chaplaincy Services	Yes	
Ms Helen Barlow	Knowledge Service Manager	Yes	
Professor Nigel Beail	Consultant Clinical Psychologist & Professor of Psychology	Yes	
Mr Ian Cawthorne	Chief Pharmacist	Yes	
Ms Susan Hampshaw	Head of Research, Evaluation and Innovation	Yes	
Mr Neil Marsden	Police Staff	Yes	
Dr Anton Mayer	Consultant in Paediatric Intensive Care	Yes	
Mrs Andrea Porritt	Community Specialist Practitioner	Yes	
Mr Jaydip Ray	Consultant ENT Surgeon	No	
Ms Stephanie Rhodes	Neonatal Sister	Yes	
Dr Paul Spencer	Consultant Radiologist	Yes	
Mrs Carole Taylor	Deputy Chief Pharmacist	No	

Also in attendance:

Name	*Position (or reason for attending)*
Richard Baetke	Observer
Miss Sarah Grimshaw	Committee Coordinator
Louise Jackson	Observer

5.9 Permissions from co-authors

Letters granting permission for elements of previously published works to be included in this thesis have been provided by the co-authors of the relevant publications. See attached.

The University Of Sheffield.

Department Of Infection, Immunity & Cardiovascular Disease.

Faculty of Medicine Dentistry & Health
Professor Dame Pamela J Shaw - *Pro-Vice-Chancello*

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S10 2RX

24th October 2019

I give permission for elements from the following publications, of which I am a co-author, to be used in Rebecca Gosling's PhD thesis:

1. R Gosling, P Morris, P Lawford, DR Hose and J Gunn (2018) Predictive Physiological Modeling of Percutaneous Coronary Intervention – Is Virtual Treatment Planning the Future?. *Front Physiol.* 2018 Aug 13;9:1107
2. R Gosling, P Morris, D Silva-Soto, P Lawford, D.R.Hose, J Gunn. Virtual coronary intervention; a treatment planning tool based upon the angiogram. *JACC Cardiovasc Imaging.* 2019 May;12(5):865-872
3. R Gosling, P Morris, P Lawford, D. R Hose and J Gunn. Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation. *EuroIntervention.* 2019 Oct;15(8):707-713

Print name: Professor Patricia V Lawford

Signed: [redacted]

The University Of Sheffield.

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Faculty of Medicine Dentistry & Health
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Print name: Professor Julian Gunn

Signed: 

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3. R Gosling, P Morris, P Lawford, D. R Hose and J Gunn. Personalised Fractional Flow Reserve: Novel concept to optimise myocardial revascularisation. *EuroIntervention.* 2019 Oct;15(8):707-713

Print name: Dr Paul Morris

Signed: "electronically signed – Dr Paul Morris"

The University Of Sheffield.

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Print name: Professor Rodney Hose

Signed: "electronically signed – Professor Rodney Hose"