Comprehensive assessment of myocardial ischaemia: from vessel to patient.

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Abstract

Chronic coronary syndrome (CCS) is accompanied by angina and limitation to the patient's life. The significance of coronary blood flow reduction is currently best assessed by fractional flow reserve (FFR) as a guide to intervention. The beneficial effect of percutaneous coronary intervention (PCI) in these patients has been challenged, and therefore fresh evaluation of the changes in response to PCI is needed.

Using real-world data from 40 patients, detailed examination of coronary anatomy and physiology, using FFR and computational fluid dynamics (CFD) to assess absolute coronary flow, was conducted. Patients not undergoing PCI due to FFR negative lesions comprised the 'control' group. A novel method to assess the myocardial ischemic burden and address the global flow reduction named 'cumulative FFR' (FFR_{CUM}) was developed. Fitness trackers monitored everyday physical activity, and six-minute walk tests were performed, before and three months after the procedure. Questionnaires were used to evaluate the change as reported by the patients.

I found a clear and significant physiological improvement following PCI in FFR, hyperaemic stenosis resistance (HSR), microvascular resistance (MVR), absolute flow (which increased 80%) and FFR_{cum} (which increased from 0.72 to 0.83). The change in FFR_{cum} was a predictor of the change in quality of life at follow up. Improvement in spontaneous and observed physical activity, which was highly variable between patients, was minimal, with similar findings in PCI and 'control' patients. This was also observed with questionnaires in all domains except angina frequency.

Taken together, this work shows that physiological improvement (FFR and FFR_{cum}), and absolute flow restoration, are achieved with FFR-guided PCI. However, that does not necessarily result in measured improvement in everyday physical activity, or self-reported general health status, but it does result in improved angina status, at three months. Overall, these findings indicate that physiological improvements in myocardial perfusion produced by PCI tend not to lead to a major change in objective measures of activity or wellbeing in everyday life, but are worth pursuing in terms of angina, specifically.

Declaration

I, the author, declare that the work presented in this thesis is my own. I contributed to the design of VIRTU-5, writing the protocol and obtaining ethical approval. I presented the study protocol in the Cardiothoracic Directorate Research Executive (CDRE) and NIHR Cardiovascular Patient Panel (CPP) for regulatory approval. Patients' screening, home visits and recruitment as well as data collection including (questionnaires, daily physical monitoring and six-minute walk tests) were done in collaboration with Dr Gareth Williams. Coronary procedures were operated by Professor Julian Gunn and Dr Paul Morris. Virtual FFR and virtu-Q (the measure of absolute flow) were developed by Dr Paul Morris. I was present at the catheterisation laboratory for all cases, and recorded and downloaded all coronary physiology data and angiograms DICOMs files. I processed and interpreted the data, and carried out the statistics and analysis for each assessment method used in this thesis. The deriving equations of virtual FFR are described before in Dr Rebecca Gosling PhD thesis (2019).

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List of abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
ATS	American Thoracic Society
BARI	Bypass angioplasty revascularisation investigation
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBF	Coronary blood flow
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomography angiography
CDRE	Cardiothoracic directorate research executive
CFD	Computational fluid dynamics
CFR	Coronary flow reserve
CMR	Cardiac magnetic resonance
CPP	Cardiology patient panel
CPP	Coronary perfusion pressure
CTO	Chronic total occlusion
DBS	Disclosure and barring service
DES	Drug eluting stent
2DM	Type two diabetes mellitus
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
EQ-5D	Euro Quality of life 5 dimensions
FFR	Fractional flow reserve
FSS	Functional syntax score
HF	Heart failure
HSR	Hyperemic stenosis resistance
ICA	Invasive coronary angiography

IQR	Interquartile range
iFR	Instantaneous wave-free ratio
IHD	Ischemic heart disease
IRA	Infarct-related artery
IRAS	Integrated research approval system
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LCX	Left circumflex
LHC	Left heart catheter
LIMA	Left internal mammary artery
LMS	Left main stem
LVEDP	Left ventricular diastolic pressure
MACE	Major adverse cardiac events
MCS	Mental component summary
MET	Metabolic equivalent task
MEMS	Micro-electromechanical system
MI	Myocardial infarction
MCID	Minimal clinically important difference
MJI	Myocardial jeopardy index
MVD	Multi-vessel disease
MVR	Microvascular resistance
MVPA	Moderate to vigorous physical activity
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST-elevation myocardial infarction
NSTEACS	Non-ST segment elevation acute coronary syndrome
OCT	Optical coherence tomography
OM	Obtuse marginal (artery)
OMT	Optimal medical therapy
PA	Physical activity

P_a	Aortic coronary pressure
PCI	Percutaneous coronary intervention
PCS	Physical component summary
P_d	Distal coronary pressure
PD	Pressure signal drift
PET	Positron emission tomography
PIS	Patient information sheet
PPG	Photoplethysmography
PROMs	Patient reported outcomes measures
P_v	Venous pressure
QCA	Quantitative coronary angiography
QFR	Quantitative flow ratio
RCA	Right coronary artery
RFR	Resting full cycle ratio
SAQ	Seattle angina questionnaire
SHC	Sheffield Hospitals Charity
SPECT	Single photon emission computed tomography
STEMI	ST-elevation myocardial infarction
STH	Sheffield Teaching Hospitals
SVG	Saphenous vein graft
TIMI	Thrombolysis in myocardial infarction
VAS	Visual analogue scale
VCI	Virtual coronary intervention
vFFR	Virtual fractional flow reserve
vFAI	Virtual functional assessment index

Chapter one: Introduction and background

1.1 Ischemic heart disease

1.1.1 Epidemiology of Ischemic heart disease

Coronary artery disease (CAD) is the third leading cause of death in the United Kingdom, and is responsible for around 64,000 deaths every year. In 2021, it is reported that the number of people living with CAD in the UK can reach up to 2.3 million, around 83,000 are women and 1.5 million are men. Despite the fact that these numbers are significantly high and the issue needs to be addressed, the mortality rate of cardiovascular disease including CAD has declined by three quarters in 2020 compared to 1969. Nationwide mortality caused by CAD is estimated to be around 177,992 deaths per year in 1981 whilst today it has dropped to 64,170 death per year (BHF, 2022). CAD is not only a lethal disease; it imposes high costs on economy and healthcare systems around the world. In the UK, the costs of CAD account for one third of the total costs of cardiovascular disease and stroke, resulting in a total cost of £7.6 billion merely due to CAD in 2015. Not all of these costs are healthcare related, productivity loss due to morbidity and mortality are responsible for a total of 33% of the total costs contributing for around £2.5 billion (BHF, 2022).

1.1.2 Coronary artery disease: clinical presentations

As a consequence of plaque development, luminal diameter starts to get reduced progressively. Early stages of the disease are often asymptomatic; however, when the lesions start to be more flow limiting, symptoms are likely. Myocardial ischemia can result from stenotic flow limitation and it is caused by oxygen supply-demand mismatch. When the flow can no longer be increased to achieve myocardial demands, a characteristic chest pain or discomfort can arise (Shao *et al.*, 2020). Fundamentally, coronary artery disease can be stable for prolonged periods, but due to its chronic nature, progression to unstable disease can occur. Acute atherothrombotic events like plaque rupture and erosion cause this serious change of disease stability. Based on that, CAD is categorised into two types of clinical presentations, which are chronic coronary syndrome (CCS) and acute coronary syndrome (ACS).

1.1.3.1 Chronic coronary syndrome

The term 'chronic coronary syndrome' was proposed by the European Society of Cardiology (ESC) to replace the old term 'stable coronary artery disease'. The term is thought to be a distinctive name that better describe the dynamic nature of the disease. Stable angina is the distinctive and typical symptom for CCS. It is best described as short episodes of exertional central chest pain or tightness that may last for few minutes or even less and is relieved by rest. Typical angina can have other triggers such as emotional stress and cold weather. Pain might radiate to other parts including neck, back and left arm (Saraste and Knuuti, 2020).

1.1.3.2 Acute coronary syndrome (ACS)

There is a spectrum of possible clinical presentations of ACS ranging from cardiac arrest, to severe pain. However, the typical symptom of ACS is acute and persistent chest discomfort at rest that can also radiate to other part of the upper body and can be described as pain or tightness. ESC guidelines has suggested two main clinical investigation to identify ACS based on ECG (Thiele and Jobs, 2021):

1- Acute chest pain and persistent ST segment elevation myocardial infarction (STEMI)
2- Acute chest pain but no persistent ST elevation; non-ST segment elevation acute coronary syndrome (NSTEACS)

1.1.3 Coronary blood flow in health and disease

Coronary anatomy

The coronary arteries originate from the aortic sinus just superior to the aortic valve. The left and right coronary arteries supply the myocardium and epicardium. The left coronary artery (LCA starts at the left main stem coronary artery (LMS), which divides into left anterior descending (LAD) artery and left circumflex artery (LCx). Moreover, the LAD supplies the anterolateral left ventricle and two thirds of the anteroseptum segments of the LV through the diagonal and septal branches. The LCx supplies the left atrium and one third of the posterolateral free walls of LV. Furthermore, the LCx branches into a variable number of obtuse marginal branches. The largest is usually the terminal branch. In a minority of the population, the posterior descending artery (PDA) branches

from the LCx to supply the inferior segments of both ventricles. The right coronary artery (RCA) which originates from the right sinus supplies the right side of the heart, and the inferior wall if it is a right dominant system. A right dominant system is more common among the population (70%) and supplies the PDA branch along with the acute marginal artery. The RCA and its branches supply the right ventricle, SA and AV nodes and one third of the septum and inferior segments of the ventricles. An illustration of the coronary artery tree is shown in figure 1.1.

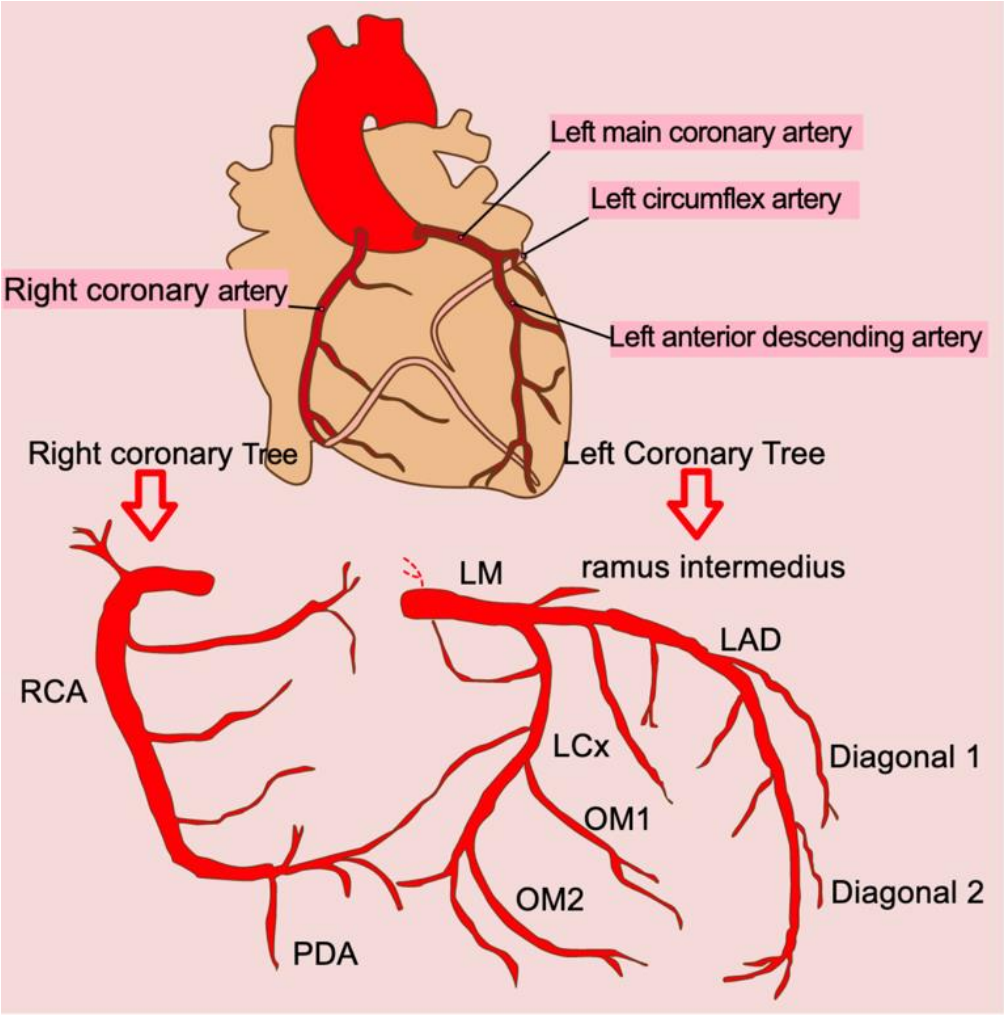

Figure 1.1 Illustration of coronary artery tree

Coronary physiology

Myocardial oxygen demand is susceptible to an increase in heart rate, left ventricular contractility or wall tension. This increase in demand requires an increase in supply to maintain myocardium perfusion, and failure to achieve sufficient oxygen supply can result in myocardial ischemia. An increase in oxygen demand can only be met by increasing blood flow to the myocardium, due to fact that oxygen extraction is already near maximal levels at rest. To match demand, the increase in flow may need to be by four to five fold (Detry, 1996). In normal adults, coronary blood flow (CBF) represents five percent of the total cardiac output. Change in coronary vascular resistance is responsible for coronary blood flow regulation. However, epicardial coronary arteries are not the major contributor to resistance across the coronary bed; they only account for five percent of the total coronary vascular resistance, whereas the microvasculature (<300 μm) that branch off the coronary arteries constitute the remaining 95% (O'Brien and Nathan, 2008). CBF is regulated by multiple factors that include metabolites (adenosine, hypoxia), endothelium derived agents (nitrous oxide and endothelin-1) and other neuro-hormonal mechanisms (epinephrine and acetylcholine). This autoregulation process is essential in controlling vasodilation and vasoconstriction phenomena, maintaining appropriate coronary blood flow to the myocardium (Johnson, Gould and De Bruyne, 2021). In healthy individuals and under resting conditions, the mean aortic pressure of 60 to 140 mmHg is sufficient to maintain myocardial perfusion. However, if pressure exceeds or drops below this range, autoregulation fails and CBF becomes purely pressure-dependent (Duncker *et al.*, 2015). Coronary perfusion pressure (CPP) is essential for maintaining coronary blood flow. CPP refers to the pressure gradient between aortic diastolic pressure and left ventricle end diastolic pressure (LVEDP). Most of coronary perfusion takes place during diastole, because myocardial contraction compresses the arterial walls, limiting flow. CPP provides sufficient pressure to drive coronary perfusion from epicardial to endocardial regions (Heward and Widrich, 2022).

Effects of coronary stenosis upon coronary blood flow

Healthy coronary arteries can respond to myocardial demands by increasing flow up to five times compared to resting flow, subject to the absence of microvascular dysfunction. This mechanism is defined as coronary flow reserve (CFR). However, in the presence of stenosis, epicardial resistance increases due to flow obstruction. As a response, autoregulation mechanism attempts to reduce microvasculature resistance to preserve blood flow. CBF can thereby be maintained. Eventually, with increase in stenosis severity to approximately 70% by diameter, the microvasculature becomes exhausted and fails to reduce its resistance, and the inability to meet the myocardial metabolic demands becomes impaired, resulting in myocardial ischemia. Nevertheless, resting can restore the balance by reducing myocardial demands (Duncker *et al.*, 2015; Johnson, Gould and De Bruyne, 2021). Further details on pressure-flow relationship is provided in section 1.3.4.

1.2 Management of coronary artery disease (CAD)

There are three principal objectives in the management of CAD: eradicating angina, reducing cardiac events, and improving quality of life. These objectives can be achieved through a conservative treatment strategy ('medical management'), coronary revascularisation, or a combination of the two. Both strategies have been in routine clinical practice for several decades and can, in different circumstances, reduce the mortality and morbidity of CAD. In addition, risk factor modifications, such as increased physical activity, low fat diet and smoking cessation have shown positive outcomes in preventing ('primary prevention') and slowing the progression of ('secondary prevention') coronary artery disease (Chow *et al.*, 2010).

1.2.1 Medical management

Medical management is aimed at reducing symptoms and preventing cardiovascular events. The first is nitrates or nitric oxide donating drugs such as glyceryl trinitrate. Nitrates have vasodilator effects that helps relieving angina attacks when they occur within minutes by reducing preload and increasing blood flow to the myocardium by coronary vasodilatation (Wight *et al.*, 1992). Beta-

blockers are used to control heart rate and the force of myocardial contraction, which helps to reduce exertional angina, and prevent angina attacks, by reducing myocardial oxygen demand (Diaz *et al.*, 2005). Calcium channel blockers reduce afterload by peripheral arteriolar vasodilatation and reducing arterial blood pressure (Husted and Ohman, 2015). To minimise the risk of future cardiac events, two approaches are used, namely, anti-thrombotic (anti-platelet) agents and lipid lowering therapy (plaque stabilisation). Aspirin's mechanism of action is as a cyclo-oxygenase inhibitor, causing inhibition of platelet aggregation. Moreover, aspirin is associated with reduced risk of death from MI (The RISC Group, 1990). Statins are lipid lowering drugs and are used to lower cholesterol levels by inhibiting the formation of LDL cholesterol via HMG-CoA reductase. They can reduce LDL cholesterol by 50% and reduce the incidence of cardiac events (Ridker *et al.*, 2008).

1.2.2 Revascularisation

The principal goal of coronary revascularisation is to improve coronary blood flow by improving blood supply, thereby relieving ischemia, reducing symptoms, improving quality of life and increasing exercise capacity. Revascularisation can be achieved by two strategies; coronary artery bypass grafting (CABG), and percutaneous coronary intervention (PCI). The earlier is the original technique to restore flow in stenosed arteries. The first successful CABG surgery was in the early 1960s (Goetz *et al.*, 1961). CABG can be defined as a vascular conduit grafted beyond the stenosis to restore blood flow to the myocardium. Routinely used conduits are saphenous vein grafts (SVG) and the internal mammary artery (LIMA). The choice of conduits depends upon different factors including lesion location and anatomy. The LIMA which, being arterial, is more resistant to degeneration than vein grafts, is usually applied to the LAD. Generally, CABG is recommended when PCI fails, in the presence of complex three-vessel disease with high SYNTAX score or when there is left main stenosis (Sousa-Uva *et al.*, 2019). The SYNTAX score is used as angiographic grading system, that helps in evaluating the complexity of CAD (Sianos *et al.*, 2005). Alternatively, PCI, which is minimally invasive, is used more widely than CABG. The first successful in human angioplasty was performed in 1977 (Grüntzig, Senning and Siegenthaler, 1979). The technique involves gaining access to coronary vasculature through a catheter inserted into the radial or

femoral artery. The catheter is inserted into one of the major epicardial vessels under Xray guidance, and contrast agent is injected to visualise the coronary vessels. This is angiographic guidance. The coronary angiogram is the gold standard diagnostic tool in the catheterisation laboratory (see section 1.3.2). Once the lesion of interest is identified and located, a guide wire is advanced across the lesion followed by a balloon inflation and stent deployment to maintain vessel patency. Each strategy has its own benefits and limitations, however, both have been evidenced to be effective and safe in treating ischemic heart disease. A summary of the European guidelines on myocardial revascularisation is presented in figure 1.2. Both strategies have been shown to reduce symptoms, the risk of myocardial infarction and cardiovascular death (Sousa-Uva *et al.*, 2019). Both interventions have proven effectiveness when compared to optimal medical therapy alone (OMT) in CCS. The superiority of CABG to OMT in terms of survival, especially in left main stem and three-vessel disease, was reported in a meta-analysis (Yusuf *et al.*, 1994). The FAME-2 randomised clinical trial compared PCI and OMT vs OMT alone in CCS patients with at least one physiologically significant stenosis, with a significant reduction (4.3% vs 12.7%) in cardiovascular events at three year follow up. Additional benefits were improved quality of life and exercise capacity and reduced anti-angina medication. This trial was guided by the use of fractional flow reserve (FFR) (see section1.3.3) (Fearon *et al.*, 2018). A large meta-analysis that included 100 trials compared PCI and OMT and concluded that revascularisation with new generation drug eluting stents (DES) is associated with improved survival (Windecker *et al.*, 2014).

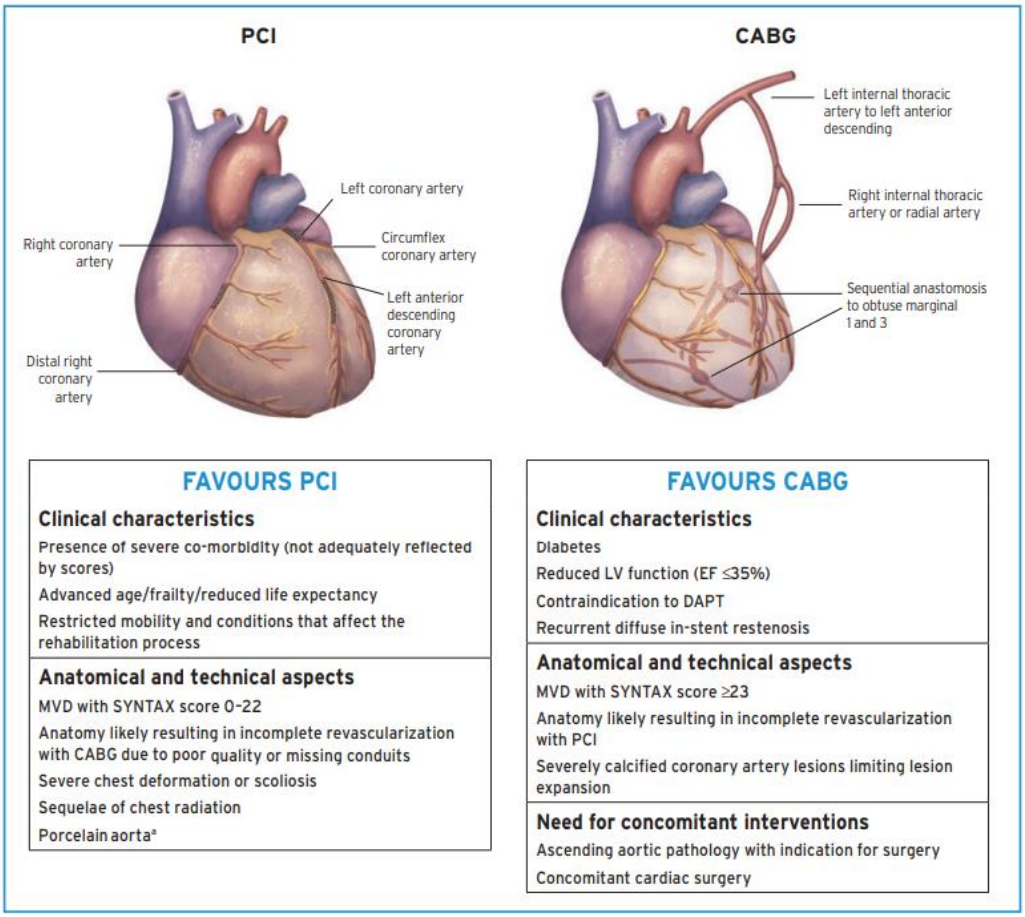

Figure 1.2 Main aspects that need to be considered for decision making in CABG and PCI.

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1.3 Assessment of Ischemic heart disease

1.3.1 Non-invasive investigation

Cardiac diagnostic tools vary in their availability, utility and accuracy, which makes it important to determine the most suitable test depending on the condition and urgency (Sousa-Uva *et al.*, 2019). One illustration of their use in the diagnosis of CAD is presented in figure 1.3. To identify ischaemia in patients with suspected CAD, an exercise stress test can be used as a diagnostic tool. The aim is to reproduce a state in which the oxygen demand/supply mismatch occurs. The patient can be stressed physically, using a bicycle or a treadmill. If the patient is unable to exercise, pharmacological stress, using dobutamine or adenosine, can be used (Banerjee *et al.*, 2012). In stress echocardiography, abnormal LV wall contraction and motion are induced by ischaemia

which resolves under resting conditions. Contrast can be administered to enhance image quality if required (Sousa-Uva *et al.*, 2019). Alternatively, in single photon emission computed tomography (SPECT), radiopharmaceutical tracers (Technetium-99m or Thallium 201) are administered under stress and rest conditions. Tracer uptake reflects perfusion and therefore local myocardial blood flow. CAD can be predicted with high sensitivity (Germano and Berman, 2007). Computed tomography coronary angiography, now recommended by NICE as a first-line investigation of stable chest pain (NICE, 2017), is an *anatomical* modality that acquires coronary lumen images with an intravenously administered contrast agent. Certain factors can degrade image quality, such as heart rate >60 bpm, inability to hold the breath, obesity, high calcium score and arrhythmia. This tool has demonstrated sensitivity of 95-99% and 97-99% in CAD prediction in different multicentre studies (Meijboom *et al.*, 2007, 2008). Cardiovascular magnetic resonance (CMR) imaging is a tool that generates images from hydrogen nuclei using radio waves in a magnetic field. It can detect either myocardial perfusion (vasodilator stress CMR) or ischaemia-induced regional wall motion abnormalities (dobutamine stress CMR). This technique can perform complete quantification of perfusion, and provide cardiac structure information and high spatial resolution (Kato *et al.*, 2010; Sakuma, 2011).

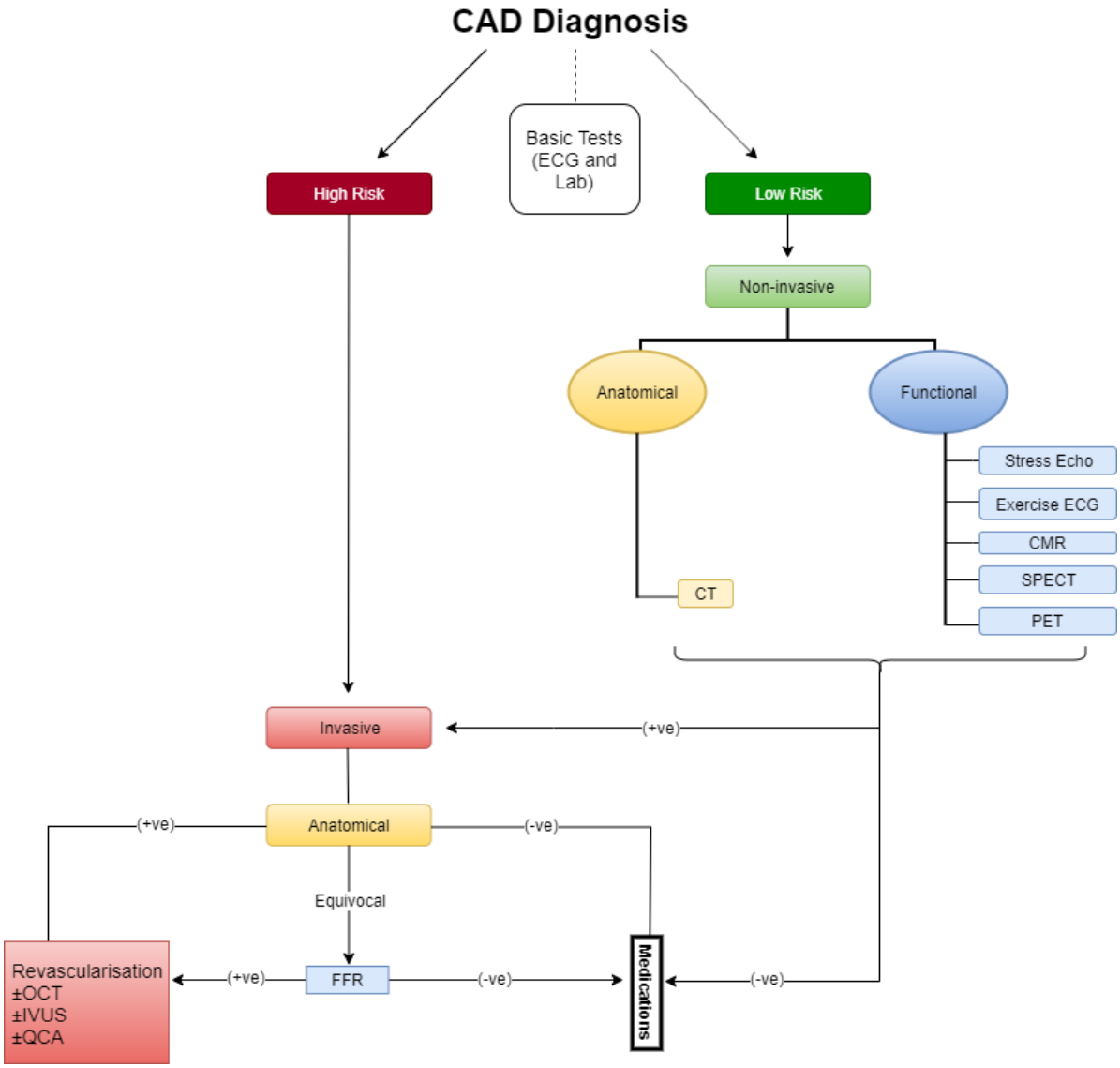


Figure 1.3 Commonly used algorithms in the diagnosis of CAD.

This algorithm separates diagnostic tools based on risk degree (high/low) and type of test (functional or anatomical). Created with Draw.io

1.3.2 Invasive coronary angiography

Invasive coronary angiography (ICA) is the gold standard tool for diagnosis, management planning and intervention with PCI. Images are visible after injecting contrast media into the coronaries through catheters inserted via the radial or femoral arteries. ICA is used to identify the severity and location of lesions, and it is also valuable in visualising branches and collateral vessels (Figure

1.4). The main purpose of the coronary angiogram is determine the number, position, importance and degree of luminal narrowings. Coronary stenoses which are estimated to be greater than 50% of a vessel's cross-sectional area or 70% of its diameter are regarded as probably flow-limiting (Feldman *et al.*, 1978). ICA captures a series of two-dimensional images from different angles, creating a conceptualisation of three-dimensional coronary anatomy. Over 250,000 ICAs are performed, and about 100,000 PCI procedures, each year in the UK (NAPCI, 2021). ICA carries a risk of major complications of considerably less than 1:1000. Additionally, its spatial and temporal resolution is superior to other imaging tools (Collet *et al.*, 2017). However, ICA has some limitations. The three-dimensional (3D) nature of the coronary anatomy makes two-dimensional (2D) images unrepresentative in some cases. For instance, an eccentric stenosis can be under-estimated, an ostial lesion missed, or long diffusely diseased vessels incorrectly classified. Finally, ICA is limited to anatomical assessment, so it does not inform about the functional severity of coronary stenosis. Functional severity carries valuable prognostic value in coronary artery disease. To overcome these limitations, several adjunctive invasive diagnostic techniques were developed to guide treatment and improve coronary artery disease assessment.

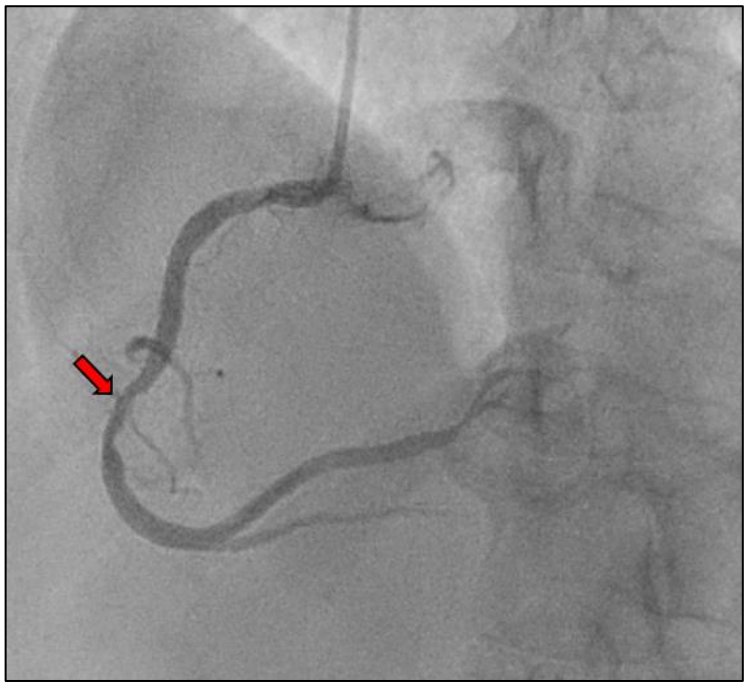


Figure 1.4 Right coronary artery angiogram showing a moderate stenosis in the mid segment.

The red arrow points at the stenosis location

1.3.3 Fractional Flow Reserve (FFR)

ICA is particularly inadequate to identify the functional severity of mild to moderate lesions (25-70% diameter stenosis), for which visual assessment is poor (Brueren *et al.*, 2002). Sixty five percent of stenoses with angiographic severity 50%-70% were found to be functionally non-significant (Tonino *et al.*, 2010). Therefore, there was a need to provide a complementary functional diagnostic tool to distinguish flow-limiting disease. Fractional flow reserve (FFR) is a pressure-derived index representing the extent to which myocardial blood flow is limited by the presence of a coronary stenosis in hyperaemic conditions. To elaborate, maximal myocardial blood flow is assumed to be similar across the normal artery to govern adequate supply to myocardium; whereas, in the presence of an epicardial stenosis, myocardial blood flow is reduced by the effects of epicardial resistance. This is demonstrated in figure 1.5A. The simplified ratio of these two flows, with fundamental assumptions, represents FFR. In practice, FFR is measured by advancing a pressure-sensitive wire across the coronary lesion, whereas the proximal coronary pressure is measured from the tip of coronary guide catheter (figure 1.5B). Hyperaemia is then induced by infusing a pharmacological microvascular vasodilator (adenosine) intravenously. The mean distal coronary pressure (P_d) and mean proximal coronary pressure (P_a) are measured simultaneously and the ratio of the two mean pressures is calculated. The ratio (P_d/P_a) when maximal hyperaemia is most stable is calculated as the FFR. The threshold for significant flow limiting stenosis is ≤ 0.8, however, the range 0.75 to 0.8 is still considered a grey area.

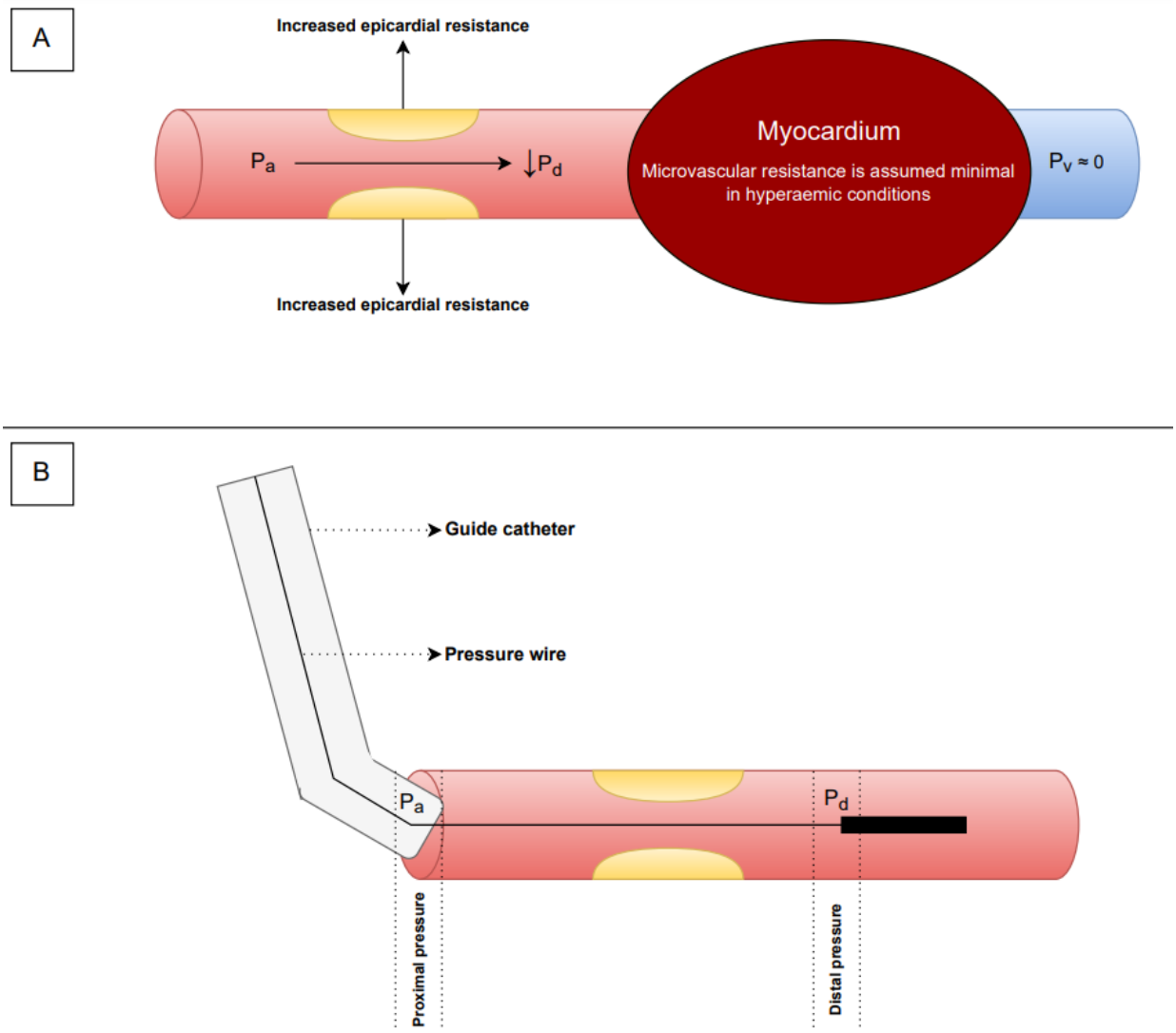


Figure 1.5 Demonstration of basic theoretical and technical principles of FFR.

A) Representation of pressure drop in response to increased resistance at the presence of stenosis and at hyperaemia. B) Technical demonstration of FFR measurement in downstream diseased coronary artery. P_a: Proximal aortic pressure, P_d: Distal pressure, P_v: Venous pressure (created with draw.io).

1.3.3.1 Theory of FFR

Pressure-flow relationship

It is important to understand the relationship between pressure and flow in the context of CBF. Generally, CBF increases as a response to increase in demand, but this increase is limited by the resistance in the coronary system. The resistance can be either epicardial, a coronary stenosis, or microvascular, which accounts for most of the resistance in the system. In hyperaemia, the resistance of healthy microvasculature drops to the minimum, and the only resistance that can affect the flow is epicardial stenosis. CBF is driven by coronary perfusion pressure. Pressure loss in the absence of coronary stenosis is unlikely, therefore, a positive linear relationship can be observed. The pressure gradient-flow velocity relationship is described by Poiseuille's law, which assumes that flow is laminar through a pipe under constant velocity and circular cross section. Given that in a coronary artery viscosity is constant, vessel radius is the determining factor (to the fourth power) in a pressure drop. This explains the exponential increase in pressure gradient with increase in stenosis severity. Across the stenosis, the flow accelerates due to the reduced cross sectional area according to Bernoulli's law. Distal to the stenosis, pressure drops due to energy loss caused by friction through the stenosis, and flow slows.

Derivation of FFR

FFR is the ratio of flow through a stenosis ($Q_{stenosis}$), to the flow without the stenosis (Q_{Normal}) assuming the flow before the stenosis to be normal. This can be represented by the following equation:

$$FFR = \frac{Q_{Stenosis}}{Q_{Normal}}$$

Flow is derived from Ohm's low where flow is equal to pressure difference (ΔP) divided by resistance (R):

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

$$Q_{Stenosis} = \frac{P_d - P_v}{R_{Hyperaemia}}$$

$$Q_{Normal} = \frac{P_a - P_v}{R_{Hyperaemia}}$$

Where: P_d is pressure distal to stenosis

P_a is pressure proximal to stenosis

P_v is venous pressure

R is resistance

Therefore:

$$FFR = \frac{(P_d - P_v)/R}{(P_a - P_v)/R}$$

Measurements are obtained under hyperaemic conditions, therefore resistances are minimal and equal, and they cancel out:

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

Venous pressure is negligible compared to aortic pressure, therefore assumed zero, leading to the simplest form of the equation:

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

1.3.3.2 Validation of FFR

Non-invasive ischemia tests were the reference tools used to validate FFR and identify the threshold of flow limiting stenosis. The accuracy of FFR was validated extensively in the past three decades, in different clinical settings including single-vessel disease, multi-vessel disease, anatomical location of disease (i.e. ostial) and in patients with previous myocardial infarction. The major studies are reviewed in this section. All are limited by the lack of a 'gold standard' investigation with which to compare FFR.

FFR was first validated against exercise testing in patients with single vessel disease. The earliest study to produce a valid cut off value for FFR that could be assumed to induce ischemia was done in 1995. The study showed strong correlation (r=-0.75) between lesions with FFR >0.72 and ECG changes (ST-segment depression) at peak exercise with a diagnostic accuracy of 87% (De Bruyne *et al.*, 1995). All patients who were positive at ET underwent single vessel PCI and had FFR measurement before and after revascularisation. Repeat ET was completed one week after the procedure to identify FFR values that were associated with a normal ET, and which were ischemia inducible values. The study suggested a value of 0.74 to be a reliable threshold to determine functional severity with a diagnostic accuracy of 97% (Pijls *et al.*, 1995). One year later, the same group conducted another validation study, but with three non-invasive stress tests (ET, dobutamine stress echocardiogram (DSE) and thallium scintigraphy). All patients with FFR value of ≤0.75 showed reversible ischemia on at least one of these tests, which were repeated after revascularisation (PCI or CABG), and the diagnostic accuracy was 93% (Pijls *et al.*, 1996). Other studies have validated FFR in multi-vessel disease by comparing it with DSE and thallium scintigraphy mainly. A cut-off value of 0.75 was agreed except for one study which suggested 0.76. However, diagnostic accuracy was lower in MVD compared to SVD, ranging from 69 to 81% (Chamuleau *et al.*, 2001; Rieber *et al.*, 2004; Erhard *et al.*, 2005). A cut off value of ≤0.80 is now used routinely in clinical practice to increase measurement sensitivity. The difference between the two cut off points (0.76-0.80) is termed the ‘grey zone’, in which the interventionist’s decision making is important to decide on revascularisation (De Bruyne and Sarma, 2008).

1.3.3.3 Evidence for the clinical utility of FFR

The accuracy of FFR in discriminating functional stenoses has led to multiple studies that aimed to focus on its role in improving management of coronary artery disease in the cardiac catheterisation settings.

Benefit from FFR in moderate coronary stenosis

FFR may be most useful in moderate lesions, where the decision to intervene or not might be unclear based upon the ICA alone. The first study to report deferring the treatment of physiologically non-significant stenoses based upon FFR measurements was the DEFER study (Bech *et al.*, 1998), in which 325 patients were studied. Those with FFR >0.75 were randomly assigned to 'perform' (PCI) and 'defer' (no treatment) groups, whilst treated significant lesions were the 'reference' group. The five-year outcome showed no significant difference between the groups in event free survival (80% vs 73%, p=0.52) for 'defer' and 'perform' groups respectively. The composite rate of cardiac death and MI was higher in the 'perform' group compared to 'defer' (3.3% vs 7.9%, respectively), whilst the 'reference' group was the highest at 15.7%. It was concluded that deferring moderate stenosis with FFR of >0.75 is safe (Pijls *et al.*, 2007). At 15 years, the rate of MI was significantly higher in the 'perform' group compared to 'defer' group (10% vs 2.2%, p=0.03), whilst the difference in mortality remained non-significant between the two groups p=0.79 (Zimmermann *et al.*, 2015).

FFR utilisation in CCS

As FFR has proven to be an important tool to discriminate ischemia-inducing stenoses, in addition to the proven safety in deferring lesions with an FFR of >0.75, large randomized trials were conducted to understand its utility in patients with symptomatic CAD.

FFR-guided PCI

The FAME study investigated the role of FFR-guided PCI in MVD compared to ICA-only guided PCI in 1005 patients. Patients were included if there were at least two major coronary vessels with at least 50% diameter stenosis, and then randomised to receive stents based upon FFR and angiogram (FFR-guided group) or angiographic finding alone (angiography-guided group). In the FFR group, any lesion with FFR ≤0.80 underwent PCI (Tonino *et al.*, 2010). At one year, FFR-guided

PCI was associated with a lower rate of myocardial infarction and death compared to the angiography-guided group (13.2% vs 18.3%, p=0.02, respectively). Also the FFR-guided approach resulted in a reduced number of deployed stents (1.9±1.3 vs 2.7±1.2 p<0.001). There was no significant difference in angina symptoms (p=0.2) and number of indicated lesions per patients (p=0.34). At two years, there were similar results, MACE being significantly lower in the FFR-guided group compared to angiography-guided group (17.9% vs 22.4%, p=0.08, respectively), as was the rate of death and myocardial infarction (8.4% vs 12.9%, p=0.02) (Pijls *et al.*, 2010). However, at five years, the difference between the two groups in MACE diminished (28% vs 31%, p=0.31) (Van Nunen *et al.*, 2015). FAME was the first trial to favour the use of FFR-guided PCI over an ICA--guided approach, and showing positive outcomes up to 5 years. FAME-2 was a multicentre randomised clinical trial that compared FFR-guided PCI with optimal medical therapy (OMT) alone in 888 patients with FFR of ≤0.80. Non-significant lesions (n=332) were entered into a registry and received OMT only (De Bruyne *et al.*, 2012). The primary endpoint (a composite of death, MI, or urgent revascularisation) was significantly different between the groups (12.7% vs 4.3%, p<0.001) for OMT vs FFR-guided intervention respectively. This was primarily driven by the high rate of urgent revascularisation in the OMT group (11.1% vs 1.6%, p<0.001). These findings resulted in halting the recruitment prematurely. At three and five years, MACE remained significantly higher in the OMT group compared to PCI-guided intervention (22% vs 10.1%, p<0.001) and (27.0% vs 13.9%, p<0.001), respectively. It was concluded that FFR-guided revascularisation provides more value compared to OMT alone in CCS, whilst medical management is adequate for non-significant lesions(Fearon *et al.*, 2018; Xaplanteris *et al.*, 2018). The findings from the FAME trials demonstrated that FFR to guide intervention is superior to ICA in assigning treatment and a proof of its clinical applicability in short and long term outcomes.

FAME 3 was a multicentre randomised trial comparing CABG with FFR-guided PCI. Multiple large randomised clinical trials have shown that treating MVD with CABG has better outcomes compared to PCI. However, it is argued that FFR-guided PCI might show non-inferiority to CABG as there was a lack of data to compare the two. The one year findings failed to prove non-inferiority of FFR-guided PCI in MVD to CABG, mortality and MI, stroke and repeat revascularisation was lower in the CABG group 6.9% vs 10.6% (Fearon *et al.*, 2022). However, there are some points that

should be considered in this trial. First, FFR was not performed equally in both groups; in fact in the CABG group FFFR was performed in 10% only. This means that some lesions were bypassed although they were not necessarily physiological significant. Moreover, the FFR-guided PCI design of the study resulted in treating only physiologically significant lesions which may result in having more complex cases on the PCI arm and negatively skewing the data.

FFR influence in management strategy

The first study to investigate the role of FFR in influencing the management plan was the FFR-R3F multicentre registry. The objective of the study was to evaluate the rate of reclassification of coronary revascularisation based upon FFR during diagnostic angiography in 1075 patients with at least one ambiguous coronary lesion. Initial revascularisation strategy were recorded before measuring FFR and based on angiography alone (Van Belle *et al.*, 2013). The initial distribution of treatment plan for medical therapy, PCI and CABG was 55%, 38% and 7%, respectively. After FFR measurement, that was changed to 58%, 32% and 10%, respectively. The final applied strategy was based upon FFR measurement in 95% of the study population, that resulted in treatment reclassification in 43% of the patients. At one year, there was no significant difference in outcome between patients whose initial strategy agreed with their final strategy and those who were reclassified. Similarly, the RIPCORD study investigated the routine use of FFR in diagnostic angiography in 200 patients with CCS. The initial strategy was recorded prior FFR disclosure, as 'medical therapy', 'PCI', 'CABG', and 'more information needed'. When FFR was given, the management plan was changed in 26% of the cases suggesting that significant stenosis was reported incorrectly in 32% of the cases based on coronary angiogram only (Curzen *et al.*, 2014). The POST-IT trial evaluated the effects of routine measurement of FFR upon management and outcomes in 918 patients with 1293 lesions (Baptista *et al.*, 2016)(Van Belle *et al.*, 2017). Patients were included in whom the FFR was measured in at least one vessel. Change in management was assessed per patient and per vessel, and management strategies were medical therapy, revascularisation, or additional stress imaging. The management plan was changed in 44.2% of the patients and 45.2% of the lesions. At one year, MACE was lower in patients with lesions FFR>0.8 compared with those who had revascularisation (5.3% vs 7.3%). The DEFINE REAL study investigated physiological assessment in MVD. Overall management was reclassified in 45.7%,

whilst vessel management was reclassified in 30.0%. (Van Belle *et al.*, 2018). It can be concluded that incorporating FFR in routine diagnostic angiography is associated with a reduction in intervention and a considerable change in management strategy.

FFR utilisation in acute coronary syndrome (ACS) patients

Although FFR is well-established in CCS, its role in ACS is less clear. The FAMOUS-NSTEMI study randomised patients with non-ST segment myocardial infarction (NSTEMI) with one or more coronary stenosis >30% to FFR-guided PCI and angiogram-guided PCI. The FFR group was associated with more deferral (22.7% vs 13.2%, p=0.02). At one year, the FFR group had a lower revascularisation rate compared to the angiogram-guided group (79% vs 86.8%, p=0.054) and there was no significant difference in MACE rates (p=0.89). FFR-guided PCI was responsible for changes in treatment plans in 21.6% of the patients (Layland *et al.*, 2015). In the COMPARE-ACUTE trial, FFR-guided complete revascularisation of the non-infarct related artery was compared to culprit only revascularisation in STEMI patients with MVD. Patients were randomly allocated in each group in a 1:2 ratio, complete and culprit only respectively. FFR was performed in both groups but was disclosed only in the FFR-guided group. At one year, the rate of MACE was significantly lower in the FFR guided complete revascularisation compared to culprit only revascularisation group (8% vs 21%, p<0.001), respectively. Interestingly, half of the non-infarct related lesions that were considered significant on the ICA were found to be functionally non-significant and deferring these lesions was safe and efficient (Smits *et al.*, 2017). The DANAMI-3-PRIMULTI study, of similar design, randomised patients with STEMI to FFR-guided complete revascularisation vs culprit only revascularisation in MVD patients with STEMI (Engstrøm *et al.*, 2015). The findings in 627 patients were significant reductions in all-cause mortality, recurrent MI and repeat revascularisation in the complete revascularisation group (13% vs 22%, p=0.004). This finding was mainly driven by the reduction in repeat revascularisation.

Theoretical Limitations of FFR

Despite the strong clinical evidence for FFR and the positive outcomes that have followed over the years, FFR still has theoretical and practical limitations. Theoretically, FFR is based upon multiple physiological assumptions, and therefore may not be completely accurate. In FFR, pressure is used as a surrogate to quantify flow, assuming a perfect linear relationship, with MVR being minimal and constant. However, the relationship between pressure and flow can be more complicated, particularly when perfusion pressure is low. Perfusion pressure is the dynamic force that drives flow across the artery, therefore, low perfusion pressure results in low flow velocity. It is known that flow acceleration (Bernoulli's law) and energy loss (due to friction) are determining factors in pressure drop. Low velocity might underestimates the pressure gradient at the presence of a stenosis and therefore, FFR (van de Hoef *et al.*, 2012). FFR also fails to take microvascular dysfunction into account. Microvascular resistance (MVR) is assumed constant and minimal at hyperaemia in the presence ($R_{Stenosis}$) and absence (R_{Normal}) of coronary stenosis and, therefore, these cancel out when calculating FFR=$\frac{(P_d-P_v)/\cancel{R_{Stenosis}}}{(P_a-P_v)/\cancel{R_{Normal}}}$. Omitting MVR resistance is governed by achieving maximal hyperaemia, and failure to do so will influence FFR measurement. Therefore, external factors such as caffeine intake before the procedure might affect vasodilatation and result in inaccurate FFR (Matsumoto *et al.*, 2014). In addition to the two assumptions discussed above, venous pressure is negligible and assumed to be zero, FFR=$\frac{(P_d-\cancel{P_v})}{(P_a-\cancel{P_v})}$ leading us to the simplest form of the equation FFR=P_d/P_a. Venous pressure is typically close to zero (1-6 mmHg); however, using a fixed value such as 5 or 10 mmHg or assuming *Pv* is zero is associated with significant error in low FFR values. The sensitivity of FFR is significantly reduced (64%) when Pv is assumed to be zero. However, that was during the >0.75 threshold era, and the adoption of a ≤0.8 threshold reduced this misclassification (Divaka *et al.*, 2004). It is understandable that acquiring a true individual value for P_v is not simple, because it requires extra vascular access and is time consuming. It is also important to state that the first study to validate FFR by Pijls and colleagues considered simultaneous P_v *(central venous pressure),* P_d and P_a measurements to produce the outstanding early findings of FFR.

Practical Limitations of FFR

Decision making in medicine is driven by different factors, but it is most favoured when there is a binary cut-off value that aids excluding interventions (treat vs defer). This was applied in FFR and early findings showed high accuracy in detecting ischemia inducing lesions at a cut off value of ≤0.75 and it was later evidenced by the DEFER trial (Pijls *et al.*, 1995, 1996; Bech *et al.*, 1998). However, the landmark trials of FAME and FAME 2 increased the FFR cut off value to ≤0.8, justifying that by the small number of patients that FFR was previously validated on, and the fact that the non-invasive imaging modalities that were used had their own limitations as well (Tonino *et al.*, 2010; De Bruyne *et al.*, 2012). Both cut off values yielded significant outcomes in favour of physiological assessment to discriminate flow-limiting stenoses. This led to create a grey-zone between the two cut off values. On the one hand, FFR carries significant prognostic and diagnostic values; the lower the value, the more the benefits gained from revascularisation. On the other hand, other factors need to be considered when the FFR value is measured in the grey zone. Following from that, it was reported that decision making certainty was at its lowest when FFR values were measured at 0.8 compared to a closer range (0.77 to 0.83) and a wider range (<0.75 and >0.85). FFR was associated with a diagnostic certainty of 50%, 80% and 95% respectively (Petraco *et al.*, 2013). Other procedural difficulties include pressure signal drift (PD) from the wire transducer. Analysis of 1218 FFR measurements revealed that 39.3% showed pressure drift, resulting in 3.6% reclassification (Wakasa *et al.*, 2016). It is recommended that PD difference of >5 mmHg requires repeat FFR measurement and ±5 mmHg should be taken into account when calculating FFR (Vranckx *et al.*, 2012). FFR is time consuming and increases the up-front costs; especially for the pressure wire (about £500). Also administration of hyperemia can cause discomfort for patients and it is contraindicated for severe asthmatics.

1.3.4 Resting pressure indices

FFR remains the gold standard tool to assess functional ischemia, and the body of evidence that support its use is robust. However, some of its limitations have been addressed earlier and one of them is the induction of hyperaemia. Alternatively, non-hyperaemic pressure ratios (NHPRs) have been introduced as a possible alternatives to FFR. To understand how the resting indices work, it is important to remember that most of the myocardial perfusion takes place during diastole. This highlights two main points which are resting blood flow should be high and microvascular resistance ideally should be constant but not necessarily minimal. This form the fundamental methodological concept of what is known as diastolic indices . Alternatively, whole-cycle indices, which follow similar assumptions of FFR (P_d/P_a) form the second category of the resting indices. Figure 1.6 illustrates different resting indices and the period in which they were measured.

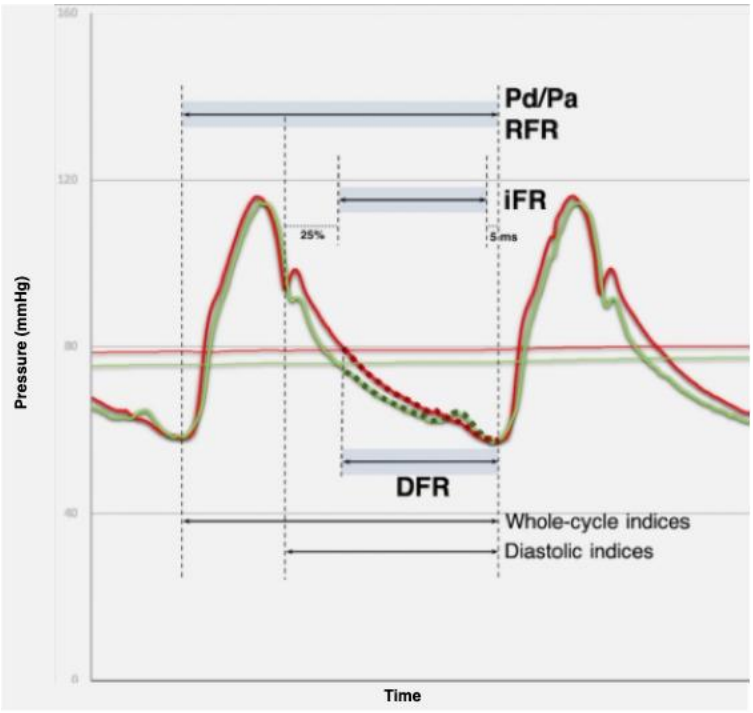


Figure 1.6 Commonly available resting pressure indices.

Period of cardiac cycle is represented for each index. Pd/Pa, ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state; RFR, resting full-cycle ratio; iFR, instantaneous wave. Reproduced with the permission of BMJ – Open Heart via copy rights clearance (5490261420838).

1.3.5.1 Instantaneous wave-free ratio

Instantaneous wave-free ratio (iFR) was developed as an adenosine-free alternative to FFR. iFR is measured during the wave-free period, which is a portion of diastole where MVR is low and stable (Sen *et al.*, 2012). The ADVISE study demonstrated the concept of iFR and validated it against FFR. iFR showed similar resting resistance during the wave-free period to the values reached during adenosine hyperaemia and the Pd/Pa ratio obtained by iFR during the wave-free period showed close correlation with FFR. It was concluded that diastolic resistance during the wave-free period can produce an index that is efficient in identifying ischaemic stenosis (Sen *et al.*, 2012). The VERIFY study showed that the agreement between iFR and FFR was weak, particularly in the context of decision making, and iFR was not hyperaemia-independent since the parameters changed markedly (Berry *et al.*, 2013). Conversely, the CLARIFY study demonstrated close agreement between iFR and FFR with hyperaemic stenosis resistance (HSR) and they were both able to equivalently classify stenosis severity (Sen *et al.*, 2013). The iFR SWEDEHEART study was a randomised control multicentre trial aimed to compare MACE in iFR-guided vs FFR-guided PCI (Götberg *et al.*, 2017). A total of 2037 patients were recruited for the study. At one year, there was no significant difference in MACE between the two groups (6.7% vs 6.1%, p=0.007) for iFR and FFR respectively. The difference remained non-significant at 5 years (21.5% vs 19.9%). The DEFINE-FLAIR study was a multicenter, international, randomized, blinded trial with similar objective and design to the earlier study (Davies *et al.*, 2017). A total of 2492 patients were randomly allocated to FFR-guided and iFR-guided groups. At one year, there was no significant difference in MACE rate in the iFR and FFR groups (6.8% vs 7.0%, p<0.001) respectively, suggesting non-inferiority of iFR to FFR in guiding angioplasty.

1.3.5.2 Resting full cycle ratio

Resting full cycle ratio (RFR) is a full cardiac-cycle index that is based on the maximal relative pressure difference proximal and distal to stenosis. RFR is calculated as the lowest averaged pressure ratio (P_d/P_a) in five consecutive full cardiac cycles. The suggested cut off value for RFR is ≤0.89 to determine physiological significance of a stenosis. The VALIDATE-RFR study aimed to validate RFR against iFR (Svanerud *et al.*, 2018). The study compared the agreement between RFR and iFR in 651 waveforms which were obtained for iFR assessment. Correlation between the two

indices was high (R^2=0.99, p<0.001) and there was a diagnostic accuracy of RFR of 97.4%. The RE-VALIDATE RFR trial was a prospective study that aimed to validate diagnostic equivalence between RFR and iFR in clinical practice with a cut off value of 0.89 for both indices (Kumar *et al.*, 2020). FFR was used as a reference standard. The mean value for FFR, RFR and iFR was 0.80 ± 0.09, 0.90 ± 0.08, and 0.90 ± 0.08, respectively. RFR was found equivalent to iFR (95% CI:0.025-0.019) with high diagnostic accuracy (97.8%). Moreover, RFR diagnostic performance has also been compared to FFR in 'real world' settings. Findings from 712 coronary lesions (617 patients) demonstrated a correlation between RFR and FFR (r=0.766, P<0.01) with diagnostic accuracy of 78% (Wienemann *et al.*, 2021).

1.3.5 Assessment of flow

Reduced blood flow to the myocardium is the fundamental pathophysiology of ischemic heart disease. Thus, the assessment of CBF is an attractive choice to assess the significance of CAD, especially because FFR is only a surrogate for flow. Coronary flow reserve (CFR) is defined as the ratio of maximal flow at hyperaemia to the resting flow. CFR measures flow in the entire coronary circulation, including epicardial and microvascular flow, unlike FFR, which simply assesses the epicardial stenosis (Figure 1.7) (Joye *et al.*, 1994)). CFR can be measured invasively through two methods; thermodilution (CFR_{thermo}) and Doppler velocity ultrasound ($CFR_{Doppler}$). In the case of thermodilution, CFR_{thermo} is measured by injecting room temperature normal saline through the coronary artery and calculating the mean transit time at the end of the pressure-wire which is supplied with a thermistor. The resting and hyperaemic mean transit time is then calculated and the ratio of the two is reported as the CFR (Barbato *et al.*, 2004). $CFR_{Doppler}$ is measured using a Doppler tipped guidewire that is able to measure coronary flow velocity, assuming velocity and flow are proportional. The ratio of average peak velocity is measured at rest and hyperaemia to calculate CFR (Piek *et al.*, 2000). Both flow assessments are technically challenging and possess some practical limitations (consistency of saline injection for thermodilution, and directionality of the Doppler wire) that made their use mainly confined to research. Moreover, invasive CFR is not routinely utilised in today's practice, which can be attributed to the complexity of the technique, skill and experience required to produce reliable and accurate outcomes. One of the limitations is

that changes in systemic hemodynamic (HR, blood pressure or LV contractility) have significant impact upon resting flow, and therefore CFR (de Bruyne *et al.*, 1996). A clear cut-off value for CFR might be difficult to be identified, due to the wide range of normal CFR value (2 to 6), and any given value in this range might be normal for some patients and abnormal in others (Fearon, 2018). Also CFR, measuring flow in the entire coronary system, cannot distinguish a significant stenosis from a microvascular dysfunction (Ng, Yeung and Fearon, 2006).

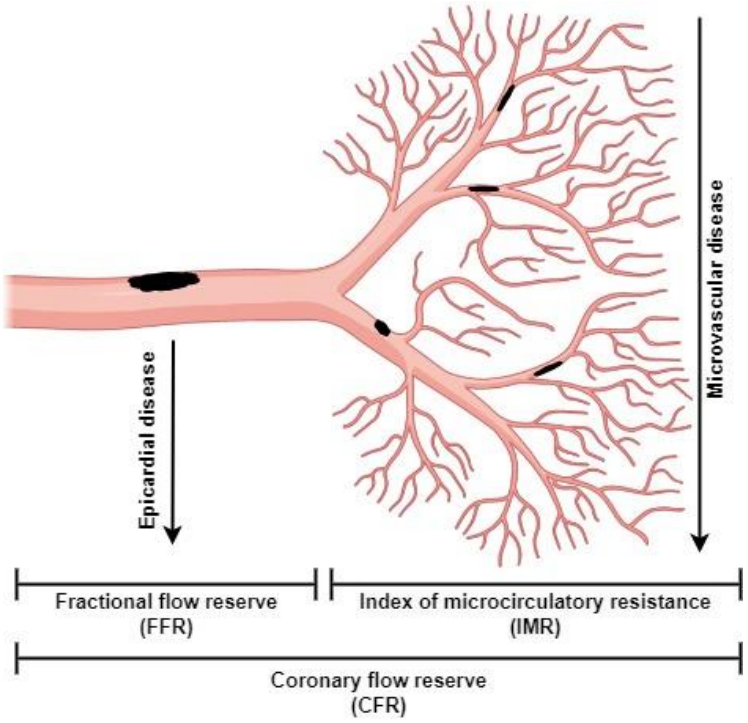


Figure 1.7 Demonstration of coronary vasculature at presence of epicardial and microvascular diseases.

FFR neglects the increase in microvascular resistance whilst CFR relies upon microvascular resistance in its calculation. Created with (BioRender)

1.4 Computational modelling of coronary blood flow

Computational fluid dynamics (CFD) is a field in which systems that involve flow of fluid, transfer of heat or related phenomena are analysed using computer-based simulation. It is a powerful and safe tool and it is used in different applications including aerodynamics, hydrodynamics, and other engineering uses (Katz, 2012). CFD is a technique that analyses and predicts the fluid's dynamic properties by solving the Navier-Stokes equations governing fluid flow, encompassing energy,

momentum and conservation of mass (Morris *et al.*, 2015). CFD has been used to model blood flow within arteries and veins, especially coronary arteries. The benefit of CFD is its ability to simulate fluid dynamics in specific regions which are difficult to study through seven essential stages (table1.1). CFD has been applied to the physiological assessment of CAD. To produce functional information, including FFR, both anatomical and physiological inputs are required. Fluid movement is solved by using CFD, and anatomy is reconstructed from coronary imaging. Different software systems have been utilised to construct 'virtual' FFR (vFFR) using invasive coronary angiography and CT coronary angiography. Both have demonstrated promising outcomes and have been investigated. Development of computer-based vFFR can provide wide availability of physiological assessment, as FFR is being measured in less than 10% of PCI procedures around the United Kingdom and even fewer in diagnostic procedures.

Table 1.1 Stages of computational fluid dynamics model construction in medicine

Stage	Description
Clinical imaging	Using different imaging modalities (CT, Angiography, MRI and Ultrasound) to provide anatomical and physiological features.
Segmentation and reconstruction	Creating physical bounds of the region of interest by obtaining clinical images and converting them to in-silico geometry.
Discretisation	Dividing the geometry into fixed and limited elements or time periods in order to prepare the constructed geometry for analysis (This is also known as 'meshing').
Boundary conditions	Wall, inlet and outlet are considered specific physical and physiological boundaries that are necessary to permit CFD analysis.
Simulation	Creating a solution and computer file that is able to define both boundaries' conditions and other properties (i.e. fluid movement, model and meshing details).
Post-processing	Extracting and illustrating the applicable data from the overall element.
Validation	Using the acceptable standards as a method of validating the modelled results by comparison.

These stages are reproduced from (Morris *et al.*, 2016).

1.4.1 VIRTUheart™ system: the Sheffield group

The VIRTUheart system (the University of Sheffield, Sheffield, United Kingdom) is based upon invasive coronary angiography and can generate vFFR using CFD techniques by solving the Navier-Stokes continuity equations and applying boundary conditions. Two clear diastolic ICA images with angle difference ≥30° are needed to generate vFFR in addition to good opacification and adequate contrast media injection. The first study to derive vFFR based upon ICA was VIRTU-1. This was a feasibility study that computed vFFR in 19 patients. The patients underwent elective PCI, and lesions identified were relatively simple, in native vessels with >50% diameter stenosis. Rotational coronary angiography images were used for segmentation (3D reconstruction of the coronary artery) and vFFR prediction because that system was available and thought to be necessary; later, this was changed in recognition that it is not available in all centres, and due to the limited number of images taken at end diastole. The study aimed to compare vFFR to wire-based FFR as the first of its kind and to assess the system feasibility and reliability. FFR was measured in intermediate lesions if indicated and post stent FFR was measured in stented vessels. Thirty five matched data sets were analysed, 12 left coronary artery (LCA) and 10 right coronary artery (RCA). A binary cut off value ≥0.80 was used for both vFFR and FFR for diagnostic accuracy. Measured and virtual FFR were highly correlated (R=0.84); the average absolute error was ±0.06 (p=0.08) and diagnostic accuracy was 97% (Morris *et al.*, 2013). There were some limitations: the number of patients was modest, which is understandable for a feasibility and hypothesis generating study; and the computation time was long (up to 24 hours), which is impractical, although this was improved significantly in later studies. However, the outcomes of VIRTU-1 were encouraging and led to subsequent studies and developments to the system. The VIRTU-FAST study aimed to address the long processing time due to using a fully transient CFD analysis. The study proposed pseudo-transient (nine parameters) and steady state (four parameters) novel protocols to perform CFD analyses. The findings were that the novel pseudo-transient protocol was able to generate vFFR in <4 minutes with 100% accuracy compared to the fully transient CFD analysis. The pseudo-transient model proposed by Morris et al., (2017) takes the luminal boundary condition, derived from angiograms, and using less expensive steady-state calculations, extracts from this geometry a Bernoulli resistance to represent any stenosis. Furthermore, the workflow then adds, a micro-

vascular resistance to produce a compartmental or 0D representation of the artery, This was then subject to pulsatile pressure and/or flow boundary conditions, resulting in pseudo-time-dependant flow. Of course, this computation of flow contains much less information than would be obtained from the full velocity field computed by the expensive, traditional fully transient analysis. Steady state analysis, which is even simpler, yielded similar results, suggesting that reliable vFFR can be generated with standard computers and therefore utilisation in clinical practice is feasible. Furthermore, the authors concluded that MVR had the highest impact upon vFFR sensitivity. Thus, a more personalised, patient-specific tuning is needed to improve vFFR accuracy and to accurately represent MVR (Morris *et al.*, 2017).

The Sheffield group has developed another novel technology, virtual coronary intervention (VCI), introduced to plan treatment based upon angiogram images. The aim was to predict physiological responses to stent deployment using CFD including a radius correction tool to replicate a deployed stent. This study was the first to simulate stent implantation based solely upon ICA and to obtain accurate physiological responses post-stenting. FFR was measured pre and post-PCI, vFFR was then generated before PCI and post VCI in 59 vessels. Pre-PCI mFFR and vFFR showed high correlation (R=0.87), with diagnostic accuracy of 93%. Post-PCI mFFR and post VCI vFFR showed good correlation as well (R=0.80). Interestingly, this model was able to produce these outcomes with comparable time to FFR which makes it practical for patient-specific treatment-planning (Gosling *et al.*, 2019).

A further development of the VIRTUheart system is a tool for novel measurement of coronary absolute flow (Q_{CFD}) and MVR (Morris *et al.*, 2021). Absolute flow was measured *in vitro* (flow circuit) and *in vivo* to validate the tool. *In vitro*, Q_{CFD} and experimental flow agreed closely (R^2=0.999 p<0.001). *In vivo,* Q_{CFD} and MVR at rest and hyperaemia were used to calculate Q_{CFD}-derived CFR which showed good correlation with pressure-derived CFR (R^2=0.92, p<0.001) in 40 patients. Further comparison with Doppler-derived flow showed that this method was significantly more accurate *in vitro* and *in vivo than Doppler.* Incorporating coronary absolute flow and MVR alongside FFR in decision-making could have a key role, and further studies are needed to evaluate the tool. This modelling software will be used in this study.

As mentioned above, the VIRTUheart system provides wide range of advantages and robust potentials. Starting from the high diagnostic accuracy, to post-PCI assessment, virtual stenting and detailed virtual physiological assessment of coronary vessels.

Some of the limitations that can be linked to VIRTUheart technique in generating vFFR is that most of the studies that were used to validate it were of a modest sample size and are carefully chosen under controlled conditions. Also, personalisation are needed to tune the model, as for most of the earlier published work, population-averaged values were used. However, in later publications, some personalised inputs improved the accuracy of vFFR (Gosling *et al.*, 2022). Additionally, complex diseases, LMS stenosis and previous CABG are not suitable for modelling for various reasons including difficulty of segmentation or failure to produce the volume mesh in the cases of complex disease.

1.4.2 Other systems

The principle of deriving FFR from ICA has shown promising and encouraging outcomes which have led to the development of different systems.

CAAS™ system: PIE Medical Imaging

CAAS 3D-QCA system (Pie Medical Imaging, Maastricht, Netherlands) has been developed to include lesion assessment of functional severity. Early version of CAAS system did not actually provide vFFR, but it gives virtual functional assessment index (vFAI) based upon pressure gradients at pre-specified flow rates using CFD (Papafaklis *et al.*, 2014). The first validation study showed reasonable correlation between vFAI and FFR ($R=0.78$, $p<0.0001$) and modest agreement ($p=0.59$). vFFR was then utilised into the CAAS workstation (conventional method of Pd/Pa). The CAAS vFFR was first evaluated in the FAST I study, which assessed 100 patients and demonstrated high accuracy and reproducibility (93% and 95%) when compared with wire-based FFR (Masdjedi *et al.*, 2020). This was followed by the FAST EXTEND study which was of a larger study population ($n=296$). The diagnostic accuracy of core lab analysis to discriminate significant lesions (FFR <0.8) remained high 94% (Neleman *et al.*, 2021). Both studies demonstrated excellent outcomes, leading to the international multicentre FAST II study, including 334 patients to study diagnostic

accuracy of CAAS vFFR on-site (local operator in the catheterisation laboratory) and offline (core laboratory) in comparison with wire-based FFR (Masdjedi *et al.*, 2022). There was high diagnostic accuracy for on-site (91%) and blinded core lab analysis (93%). Moreover, mean vFFR value analysed on site was 0.82 ±0.10 and core lab was 0.83 ±0.09, whilst the reference mean value was 0.83±0.08. The FAST III study is designed to determine the safety and effectiveness of vFFR. This randomised controlled multicentre trial aims to compare vFFR-guided PCI strategy to FFR-guided PCI strategy to guided coronary revascularisation.

QFR™: Medis Medical Imaging

Quantitative flow ratio (QFR) is generated using a combination of anatomical reconstruction from ICA an estimate of flow derived from thrombolysis in myocardial infarction (TIMI) frame count to calculate the mean flow-rate at hyperaemia as the input for the CFD and 3D quantitative coronary angiography (QCA). QFR showed good correlation with FFR when was first analysed in 77 vessels ($R=0.81$, $p<0.001$) and high diagnostic accuracy (88%)(Tu *et al.*, 2014). The FAVOR pilot study compared wire-based FFR and QFR analysed in core laboratories. The study derived flow from three different models; (1) fixed-flow QFR [fQFR], (2) contrast-flow QFR [cQFR], and (3) adenosine-flow QFR [aQFR]. Analysis of 84 vessels showed good agreement between all three models with FFR. Overall diagnostic accuracy for each method was fQFR (80%), cQFR (86%) and aQFR (87%). (Tu *et al.*, 2016). cQFR showed close diagnostic accuracy to aQFR, despite the latter being at hyperaemic state. Thus, the FAVOR II study compared cQFR with invasive FFR in routine coronary angiography in a prospective multicentre study. Study findings demonstrated good agreement between the two FFR methods ($p=0.006$) and high diagnostic accuracy (92.7%) for on-site analysis, and (93.3%) for offline analysis (Xu *et al.*, 2017). The FAVOR III China was a multicentre randomised, sham-controlled trial with the objective of comparing QFR-guided strategy to angiography-guided strategy in guiding coronary revascularisation. A total of 3825 patients were randomised into each group, both stable (36.5%) and acute (63.5%) patients being included. At one year, QFR-guided strategy improved outcomes and was associated with lower MACE rates (5.8%) compared to angiography-guided strategy (8.8%) (Xu *et al.*, 2021).

1.4.3 Comparison between the current technologies

Deriving FFR from coronary angiography can be classified into two categories, the first is based on CFD and the second is based on simplifying the fluid motion using different mathematical formulas including Bernoulli and Poiseuille as described in the theory of FFR section. To elaborate, the CFD technique generates pressure throughout the produced model, requiring boundary conditions at inlet and outlet. An example of CFD model is the vFFR, in which 3D reconstruction and boundary conditions are provided to the system. Other systems that are based on mathematical formulas and 3D reconstructions require further inputs such as TIMI frame counting empiric hypermeic. A summary table showing the different techniques is presented in table 1.2.

Table 1.2 Comparison between the covered angiography-derived FFR technologies

Technology	Model	Inputs
vFFR (VIRTUheart)	CFD	• 3D model geometry • Two projections ≥30° difference • Aortic pressure • Generic outlet resistance
CAAS-FFR (Pie medical imaging)	Mathematical formula	• 3D model geometry • Two projections ≥30° difference • Aortic pressure • Empiric hyperemic flow
QFR (Medis medical imaging)	Mathematical formula	• 3D model geometry • ≥ two views ≥25° difference • TIMI frame counting

vFFR= virtual fractional flow reserve, QFR= quantitative flow ratio, CFD= computational fluid dynamics, TIMI= thrombolysis in myocardial infarction and 3D= three dimensional.

Advantages and disadvantages of angiography-derived FFR

For patients being evaluated for revascularization, especially those scheduled directly for ICA, angiography-derived FFR proves to be an ideal all-in-one test. During the procedure, vFFR (or other technologies) has the potential to provide quicker and improved decision-making. The significant benefit it offers is the ability to provide an initial physiological assessment within any diagnostic coronary angiogram, including non-tertiary centres, without requiring extra equipment, pressure-wires, interventionists, or increased costs. Most importantly, the increased availability of these technologies can result in increase the number of physiological tests (which is considerably low

where less than 10% of the procedures in the UK measure FFR). Additionally, if validated well, these techniques may provide a key role in decision making inside the cardiac catheterisation suits. Conversely, there are some limitations associated with the use of these methods. To start, all these methods fail to represent patient-specific physiology, as many variables are based on population averages as previously mentioned. There are two main component that cannot be measured precisely with angiography derived FFR, and these are microvascular resistance and hyperemic flow. Both are very important compartments in the measurement of FFR and building on the measured value. Due to the nature of the acquired images (2D), there are certain lesions that are difficult to reconstruct such as those located in a bifurcation with excessive overlapping or those located in ostiam like LMS where there is lack of healthy segment of the vessel to reconstruct.

It is worth highlighting that all these methods are dependent on high quality coronary angiogram (i.e. high contrast, minimal overlapping and no magnification) are required to generate reliable 3D reconstructions. Finally, as of many other modern assessment tools, anatomical modelling require extensive practice, understanding of coronary anatomy and computer skills (Lal *et al.*, 2019).

1.5 Living with CCS

Coronary artery disease is not only a leading cause of death, but also remains one of the greatest causes of morbidities. Treatments have improved and life expectancy is prolonged; however, patients still have to adapt to angina symptoms, complex managements, and limitation in physical activity. All of these factors may cause undesirable effects on patients, especially on their physical functioning, wellbeing, quality of life and lifestyle.

1.5.1 Patients reported outcomes measures in CAD patients

One of the major goals in the treatment of CAD patients is improving quality of life (Fihn *et al.*, 2012). Previously, core clinical outcomes were the focus in patient care, which are indeed necessary. However, since the 1990s, there has been increased focus on what constitutes quality of life (QoL) in IHD and CCS in particular. This has become an important aspect to investigate, in an objective and theoretical manner, and was the motive to produce patient reported outcome measures (PROMs) during this era. Furthermore, PROMs or questionnaires can be completed to investigate the effects of a specific disease in the population, to observe the general health of certain population suffering from a disease and to compare different management strategies. These research questions have been studied in IHD in particular to address angina and chest pain as a standalone life-limiting factor (i.e. Seattle angina questionnaire) or to observe the overall health in those patients (EuroQoL quality of life and short form – 12). QoL in association with coronary revascularisation of CCS was studied in different clinical trials. The first to report a comprehensive QoL assessment was the ACME trial (Parisi *et al*., 1992). The study randomised 212 patients with single vessel disease into PCI and OMT groups. Results at baseline reported no significant difference in the groups, whereas at six months the improvement in angina symptoms in PCI group was significant compared to OMT (64% vs 46%, $p<0.01$, respectively). Additionally, physical and physiological wellbeing domains were significantly improved in the PCI group after 6 months ($p<0.02$) (Strauss *et al.*, 1995). The ACME II trial was of a similar design, but studied patients with two vessel disease. There was no significant difference in QoL ($p=0.32$) and freedom from angina (0.09) between PCI and OMT groups at baseline and after six months (Parisi *et al.,* 1997). The findings of this study, suggested contradictory results to the earlier work, in which differences were significant between the groups. This could be attributed to the use of different

PROMs instruments and the extent of the disease. The MASS trial compared three management strategies; CABG, PCI and OMT (Hueb *et al.*, 1995). At three years, angina freedom rates were significantly higher in the CABG and PCI groups compared to OMT group (98%, 82% and 32%, respectively). These findings were confirmed in the MASS II trial, which had similar design, but studied MVD and used the SF-36 instrument to report QoL (Favarato *et al.*, 2007). The findings of RITA II study showed improvement in QoL, as scored by SF-36, in the PCI group compared to the OMT group, at one year. However, this difference was diminished at three years, unlike the MASS trials (Pocock *et al.*, 2000).

Both the FAME II and COURAGE trials suggested significant improvement in QoL and angina symptoms with PCI compared to OMT alone at two years when assessed by EQ-5D and SAQ respectively (Weintraub *et al.*, 2008; Fearon *et al.*, 2018). In the ISCHEMIA randomised trial, which examined invasive and conservative strategies in treating moderate to severe ischemia and health outcomes of the two strategies assessed by SAQ. The study reported improvement in the summary scores up to 3 years, however, despite the modest difference between the groups, the invasive strategy gained larger improvement (Spertus *et al.*, 2020). However, all these trials would some levels of placebo effect for patients who undergo coronary intervention and this should be acknowledged. This effect is not only observed in coronary artery disease but in different cardiovascular disease and other diseases. The first trial to address the placebo effect in PCI settings was the ORBITA trial. This was a true randomised, blinded, placebo-controlled trial, in which symptomatic patients with single vessel disease were randomised to placebo (sham) procedure or PCI (Al-Lamee, *et al.*, 2018). Patients and follow up consultants were blinded to FFR and randomisation up to six weeks when follow up was completed. Results of the study were surprising, because there was no significant difference between the groups in QoL or symptoms. Moreover, there was no significant difference between baseline and blinding period in physical limitation and angina frequency and stability when assessed by SAQ ($p=0.42$, $p=0.26$ and $p=0.85$, respectively). Additionally, there was no significant difference between the groups in EQ-5D-5L index ($p=0.99$). These findings may indicate that using questionnaires alone might not give a complete understanding of a patient's actual quality of life and symptoms status. Instead, we

might need to relate these findings to disease severity as assessed per patient level or even per lesion level, and factor in the powerful effect of a procedure, whether therapeutic or not.

1.5.2 Physical limitation and activity monitoring

Patients with CAD are expected to be less active, due to angina upon exertion. This can result in modification to lifestyle to adapt either by reducing the intensity of activity, possibly becoming sedentary if angina is more frequent. However, physical activity and CAD are also related causally. Studies have shown that inactivity and sedentary lifestyle are significant risk factors for CAD, whilst exercise and active lifestyle are associated with reduced incidence of CAD and improve survival rates (Taylor *et al.*, 2004). There are two main ways to quantify limitation of physical activity, namely questionnaires and wearable activity monitors. Several studies have reported that physical activity is limited at baseline compared to after revascularisation. This has been reported using questionnaires including SAQ, RAND 36 and SF12 (Weintraub *et al.*, 2008). However, this remains a subjective measure and might be affected by different factors at the time of questionnaire completion. Therefore, an objective method of measuring physical activity might be more useful to understand and quantify limitation associated with CAD. Monitoring in cardiology is not a new concept, despite the notable evolution of the technology in the past decade. For example, the Holter monitor has been used for decades as an ambulatory ECG that records patients' cardiac activity (Corday, 1965). Many new wearable devices have emerged over the past decade, with a remarkable adoption by researchers, clinicians, and consumers with different parameters that can be collected including arrhythmias, heart rate, and several aspects of physical activity. Physical activity measured by accelerometer was investigated in CAD patients before and after revascularisation. Results from a post-CABG monitoring study have shown a relationship between hospitalisation and activity. Increasing activity straight after CABG was associated with decreased hospitalisation time (Cook *et al.*, 2013). A direct correlation between wearable monitoring devices and increased physical activity in CAD patients was demonstrated in rehabilitation studies (Frederix *et al.*, 2015). The TEACH trial aimed to assess physical after CAD related hospitalisation compared to baseline using worn accelerometer. The study suggested that, at one year, activity levels were proportional (those who were active before admission became more active) and those

who had CABG were more active compared to PCI. Interestingly, increased in activity levels lasted up to two months and then started to decline. Nevertheless, monitoring activity levels in CAD patients remain understudied and has been addressed mainly in rehabilitation studies, although this might not representative for CAD population since it was suggested that up to 85% of these patients do not participate in rehabilitation programs (Reid *et al.*, 2006).

1.5.3 Functional capacity

An essential necessity for most of our daily activities is the ability to perform aerobic work. These types of activities are dependent upon functional cardiovascular and pulmonary systems, and their ability to deliver oxygen to the active muscles. The ability to do these activities is a simple conceptualisation of functional exercise capacity which is defined as the maximum amount of physical exertion that a person can sustain (Larson, 2007). Exercise testing has been studied in CAD as a prognostic and diagnostic evaluation method for functional capacity and it was shown to be a strong predictor of mortality and cardiovascular events (Mark *et al.*, 1987; Kwok *et al.*, 1999; Myers *et al.*, 2002). Exercise testing protocols vary. It can be performed as a treadmill exercise, or walking or cycling, under controlled settings with or without ECG monitoring. This non-invasive stress assessment has been used as a gold standard method to validate other diagnostic tools due to its robust ability in discriminating ischemia. In a cohort of 9852 patients with known CAD, either revascularised or not, the value of functional capacity value in CAD was shown. Follow up at 11 years revealed that exercise capacity is a strong predictor of MI, revascularisation and all cause mortality. Additionally, it was suggested that patients with similar capacity levels carry equivalent mortality rate despite revascularisation status at baseline (Hung *et al.*, 2014). However, an exercise test might be difficult to perform in elderly or frail patients despite being the most commonly used functional capacity test. Other forms of test can be completed, such as 'sub-maximal', walk-based testing. The six-minute walk test (6MWT) is one of the simplest tests that can evaluate a patient's functional capacity (Enright, 2003). The test has been extensively investigated in chronic diseases, including respiratory ones, such as chronic obstructive pulmonary disease (COPD), and cardiac heart failure (HF). Measures including distance walked, changes over time and response to interventions or treatment, and relationship to disease prognosis, has been studied (Du *et al.*,

2017). However, the prognostic value of 6MWT in CAD as a predictor of future events or as a tool to measure functional exercise capacity is still under-studied. A study was conducted to evaluate 6MWT predictability of MI, HF and all-cause mortality in comparison with traditional treadmill exercise test in CCS patients. The study involved 556 patients, and follow up for cardiac events and heart failure was eight years. At follow up, cardiac events occurred in 39.2%, and those who were in the lower walked distance (87-419 m) group were at four-fold risk of cardiac events compared with those in the higher walked distance (544-837 m) group ($p<0.001$). The study suggested that a decrease in walked distance by an average 104 m was associated with 55% of cardiac events. When this was adjusted for risk factors and cardiac severity measures (EF, diastolic dysfunction, inducible ischemia, and other diagnostic blood tests), the risk of cardiac events was reduced by 30%. The study concluded that 6MWT and treadmill exercise were similar in predicting cardiac events (Beatty, Schiller and Whooley, 2012). Other studies have investigated the role of the 6MWT in rehabilitation.

1.7 Aims and hypothesis

The primary hypothesis is for this thesis is:

Assessment of coronary blood flow can predict the benefit of revascularisation in CCS patients.

My overall aim is to assess the change associated with PCI in CCS patients at different levels, from coronary physiology, through myocardium, to the patient's everyday life. This will be achieved through these experimental objectives:

1- Evaluate the effect of coronary stent upon blood flow and other coronary physiology metrics using VIRTUheart™ and virtuQ™ software.
2- Compare coronary physiology in flow limiting disease and non-flow limiting disease.
3- Develop and validate a single FFR index (Cumulative FFR) based on coronary physiology and anatomy to assess CAD severity and myocardium at risk.
4- Assess physical activity in CCS patients using wearable devices and 6MWT to evaluate the changes associated with PCI.
5- Assess changes in generic and disease specific PROMs in response to PCI.

1.8 Study design and ethics

1.8.1 Study design

This was a prospective observational single centre study of elective patients with CCS who were scheduled to undergo elective PCI or left heart catheterisation ± PCI at the Northern General Hospital, Sheffield between September 2020 and August 2022 under the care of Professor Gunn or Dr Morris. Forty patients were recruited for this study, on the basis of including 20 patients at each group (intervention and no-intervention). This is a hypothesis generating work, with limited time and fund, therefore, initial plan to include 20 patients in each group was decided upon. To maximise recruitment of suitable patients, patients were identified on the basis of documented CAD either from previous procedures or at CTCA. To these patients, an information sheet (PIS) and initial approval for contact were sent by post, and patients were contacted upon their approval. A home visit was undertaken and written informed consent obtained (see appendix for PIS and consent sheet). Baseline characteristics were collected upon recruitment. Questionnaires were completed and monitoring devices set up during the study initiation home visit. Patients were contacted again for pre-procedure assessment (6MWT and CMR) prior to the PCI. The CMR data were not used in this thesis, due to some limitations that will be discussed in the next chapters. All data were anonymised and uploaded into University of Sheffield PLOARIS database. All scans were labelled by VIRTU-5 ID and can be linked to other collected data to every participant. Patients underwent their coronary angiography, multi-vessel pressure wire examination, and PCI when indicated by the FFRs. Study participants were then grouped into 'PCI' if they had interventions based on FFR in most cases, or 'control' if no intervention was undertaken on the basis of FFR cut-off value. All pressure wire assessment and coronary angiograms were repeated after the procedure if applicable. Follow up assessment was completed after three months except for CMR in the control group. The main reason to undertake CMR analysis in this study was to produce perfusion scans, therefore, patients who did not have intervention (control) did not have a follow up scan as changes cannot be measured in response to intervention and funding limitations. An overview of the protocol is illustrated in figure 1.8 and a recruitment diagram is shown in figure 1.9.

1.8.2 Selection criteria

This study included heavy screening, but limited number of recruitment (N=40). This might have caused some sampling bias during the selection process. First, only patients with documented disease either by CTCA or ICA were recruited, this was intentionally performed due to the limited sample size and to exclude patients who were listed for diagnostic angiogram only. Second, patients with severe co-morbidities such as neuropathy, chronic kidney disease, or severe mitral valve disease were excluded to avoid any effects on physical activity monitoring and PROMs. Third, patients who suffer from significant mobility impairment were excluded for the same reasons. However, this is a hypothesis generating and a proof of concept study as mentioned in the previous section, therefore, it might be understandable that restricted selection was used for the recruitment.

1.8.3 Recruitment difficulties

Apparently, the main difficulty was the inability to allocate patients into their groups at the recruitment stage. This challenge raised from the fact that this is not a randomised nor blinded study and allocation can only be decided following the outcome of the procedure. Although it is all assessment were done alike for these participants prior to their procedures, the inability to allocate participants into groups resulted in an unequal number of participants in each group (13 vs 26) for non-PCI and PCI groups respectively. Additionally, this study was considerably selective with a design that required multiple visits, some challenges were encountered. Since the cardiac catheterisation suits in Sheffield Teaching Hospitals covers most areas in south Yorkshire, some of the study participants were referred from other district hospitals. This caused considerable challenges since the study required home visits and multiple hospital visits which resulted in increased travelling time for both researchers and participants. The study design requires high collaboration from the participants, especially with the monitoring component as the data collection depends heavily on following the instructions and compliance. Therefore, extensive communication was needed throughout the involvement period to ensure that data were being collected at high standards.

1.8.4 Ethics and funding

The study was approved by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) [IRAS: 272069]. The Sheffield Teaching Hospital Cardiothoracic Directorate Research Executive (CDRE) and NIHR Cardiovascular Patient Panel (CPP) approved the study protocol. Funding was granted from Sheffield Hospitals Charity (Grant number: 192027) and King Saud bin Abdulaziz University for Health Science (KSAU-HS) through the Saudi Arabian Cultural Bureau in the UK (UKSACB) as part of an awarded scholarship to the author.

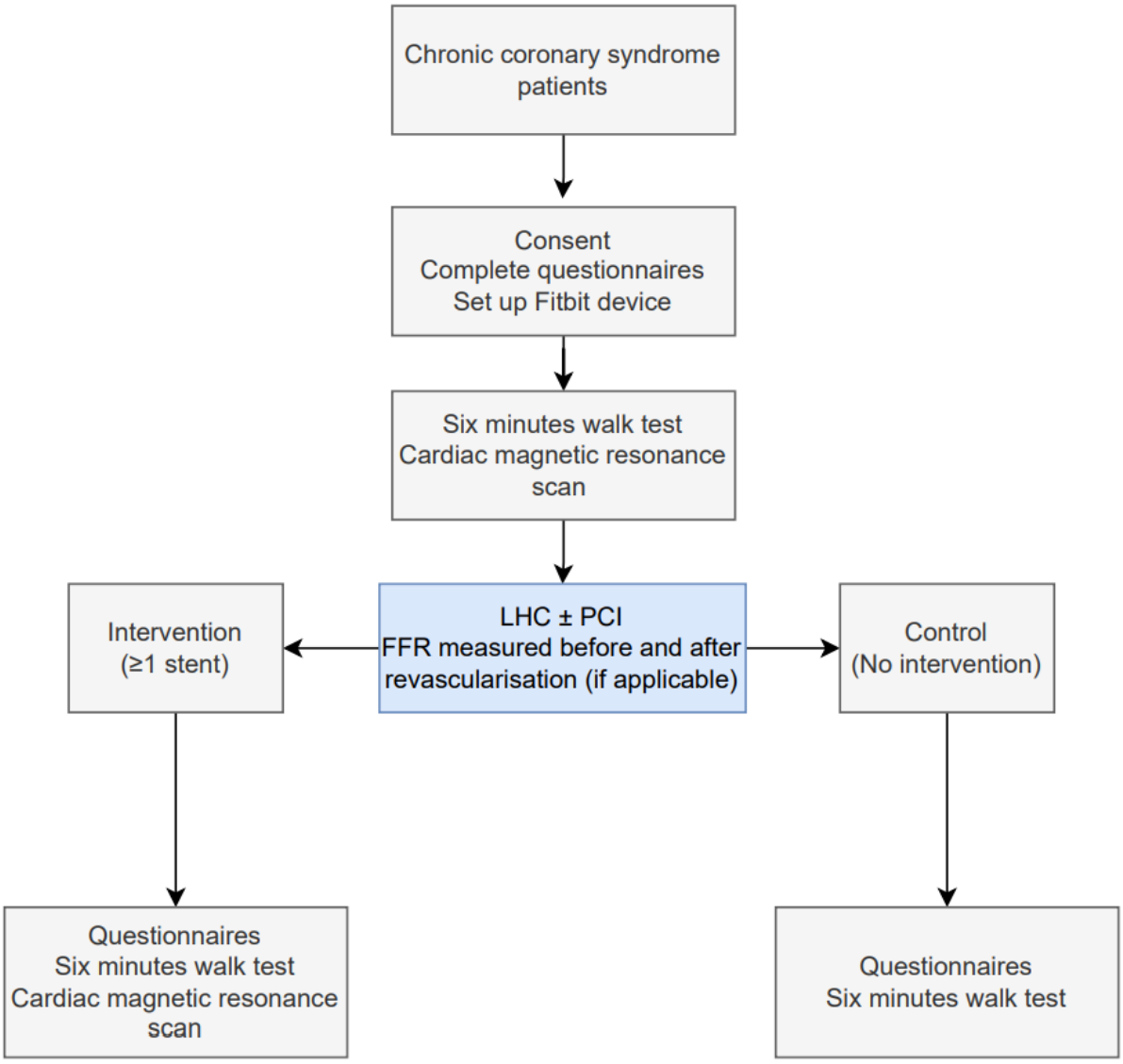


Figure 1.8 Flowchart of the overall methodology for VIRTIU-5 project.

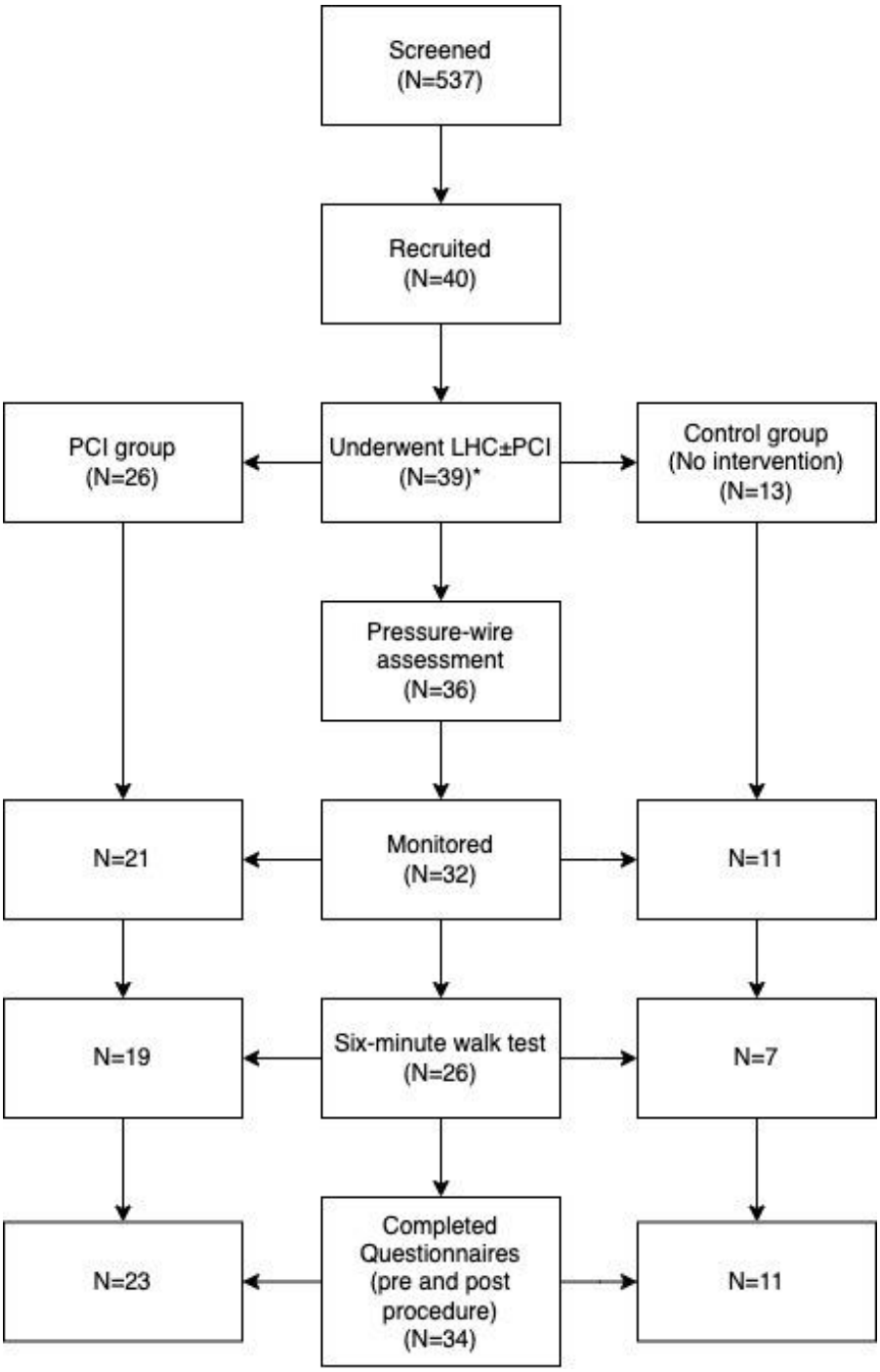


Figure 1.9 VIRTU-5 recruitment diagram

Chapter two: Revascularisation in CCS: invasive and computational assessment of coronary physiology.

2.1 Introduction

Coronary arteries response to myocardial demand by increasing blood flow significantly compared to the resting state. However, the progression of coronary stenoses results in failure to meet these demands and, when becoming flow limiting, can cause myocardial ischemia. A stenosis can be treated with PCI, aiming to dilate the narrowing and restore coronary flow. The gold standard for guiding PCI is the invasive coronary angiogram (ICA). ICA is used to assess the disease severity anatomically, but visual analysis is not accurate enough to discriminate ischemia in intermediate lesions. Up to 65% of intermediate lesions with diameter stenosis of 50-70% are not flow limiting (Tonino *et al.*, 2010). Coronary flow reserve (CFR) is used as an estimate of flow and can be measured by thermodilution or Doppler velocity ultrasound, but assessment of flow is technically challenging and has so far failed to penetrate clinical practice. However, FFR, which measures flow reduction, is more feasible, and a strong predictor of ischemia. Other physiological indices have shown to be capable to discriminate ischemia in intermediate lesions at comparable levels to FFR such as iFR (Davies *et al.*, 2017). (See Chapter1)

The past decade has seen the introduction of computational methods in the assessment of coronary artery disease. Different systems have been successful in providing reliable and non-invasive methods to assess functional severity of a stenosis, such as QFR and vFFR. The Sheffield group developed the VIRTUheart system, which was the first to derive FFR from angiographic images, with diagnostic accuracy of 97% (Morris *et al.*, 2013). The model generates vFFR using CFD techniques, and has undergone different developmental stages including reducing the processing time to five minutes, personalisation of the boundary conditions, incorporating virtual stenting and computing coronary *absolute flow and resistances* (Gosling *et al.*, 2019; Morris *et al.*, 2021; Gosling *et al.*, 2022). The tool can estimate MVR, HSR and CFR, therefore providing a comprehensive physiological assessment of coronary artery disease. (See Chapter 1)

Whilst baseline coronary assessment using FFR has been investigated extensively, post-PCI FFR (the whole point of revascularisation) has been less studied compared to pre-PCI, and its routine

use in clinical practice is considered occasional, although recent studies suggest a prognostic value (Piroth *et al.*, 2022). There is also lack of agreement in a cut-off to target best possible outcomes. The largest prospective study to investigate post-PCI FFR in stable patients reported a cut-off value of ≤0.88. It was suggested that this value was predictive of target vessel failure and cardiac death (p=0.001 and p=0.02), respectively (Li *et al.*, 2017). A combination of computational and invasive assessment could provide comprehensive physiological assessment of CAD. Additionally, the invasive measurement of FFR can be of great value to generate more information about flow and MVR.

The aim of this chapter is to evaluate the relationship between coronary physiology metrics and FFR, and to quantify the physiological change in response to PCI.

2.2 Methods

2.2.1 Patient screening and recruitment

Patients were screened who were listed for elective PCI or left heart catheterisation (LHC) ±PCI according to standard clinical criteria at the Northern General Hospital, Sheffield, between September 2020 and May 2022. See page 59 for recruitment details. All available waiting lists were screened for suitable candidates. Once candidates identified, a summary of each patient was presented to the principle investigator of the study for final selection. Patients then were contacted through the NHS prior to researchers' contact, once participants responded with intention for involvement in the study, research fellow contacted them and a visit was planned. At the home visit, baseline characteristics were collected, a monitoring device was given and questionnaires were completed (see chapters four and five for more details of those activities).

Inclusion criteria:

- Adult patients >18 years old.
- Symptomatic patients with stable angina listed for LHC±PCI.
- Previous CTCA or angiogram reporting visual stenosis of >50% in at least one coronary artery.

Exclusion criteria:

- Acute coronary syndrome.
- Severe valvular disease.
- Previous CABG or recent PCI.
- Contra-indications to CMR or adenosine.
- Renal failure (Cr >180 µmol/dL).
- Significant mobility difficulties (Further details about mobility will be discussed in chapter four).
- Multiple co-morbidities or terminal conditions.

2.2.2 Procedural protocol

Patients underwent invasive coronary angiography using standard techniques and clinical protocols, with a 6F guide catheter, in preparation for pressure wire examination and PCI. To ensure images were suitable for analysis with the VIRTUheart™ software segmentation tool, the following protocol was applied, which is the Sheffield 'standard' for modelling. The main objective was to capture at least two high quality, clear, non-overlapped images for each major vessel in diastole.

- 5-6 views for LCA and 3 of the (dominant) RCA (Figure 2.1)
- At least two views of each diseased vessel at least 30^0 apart
- Image must be centred before acquiring
- No panning or magnification
- Adequate contrast injection
- Increased Xray dose if patient is obese
- At least 4 cardiac cycles must be acquired per image
- Good catheter engagement

Patients were loaded with aspirin and clopidogrel, if not already taking those drugs, and a single dose of weight-adjusted heparin was given. A final visual assessment of all vessels was then made. Any epicardial vessels >2.5mm (i.e stentable) with diameter stenosis 30-90% were then assessed with a pressure wire (PRESSUREWIRE™ X, Abbott). This was performed according to standard practice. FFR was measured during stable hyperemia, which was induced by intravenous

adenosine infusion (70 µg/kg/min). In cases with a severe stenosis, RFR alone was recorded. The average resting pressures proximal and distal to the lesion (P_d and P_a) were also recorded. Dedicated software (Coroflow®, Coroventis, Abbott, Uppsala, Sweden) was used to measure and record FFR and RFR (Figure 2.2). Based upon the angiographic findings and the wire-based FFR assessment, a decision to proceed to PCI was made by the operator (JPG and PM). PCI was conducted according to standard contemporary practice, with implantation of a drug eluting stent. Repeat angiography and measurements of FFR were taken after PCI whenever possible. Angiogram images were anonymised and transferred to the XNAT database (University of Sheffield). Coronary pressure data were exported in the form of (.csv) files for further analysis.

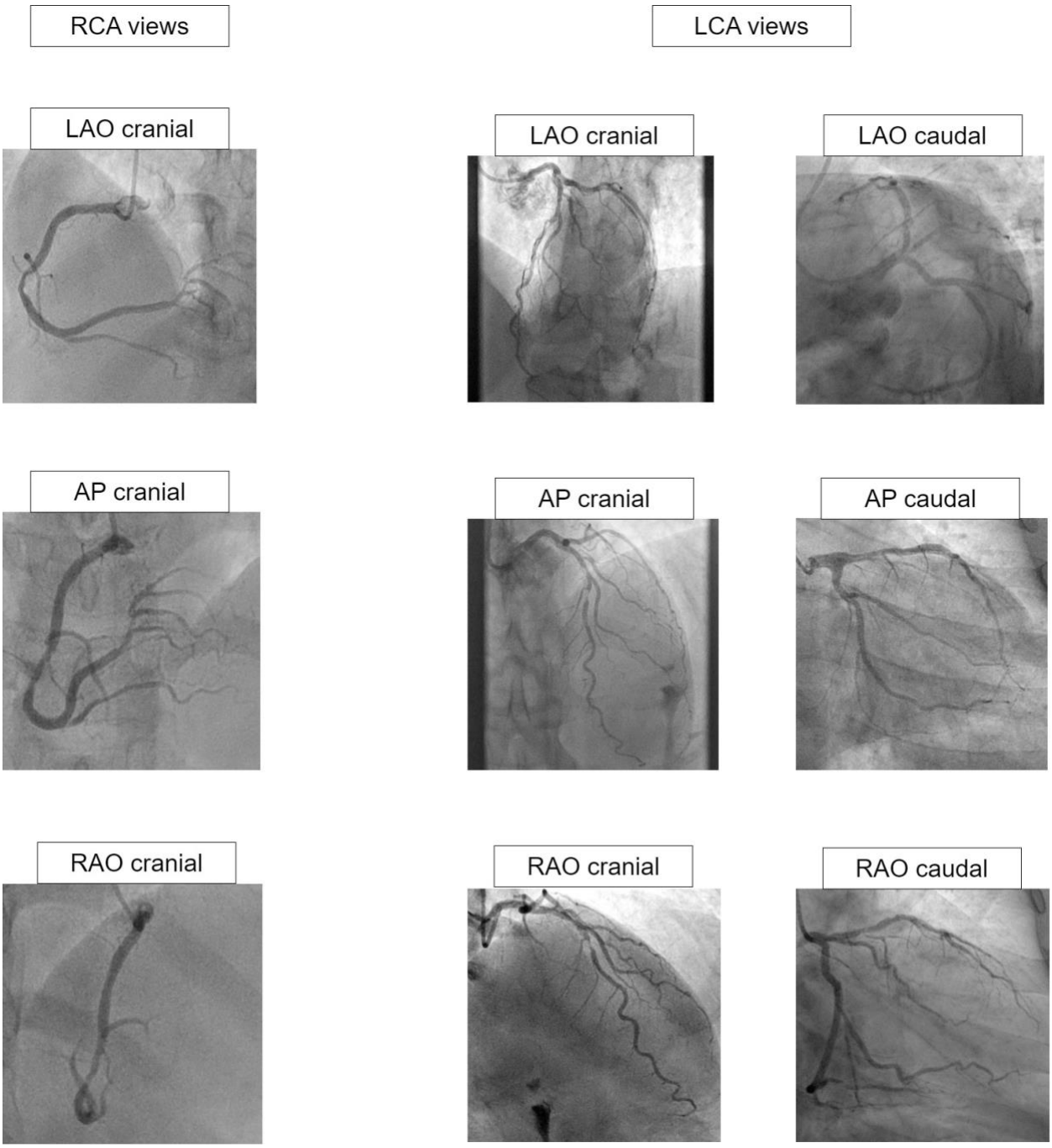


Figure 2.1 Suggested views for VIRTUheart segmentation tool.

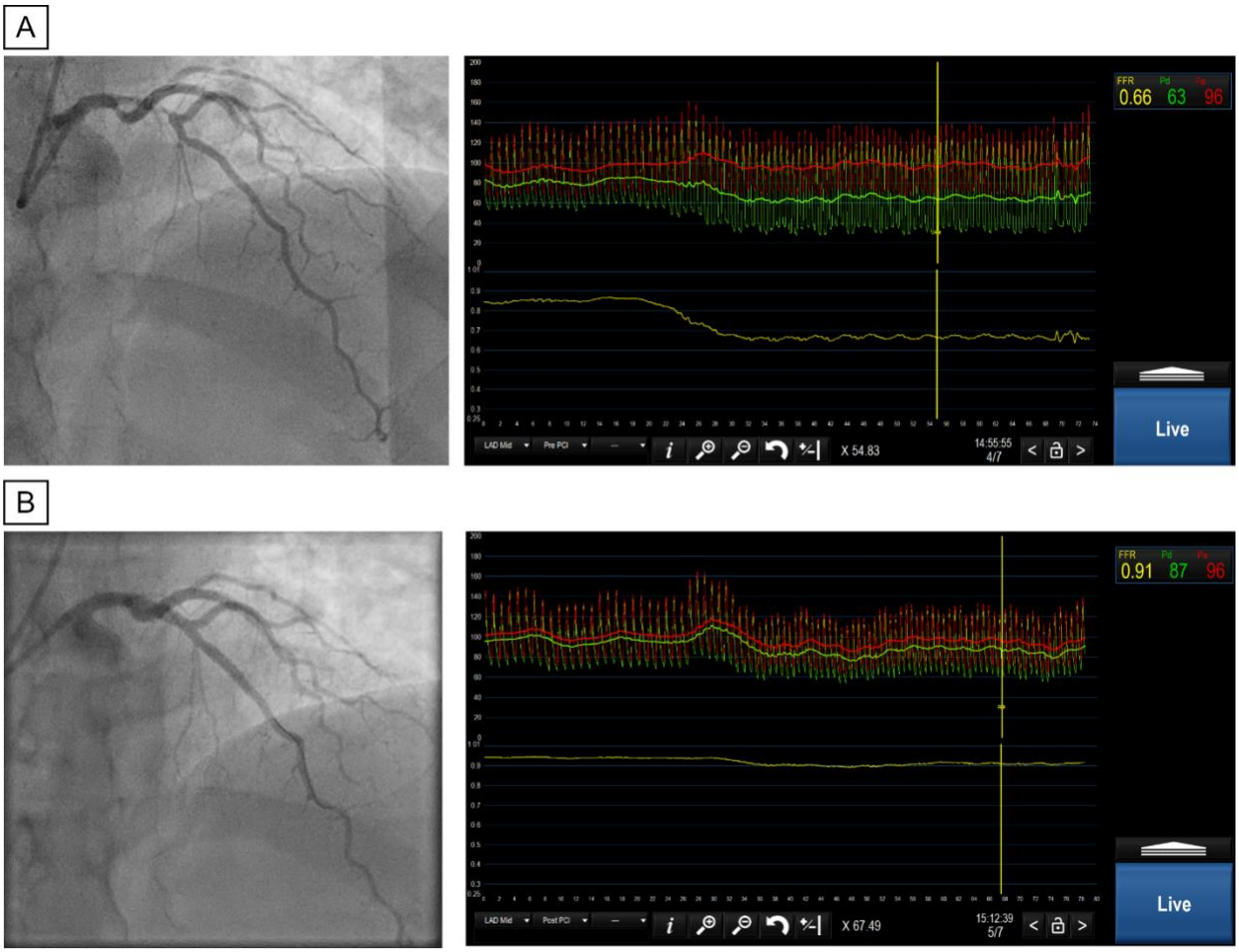
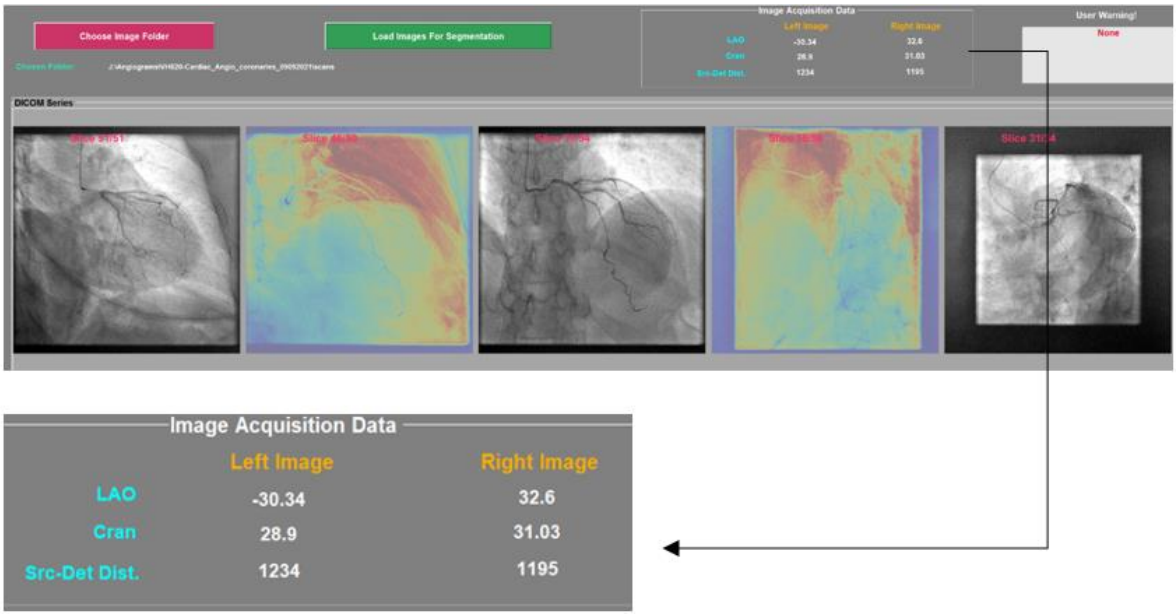


Figure 2.2 Examples of coronary angiogram before and after intervention and the corresponding invasive pressure trace as shown by Coroflow (3.0)

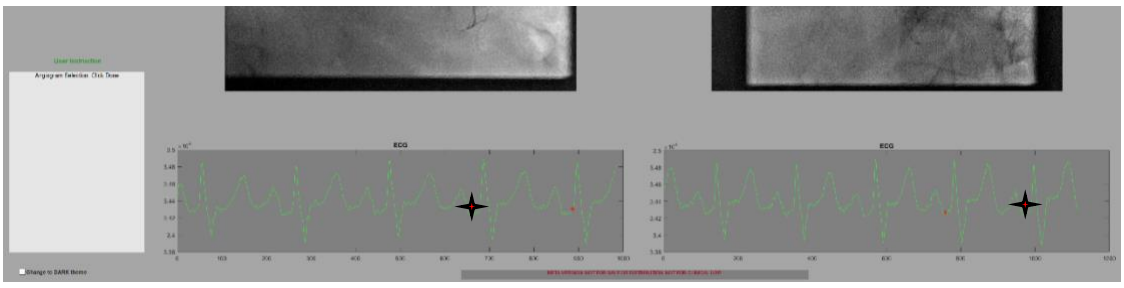
On the left, a coronary angiogram shows a proximal LAD lesion (A). The adjacent image is the Coroflow (3.0) user interface showinga pressure drop after adenosine infusion. The top right corner shows FFR (0.66) at hyperemia, averaged pressure proximal to stenosis (Pa) and averaged pressure distal to stenosis (Pd). Repeat angiogram and post stent FFR (0.91) is shown below (B).

2.2.3 Segmentation using VIRTUheart™ (v201 Beta) tool

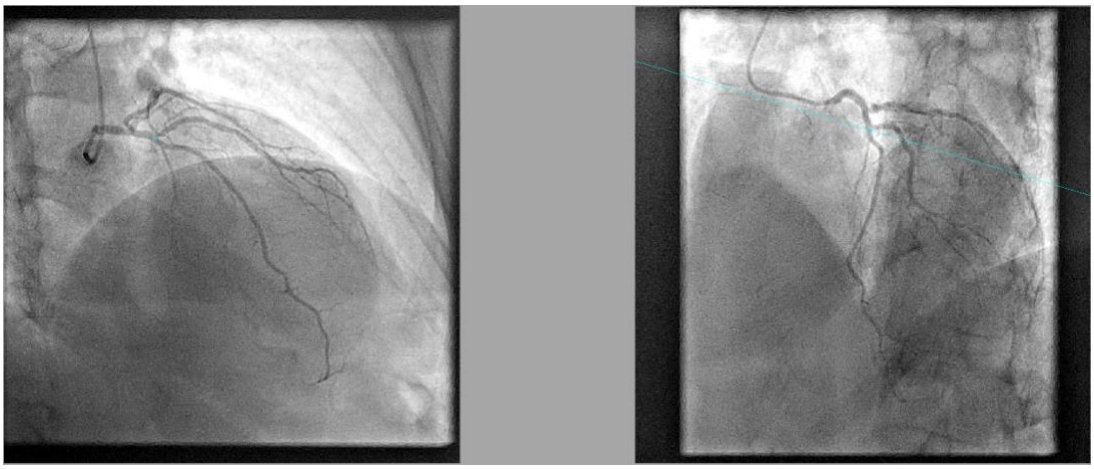
The VIRTUheart workflow bundle provides multiple tools, and the segmentation tool incorporated in it is the starting point. To generate a 3D reconstruction of the coronary artery, two high quality images with a difference of 30° are needed. DICOM images are uploaded into the software, and views (RAO and LAO) and directions (Cranial or Caudal) are indicated to provide more reliable angle difference.



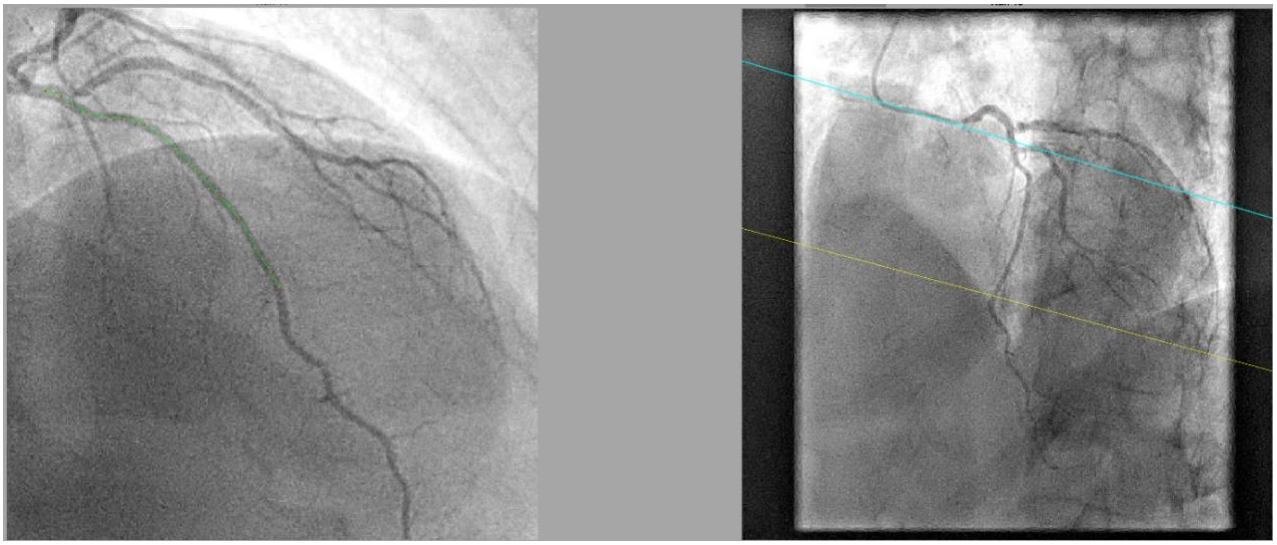
The ECG trace is imported automatically, allowing the user to identify the ideal frame, which should be in end-diastole, to capture the maximal flow at the lowest point of myocardial contractility.



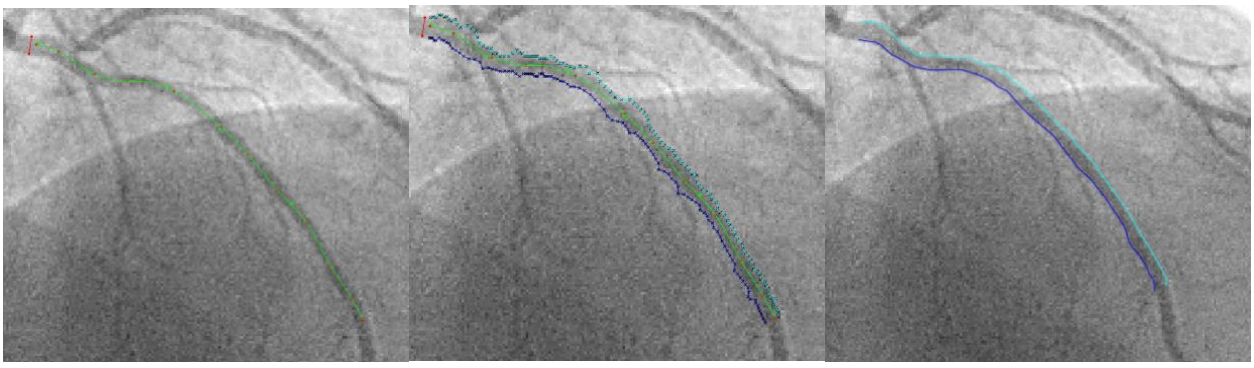
To compensate for possible table movement between two image acquisitions, images correction is performed. The process is completed by identifying one correction point at each image at the same location, correction points are crucial for the segmentation process, and therefore user judgment is necessary. To confirm confident identical points, bifurcations are used.



The centre line is drawn along the vessel by the user on the first image (left side). Two corresponding lines, known as “epipolar lines” are generated on the second image (right side) to allow better judgement of vessel reconstruction.



Diameter markers are assigned and automatic vessel edge detection is generated. Errors in edge detection are common, so manual correction is performed.



All steps are repeated on the other image (right side) and a 3D reconstruction of the artery is generated.

2.2.4 Deriving vFFR from 3D reconstruction

A 3D surface mesh is inserted into the segmentation described above to represent the arterial lumen. VIRTUheart™ then converts the 3D surface mesh to a volumetric mesh (ANSYS Inc, PA, USA) which allows computation of the trans-lesional pressure gradient using computational fluid dynamics (CFD) by solving the Navier-Stokes equations of conservation of mass and momentum, as applied to Newtonian fluids. In the computation of steady state vFFR, the distal parameters of coronary microvascular physiology are reduced to a single time averaged resistance (8.721e9 Pa/m^3s^{-1}) derived from averaged value from a previously studied cohort. vFFR can therefore be described as a function of four parameters: mean proximal pressure (mmHg), terms Z_1 (mmHg.min/ml) and Z_2 ($mmHg.min^2/ml^2$) and total distal resistance. Z_1 and Z_2 represent the linear and quadratic coefficients that describe the relationship between pressure and flow which is described as follows.

$$\mathrm{dP} = (Z_2 \cdot Q^2) + (Z_1 \cdot Q) + Z_0$$

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:

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

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

This CFD solver uses flow rates of 1ml/s and 3ml/s based on previous work to determine the optimal rates (Morris *et al.*, 2017). 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:

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

vFFR is then generated with a colour mapping system used to demonstrate the pressure drop across the vessel (figure 2.3). The pressure drop can be measured at any point across the simulated arterial lumen.

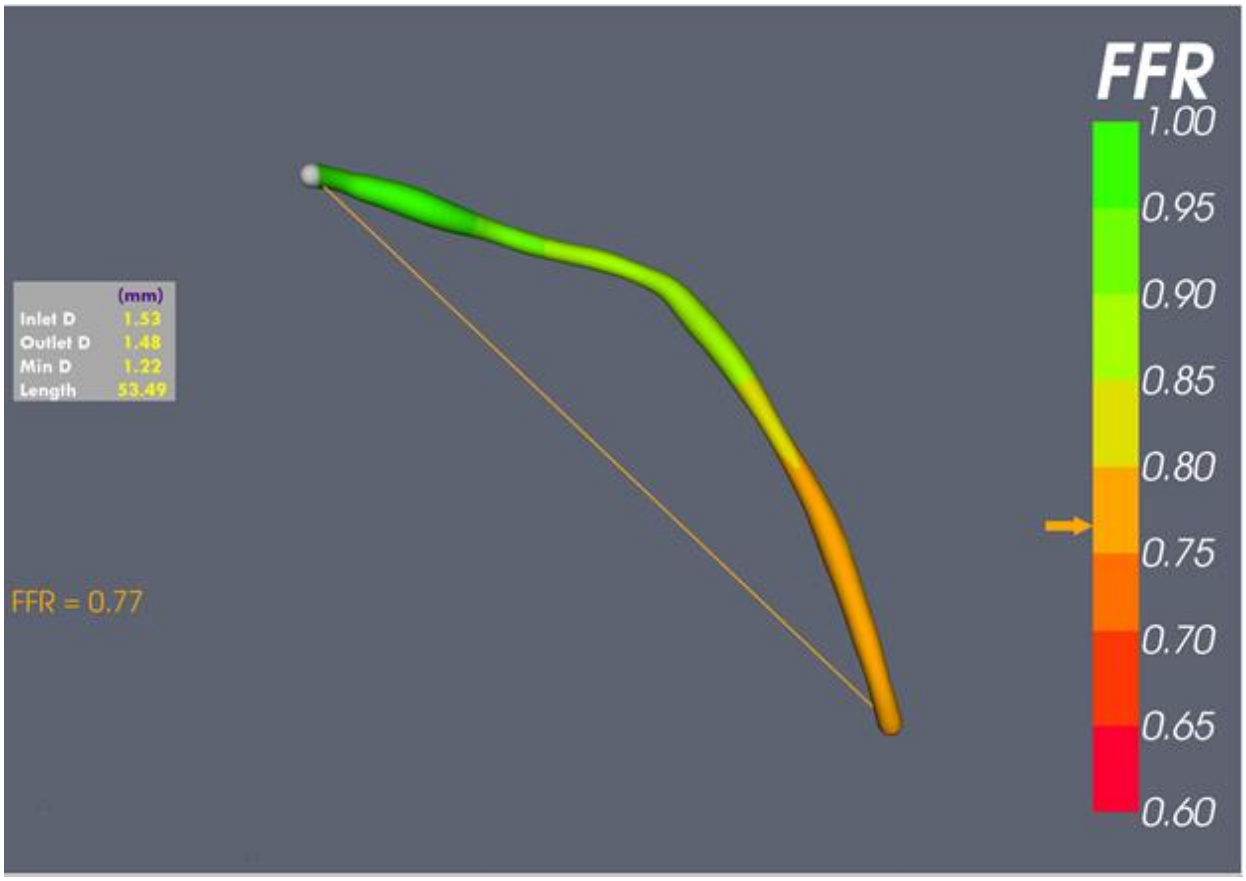


Figure 2.3 Generated vFFR (0.77) with colour map of pressure drop across the vessel.

2.2.5 virtuQ: Deriving absolute flow from angiogram and intracoronary pressure data

virtuQ™ software (University of Sheffield, Sheffield, United Kingdom) was used to compute absolute flow. This is an extension of the VIRTUheart™ software. In this case, in addition to the angiographic (anatomical) images, real (rather than modelled) pressure data from the pressure wire are used to construct a model of absolute blood flow (mL/min) also using CFD. Time-averaged proximal pressure (P_a) and distal pressure (P_d) at baseline and under hyperemic conditions are applied at inlet and outlet to tune accurate boundary conditions. Volume mesh was constructed with 1.2–1.5 M elements, CFD then computes coronary volumetric flow rate. Applying the hydraulic equivalent of Ohm's law to the computed coronary flow and already inputted pressures are used to derive HSR, MVR, CFR following these equations:

$$MVR = \frac{P_d}{Computed\ coronary\ flow}$$

$$HSR = \frac{P_a - P_d}{Computed\ coronary\ flow}$$

$$CFR = \frac{Computed\ coronary\ flow_{Hyperemia}}{Computed\ coronary\ flow_{Baseline}}$$

Model inputs and outputs are illustrated in figure 2.4. Validation and technical background have been published previously (Morris *et al.*, 2021). All outputs were reported before and after intervention (if applicable).

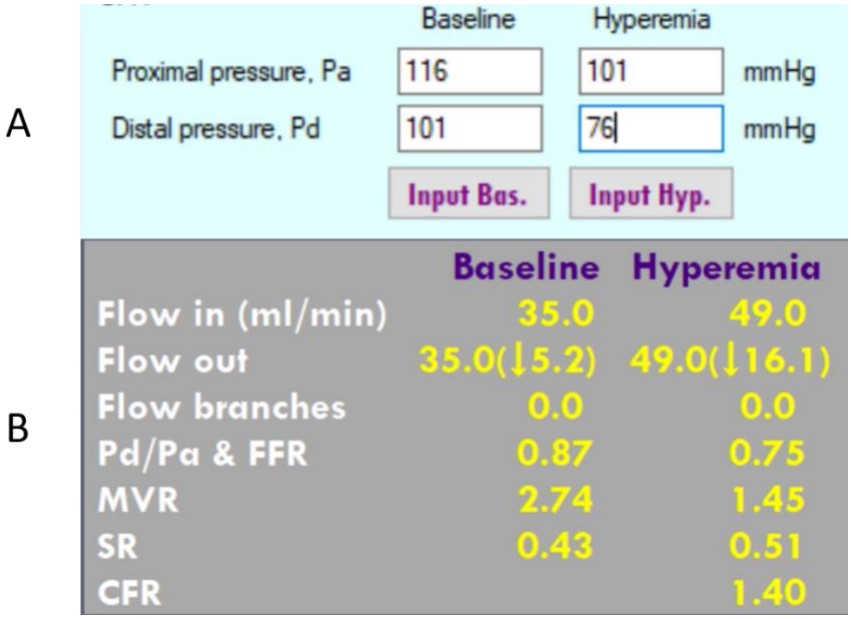


Figure 2.4 virtuQ user interface.

(A) showing inputs panel, averaged Pa and Pd at baseline and hyperemia are entered and (B) showing the model outputs (Flow, FFR, MVR, SR and CFR) at baseline and hyperemia.

2.2.6 Modelling protocol

I collected all pressure-wire based FFR data as reported by the procedure operator and the raw data in all feasible vessels pre-PCI and as many as feasible post-PCI. All lesions with pressure wire assessment were segmented and processed offline through VIRTUheart™ version 2.0 and virtuQ™ version 3.0 software (the University of Sheffield). I performed all the segmentation and processing of the modelled vessels. Moreover, vFFRs were generated for all segmented vessels and subsequent simulations through virtuQ were completed to compute coronary absolute flow, HSR, MVR and CFR at baseline and hyperemic conditions. Hyperemic physiology metrics and vFFR values were reported. To ensure accuracy of the processing, 10 cases were randomly assigned for a second operator who was a cardiologist with strong exposure to VIRTUheart system. The operator was blinded to the wire-based FFR and produced vFFR values, to ensure reliability of the results. I was not blinded to the wire-based FFR values and this was due to the nature of the data collection which requires attending all the catheterisation procedures and performing the analysis as a part of this PhD work. However, to ensure reliability and accuracy, interobserver analysis was performed as mentioned earlier.

2.2.7 Statistical analysis

Data were reported as means, standard deviations of the means and percentages unless stated otherwise. Bland-Altman plots were used to assess the limits of agreement (±1.96 SD) between wire-based FFR and vFFR. Inter-class correlation was used for inter-observer variability to assess the agreement between two operators. Histograms were used to display frequency of variables and bar charts to demonstrate differences. For each vessel, coronary physiology variables were reported before and after PCI (if applicable) and paired samples t-test was used to compare the difference. Pearson coefficient (r) was used to calculate linear correlation between FFR and other coronary metrics. Correlation matrix was used to assess the correlation coefficient in the percentages of change between the variables before and after PCI. GraphPad Prism (9.4.1) was used for statistical analysis.

2.3 Results

2.3.1. Patients and lesions characteristics

Forty patients were recruited, of which 39 underwent LHC±PCI. The mean age of study participants was 65 (±8.6), of which 31 (77%) were male, 20 (50%) were ex-smokers, 4 (10%) were current smokers, 25 (65%) had hypertension, 14 (35%) had hyperlipidaemia and 6 (15%) had type 2 diabetes. The number of diseased vessels per patient was 1.48 (±1.48). Eight patients had mild or visually absent disease (22.9%), eight patients had single vessel disease (22.9%), 13 had two vessel disease (37.1%) and six had triple vessel disease (17.1%). Three patients were referred for CABG due to the presence of a chronic total occlusion (CTO) in one vessel or more. Patients and lesions characteristics are shown in table 2.1. The total number of vessels studied before PCI was 56, of which 21 (37.5%) had a functionally significant stenosis (FFR ≤0.8). The FFR distribution is shown in figure 2.5. The mean post-stent FFR was 0.89(±0.04), measured in 22 vessels, of which 10 (45.5%) had FFR>0.9. Three patients did not have FFR pre-procedure due to a difficulty of passing the wire (2) or the absence of a significant lesion (1). Thus, the total number of patients with FFR measured in one or more vessel was 36. Studied vessels characteristics are shown in (Table 2.2).

Table 2.1 Patients and lesions characteristics

Patient characteristics	N	Percentage	Mean (±SD)
Age			65 (±8.6)
Male	31	77	
Female	9	23	
Current smokers	4	10	
Ex-smoker	20	50	
Non-smoker	16	40	
Hypertension,	25	65	
Hyperlipidaemia	14	35	
Type 2 Diabetes	6	15	
Vessel and procedural characteristics			
Number of patients	38		
Mild or absent	8	21	
Single vessel disease	9	24	
Double vessel disease	14	38	
Triple vessel disease	6	16	
Diseased vessels location	69		
LMS	9	12.3	
LAD	22	32.8	
LCx	11	15.1	
RCA	18	26.1	
RAMUS	3	4.1	
PDA	3	4.1	
OM	1	1.4	
D1	2	4.1	
Chronic total occlusions	9	13	
LAD	3	4.1	
RCA	5	8.2	
LCx	1	1.3	
Treated vessels distribution	38		
LMS	5	12.5	
LAD	14	37.5	
LCx	6	15	
RCA	10	25	
RAMUS	2	5	
PDA	1	2.5	
D1	1	2.5	
Referred to CABG	3	8.3	

LMS= left main stem artery, LAD= left anterior descending artery, LCx= left circumflex artery, RCA= right coronary artery, PDA= posterior descending artery, D1= first diagonal artery, OM1= obtuse marginal artery, CABG= coronary artery bypass graft.

Table 2.2 Summary of studied vessels before and after intervention

Functional assessment	N	Percentage	Mean ±SD
Pre-PCI			
Studied vessels	56		
FFR ≤ 0.8	21	37.5	0.69 ±0.09
FFR >0.8	37	66.1	0.90 ±0.04
Location			
LAD	28	48.3	
LCx	10	17.2	
RCA	16	27.6	
RAMUS	1	1.7	
OM1	1	1.7	
D1	2	3.4	
Post-PCI			
Studied vessels	22		
FFR >0.9	10	45.5	0.92 ±0.02
FFR <0.9	12	54.5	0.85 ±0.03
Location			
LAD	13	59.1	
LCx	2	9.1	
RCA	7	31.8	

FFR: Fractional flow reserve, PCI= percutaneous coronary intervention.

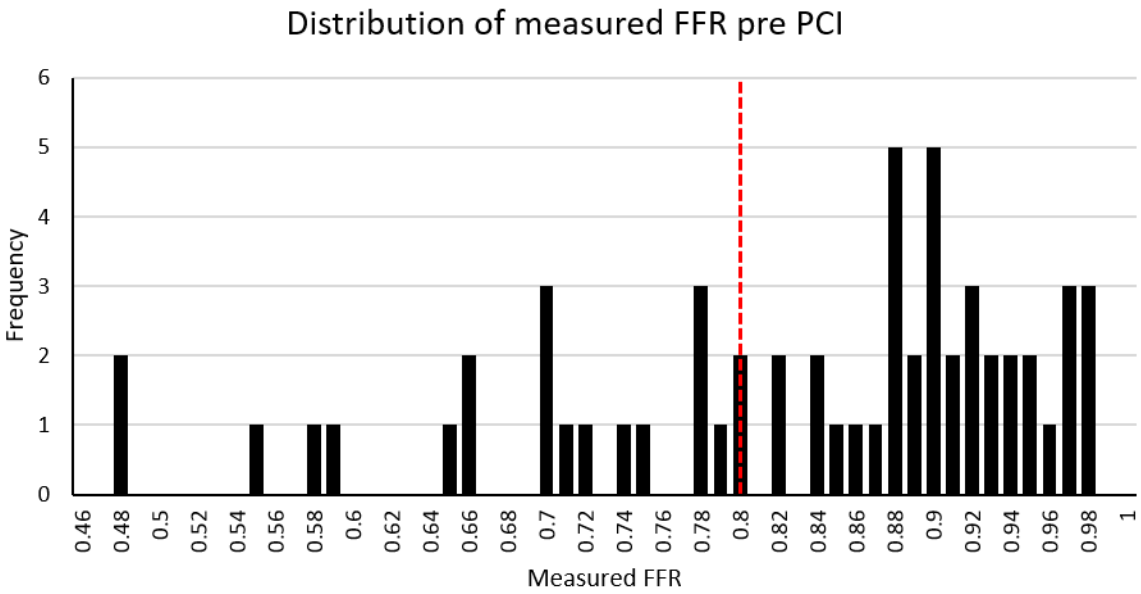


Figure 2.5 Distribution of all wire-based FFR

Represented as values of pre PCI wire-based FFR in the x axis and frequency on the y axis. The threshold for treatment (FF<0.80) is shown in red.

2.3.2 Accuracy of processing

Seventy-five vessels were successfully segmented and vFFR was generated, of which 17 were segmented twice (pre and post PCI), five were post PCI only and 36 were pre PCI only. Three lesions were excluded from the analysis because of parallel epipolar lines (n=1), and ostial and LMS lesions (n=2). There was no significant difference between wire-based FFR (0.84±0.1) and vFFR (0.85±0.1), the mean difference (bias) was (-0.01±0.04), the standard error (0.005), p=0.31 and the results were closely correlated (r=0.90). A Bland-Altman plot is shown in figure 2.5A. Inter-observer variability was calculated using inter-class correlation and Pearson's after randomly assigning 10 cases for reprocessing by another VIRTUheart™ experienced operator. The second operator was blinded to the vFFR and FFR results. The mean vFFR for the first operator was 0.83±0.13 and 0.81±15 for the second operator, the mean difference was (0.02±0.09), the agreement between observers was strong (r= 0.80, ICC= 0.89, p<0.01). Bland-Altman and correlation plots are shown in figure 2.6.

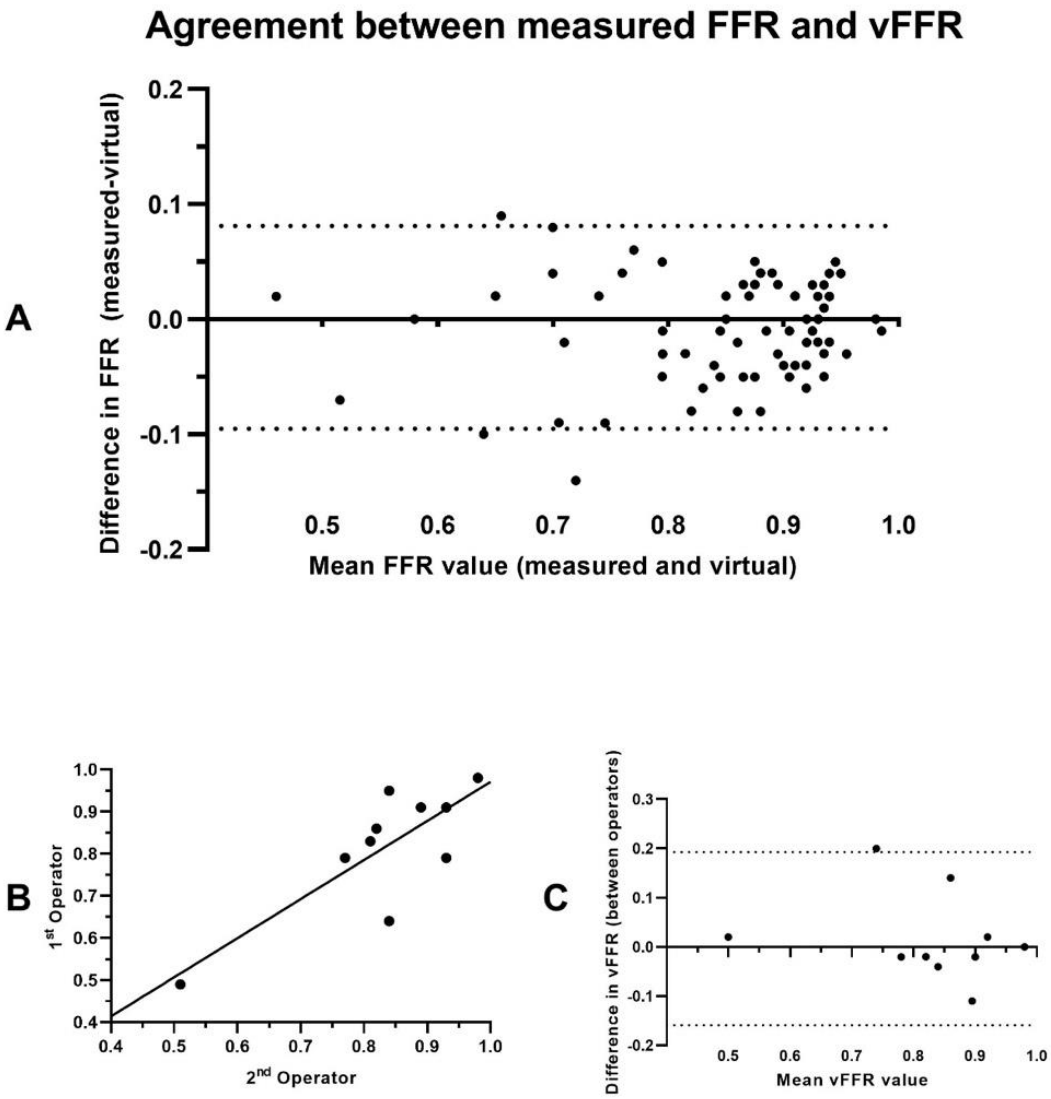


Figure 2.6 FFR agreement plots

(A) Bland-Altman plot demonstrating agreement and differences between wire-based FFR and vFFR. The upper and lower limits of agreement are shown with the interrupted line (-0.09 to 0.08), (B) Pearson's correlation for inter-observer variability, and (C) Bland-Altman plot demonstrating agreement and differences between the two operator. The upper and lower limits of agreement are shown with the interrupted line (-0.15 to 0.19).

2.3.3. Coronary physiology assessment for the full cohort at baseline

All segmented vessels with FFR at baseline (n=54), including vessels with flow limiting disease, were processed for computation of coronary physiology parameters. Absolute flow, CFR, HSR and MVR were generated using virtuQ™ software (University of Sheffield). The mean coronary absolute flow was 61.8±26.6 [range 21.4 to 132] ml/min; mean HSR was 0.29±0.29 [range 0.06 to 1.44]; mean MVR was 1.18±0.52 [range0.26 to 2.90]; and the mean CFR was 2.27±1.09 [range 0.95 to 6.02]. The distribution of coronary physiology parameters is presented in figure 2.7. In 54 vessels, there was a weak correlation between wire-based FFR and coronary absolute flow ($r=0.16$), $p=0.24$ (figure 2.8A), a strong negative correlation between wire-based FFR and HSR ($r=-0.74$), $p<0.01$ (figure 2.8B), a moderate positive correlation between wire-based FFR and MVR ($r=0.39$), $p<0.05$ (figure 2.8C), and weak positive correlation between wire-based FFR and CFR ($r=0.24$), $p=0.07$ (figure 2.8D). Same analyses were done for vFFR and showed moderate correlation with coronary absolute flow ($r=0.35$), $p<0.05$ (figure 2.8E), strong negative correlation with HSR ($r=-0.77$), $p<0.01$ (figure 2.8F), weak positive correlation with MVR ($r=0.18$), $p=0.18$ (figure 2.8G), and weak positive correlation with CFR ($r=0.23$), $p=0.08$ (figure 2.8H).

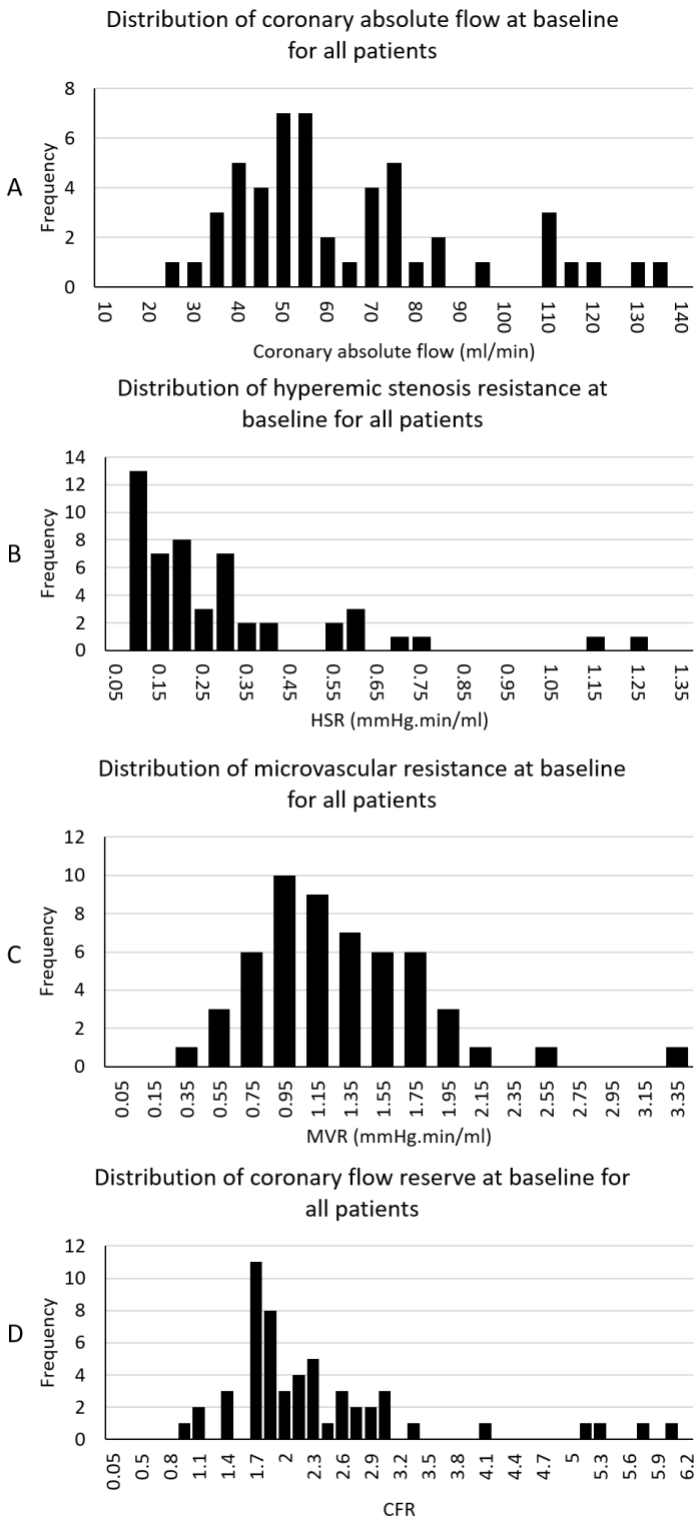


Figure 2.7 Distribution of computed coronary physiology

(A) coronary absolute flow (B) HSR (C) MVR and (D) CFR in 54 vessels at baseline.

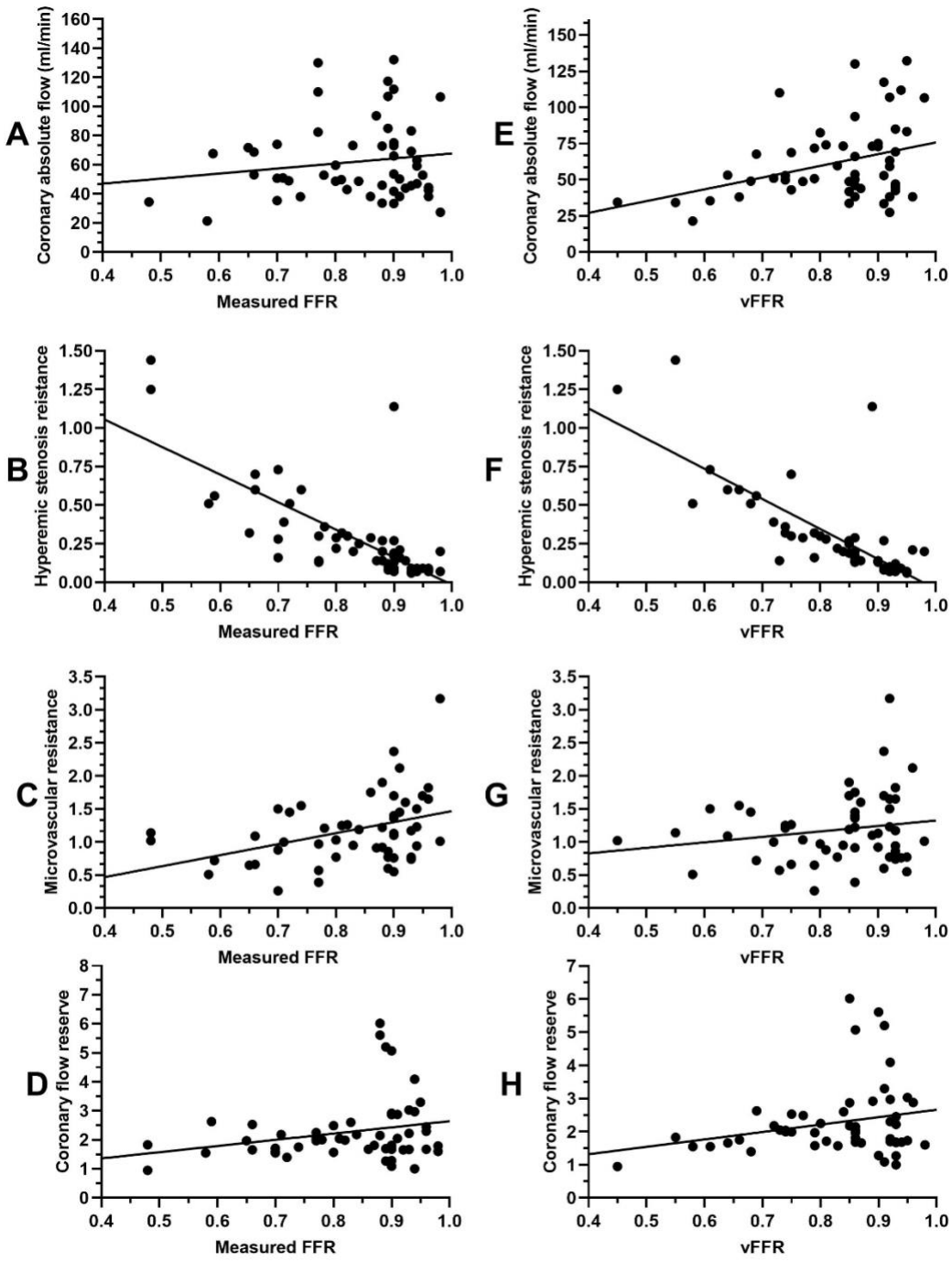


Figure 2.8 Correlation plots between wire-based FFR and coronary physiology parameters on the left and with vFFR on the right at baseline.

A) Correlation between wire-based FFR and absolute coronary flow (r=0.16), B) wire-based FFR and HSR (r=-0.74), wire-based FFR and MVR (r=0.39), D) wire-based FFR and CFR (r=0.24), E) vFFR and absolute coronary flow (r=0.35) F) vFFR and HSR (r=-0.76), G) vFFR and MVR (r=0.18), and H) vFFR and CFR (r=0.24).

2.3.4 Physiological assessment of coronary arteries in the presence of flow limiting disease

A total of 20 vessels from 16 patients who were treated with PCI after FFR revealed flow limiting disease were successfully processed and vFFR was generated. In addition, the vessels were processed for computation of coronary absolute flow, HSR, MVR and CFR based upon baseline and hyperemic pressure proximal and distal to the stenosis (Pa/Pd). Mean coronary flow was 55.5±23.3 ml/min, range 21.4 to 130 ml/min; mean HSR was 0.50±0.3, range 0.13 to 1.4; mean MVR was 0.98±0.35, range 0.26 to 1.55; and mean CFR was 1.90±0.4, range 0.95 to 2.63. The distributions of values per vessel are shown in figure 2.9. There was poor positive correlation between wire-based FFR and coronary absolute flow ($r=0.31$, $p=0.17$) (figure 2.10A), a strong negative correlation between wire-based FFR and HSR ($r=-0.80$, $p<0.01$) (figure 2.10B), a poor positive correlation between wire-based FFR and MVR ($r=0.22$, $p=0.4$) (Figure 2.10C), and a poor positive correlation between wire-based FFR and CFR ($r=0.37$, $p=0.1$) (figure 2.10D).
The same analyses were done for vFFR and showed a strong positive correlation with coronary absolute flow ($r=0.72$, $p<0.01$) (figure 2.10E), a strong negative correlation with HSR ($r=-0.86$, $p<0.01$) (figure 2.10F), a poor negative correlation with MVR ($r=-0.34$, $p=0.13$) (figure 2.10G), and a positive correlation with CFR ($r=0.57$, $p<0.01$) (figure 2.10H).

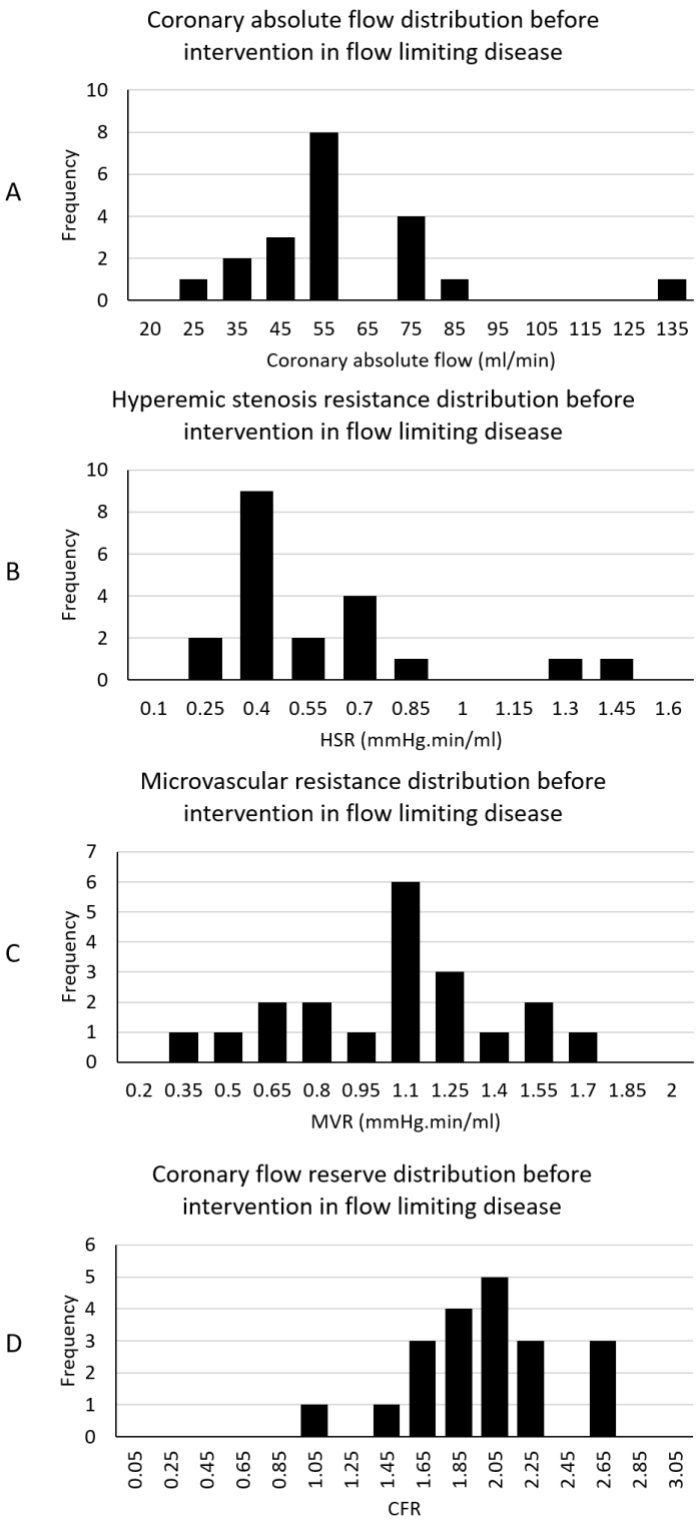


Figure 2.9 Distribution of computed coronary physiology in 20 vessels with flow limiting disease.

Absolute coronary flow (A) HSR (B) MVR (C) and CFR (D)

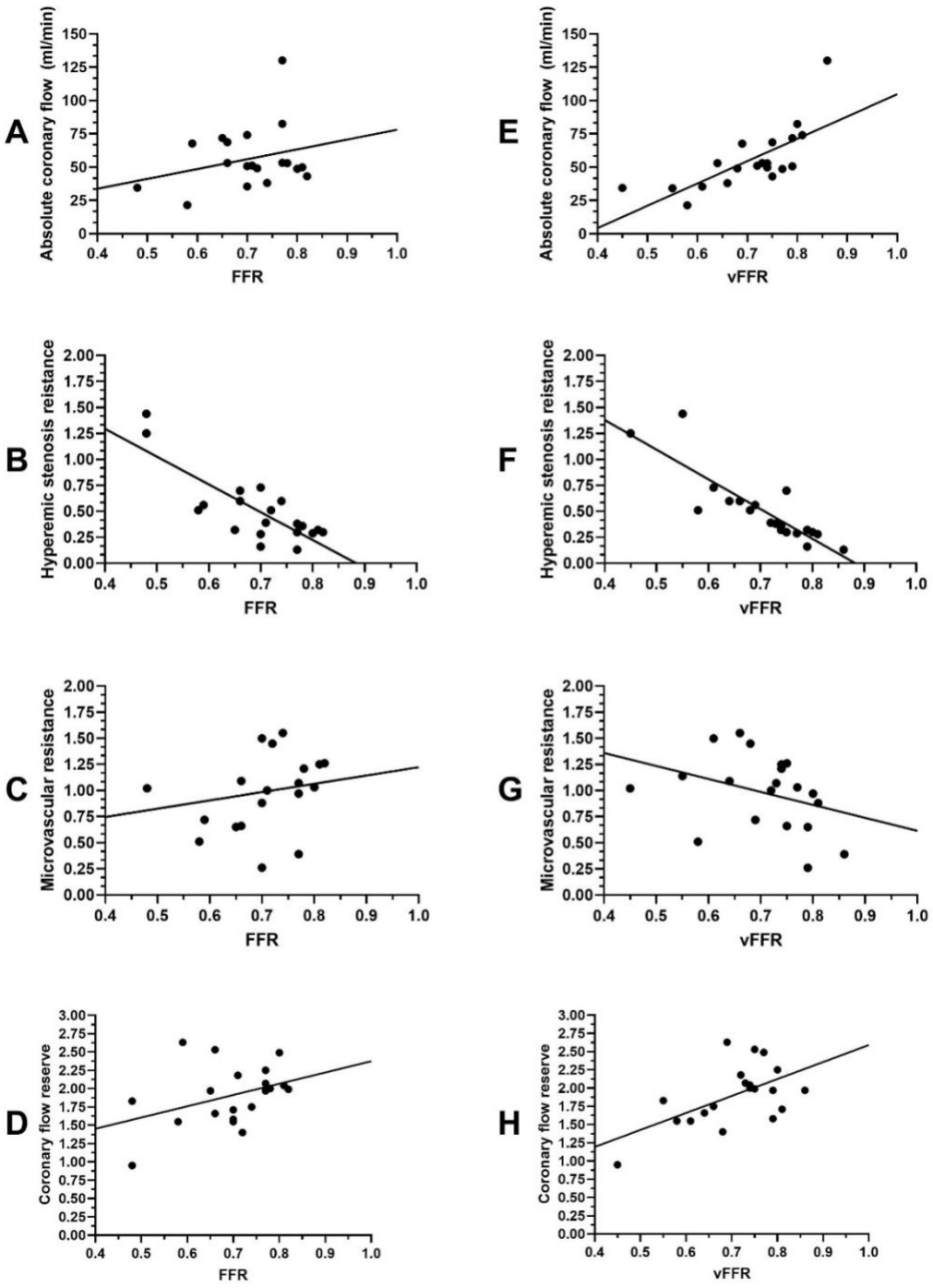


Figure 2.10 Correlation plots between wire-based FFR and coronary physiology parameters on the left and vFFR and flow parameters on the right (pre-PCI).

A) Correlation between wire-based FFR and absolute coronary flow (r=0.31), B) wire-based FFR and HSR (r=-0.8), wire-based FFR and MVR (r=0.22), D) wire-based FFR and CFR (r=0.37), E) vFFR and absolute coronary flow (r=0.72) F) vFFR and HSR (r=-0.86), G) vFFR and MVR (r=0.34), and H) vFFR and CFR (r=0.57).

2.3.5 Changes associated with coronary angioplasty in flow-limiting disease.

FFR post-PCI was measured in 17 vessels; all vessels were successfully processed, although one vessel was excluded due to parallel epipolar lines. Lower FFR values before PCI were strongly associated with higher level of changes (r=-91, p<0.01) (Figure 2.11). Summary of changes associated with PCI are listed in table 2.3 and individual changes are demonstrated in figure 2.12. There was a mild correlation between the change in coronary absolute flow and change in FFR (r=0.45, p=0.07) (figure 2.13A). A similar correlation observed with change in vFFR (r=0.44, p=0.07) (figure 2.13D), a moderate negative correlation with change in HSR (r=-0.51, p<0.05) (figure 2.13B), a moderate negative correlation with change in MVR (r=-0.56, p<0.05) (figure 2.13E) and poor correlation with change in CFR (r=0.15, p=0.55) (figure 2.13C). A correlation matrix between the percentage of changes between all metrics is shown in table 2.4.

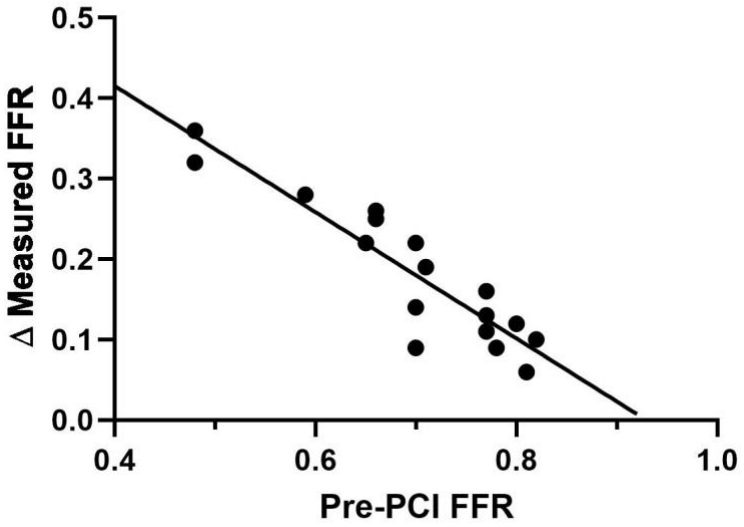


Figure 2.11 Change in FFR in response to pre-PCI FFR.

This correlation plots demonstrates the liner relationship between the baseline FFR and the increase in FFR (r=-91, p<0.01).

Table 2.3 Summary table of computation of coronary flow and resistances before and after PCI

Summary of the change in coronary physiology parameters	Mean	±SD	p-value
Number of successful computations of absolute flow	N=17		
Mean FFR before PCI	0.69	±0.10	
Mean FFR after PCI	0.87	±0.04	
Mean increase in pressure after PCI	0.18	±0.09	
Percentage of change in pressure after PCI	28	±19 %	<0.01
Coronary absolute flow			
Mean flow before PCI (ml/min)	62.22	±26.22	
Mean flow after PCI (ml/min)	112.23	±35.99	
Mean increase in flow after PCI (ml/min)	49.97	±32.61	
Percentage of change in flow after PCI (ml/min)	80	±63%	<0.01
CFR			
Mean CFR before PCI	1.96	±0.41	
Mean CFR after PCI	2.01	±0.64	
Mean increase in CFR after PCI	0.05	±0.66	
Percentage of change in CFR after PCI	6	±36%	=0.75
HSR			
Mean HSR before PCI	0.48	±0.37	
Mean HSR after PCI	0.09	±0.06	
Mean decrease in resistance after PCI	-0.38	±0.34	
Percentage of change in HSR after PCI	-74	±13%	<0.01
MVR			
Mean MVR before PCI	0.91	±0.33	
Mean MVR after PCI	0.58	±0.18	
Mean decrease in resistance after PCI	-0.33	±0.25	
Percentage of change in MVR after PCI	-32	±20%	<0.01

FFR= fractional flow reserve, HSR= hyperemic stenosis resistance, MVR= microvascular resistance, CFR= coronary flow reserve.

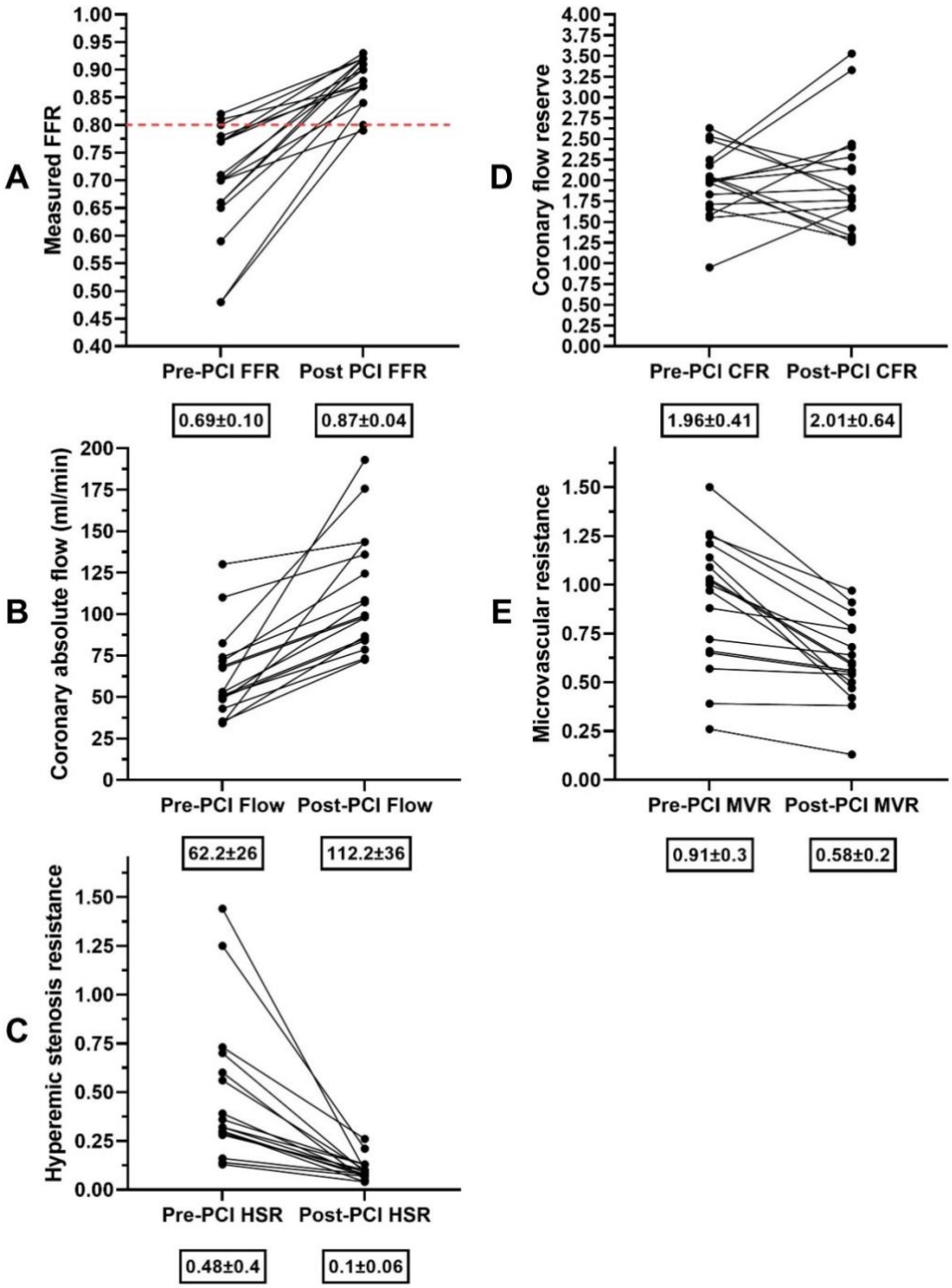


Figure 2.12 Individually plotted and matched pre-PCI coronary physiology parameters with corresponding value post-PCI.

(A) FFR, (B) coronary absolute flow, (C) HSR (D) CFR, and (E) MVR. Mean ±SD are presented in boxes. Dotted red line in graph (A) represents FFR cut-off value (0.8).

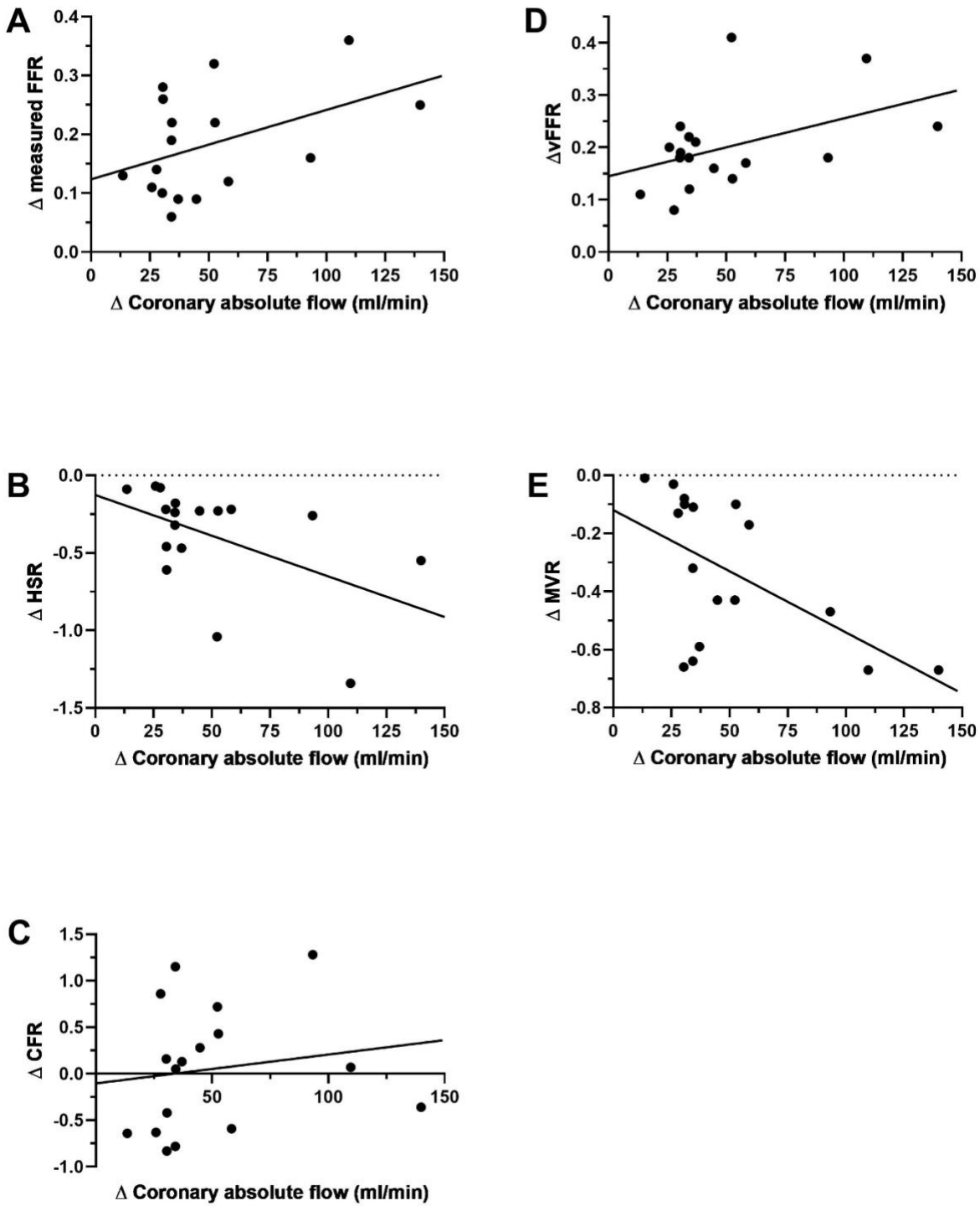


Figure 2.13 Correlation plots demonstrating the relationship between the changes in coronary absolute flow with other coronary physiology metrics post PCI.

Δ Coronary absolute flow = Flow post PCI – flow pre PCI
A) ΔFFR = FFR post PCI – FFR pre PCI, B) ΔHSR= HSR post PCI – HSR pre PCI, C) ΔCFR= CFR post PCI – CFR pre PCI, D) ΔvFFR = vFFR post PCI – vFFR pre PCI, E) ΔMVR = MVR post PCI – MVR pre PCI

Table 2.4 Means, standard deviations and Pearson's correlations matrix for correlations of percentages of change after PCI in flow limiting disease

	Mean (±SD)	Change % in FFR	Change % in coronary absolute flow	Change % in HSR	Change % in MVR	Change % in CFR
Change % in FFR	28 (±19)%	-	0.60*	-0.60*	-0.15	0.24
Change % in coronary absolute flow	97 (±82)%	-	-	-0.61**	-0.67**	0.12
Change % in HSR	-74 (±13)%	-	-	-	0.34	-0.03
Change % in MVR	-32 (±19)%	-	-	-	-	-0.38
Change % in CFR	6 (±36)%	-	-	-	-	-

* = $p<0.05$
** =$p<0.01$

2.3.6 Measurable differences in FFR positive and FFR negative vessels: a subgroup analysis

A subgroup analysis was done to compare the differences between FFR positive (n=20) and FFR negative (n=30) groups. Five flow models of branches were excluded from the analysis to match the two groups for major coronary arteries only. There was a significant difference between FFR positive group and FFR negative group in wire-based FFR ($p<0.01$), vFFR ($p<0.01$), HSR ($p<0.01$), MVR ($p<0.05$) and CFR ($p<0.05$). Although flow in FFR negative group (66.80 ±27) was higher than the FFR positive group (55.47 ±23.3), the difference was statistically not significant ($p=0.13$). Summary of the comparison is listed in table 2.5. Differences between the groups are demonstrated as histograms in figure 2.14. Coronary absolute flow in the positive group showed mild positive correlation with FFR ($r=0.31$, $p=0.17$), and moderate but significant negative correlation with MVR and HSR ($r=-0.46$, $p<0.05$ and $r=-0.48$, $p<0.05$, respectively) and modest correlation with CFR ($r=0.38$, $p=0.09$). There was no correlation between coronary absolute flow and FFR in the positive group ($r=0.01$, $p=0.95$), a significantly strong negative correlation with MVR ($r=-0.84$, $p=<0.01$), weak correlation with HSR and no correlation with CFR ($r=-0.12$, $p=0.51$ and $r=-0.05$, $p=0.78$, respectively). Correlation plots are demonstrated in figure 2.15

Table 2.5 Summary of the differences in coronary physiology metrics between FFR positive group and FFR negative group

Coronary physiology parameter	FFR positive (n=20)		FFR negative (n=30)		Difference		p-value
	Mean	±SD	Mean	±SD	Mean	±SD	
Wire-based FFR	0.69	±0.09	0.90	±0.04	0.20	±0.02	<0.01
vFFR	0.70	±0.10	0.89	±0.04	0.19	±0.02	<0.01
Coronary absolute flow	55.47	±23.3	66.80	±27	11.33	±7.46	0.13
HSR	0.51	±0.33	0.18	±0.19	-0.32	±0.07	<0.01
MVR	0.98	±0.35	1.28	±0.46	0.30	±0.12	<0.05
CFR	1.90	±0.41	2.6	±1.34	0.69	±0.31	<0.05

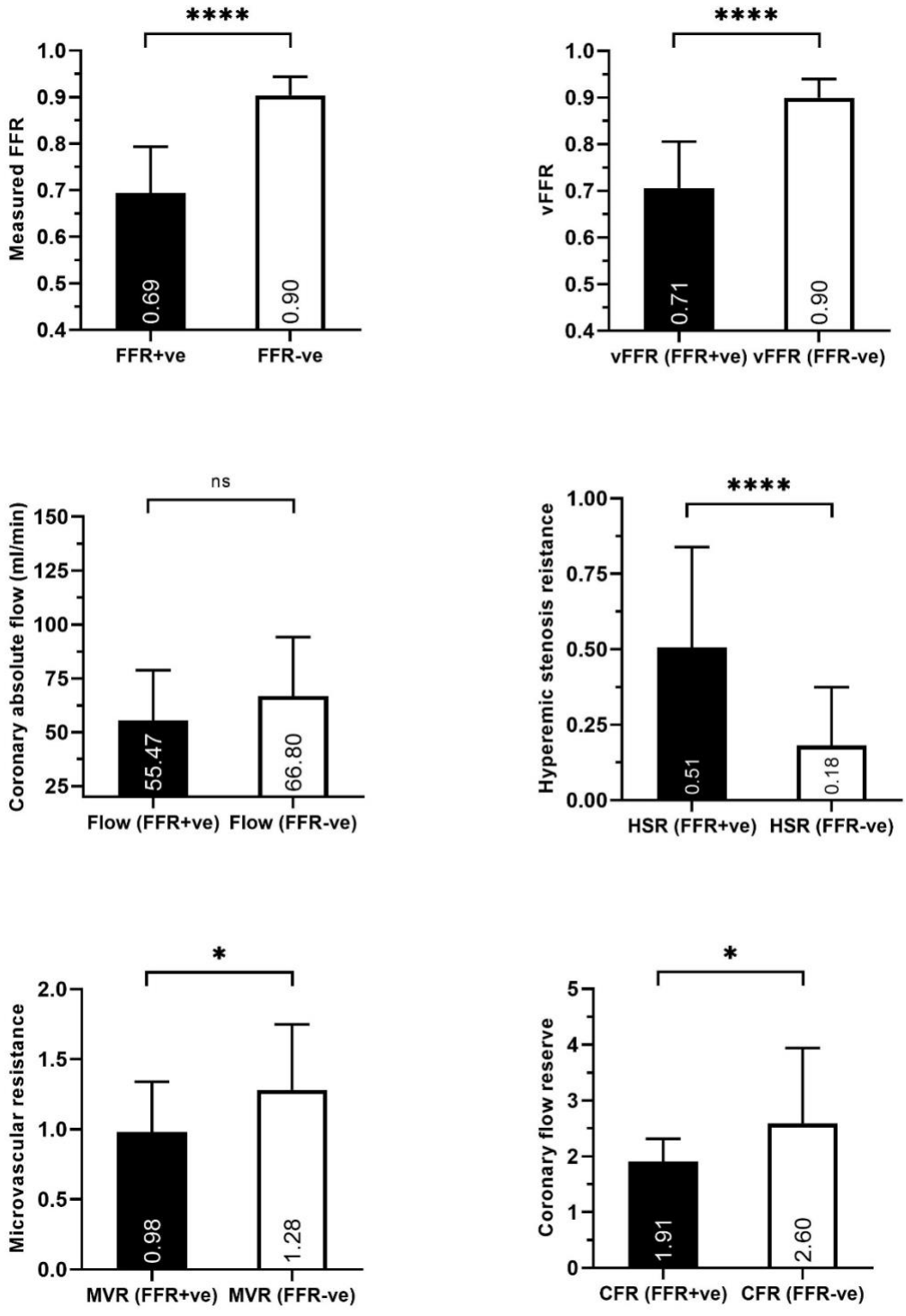


*Figure 2.14 Bar charts demonstrating the differences between FFR positive and FFR negative groups A) mFFR, B) flow, C) MVR, D) vFFR, E) HSR and F) CFR. Error bars represents SD. (*p<0.05, ****p<0.0001)*

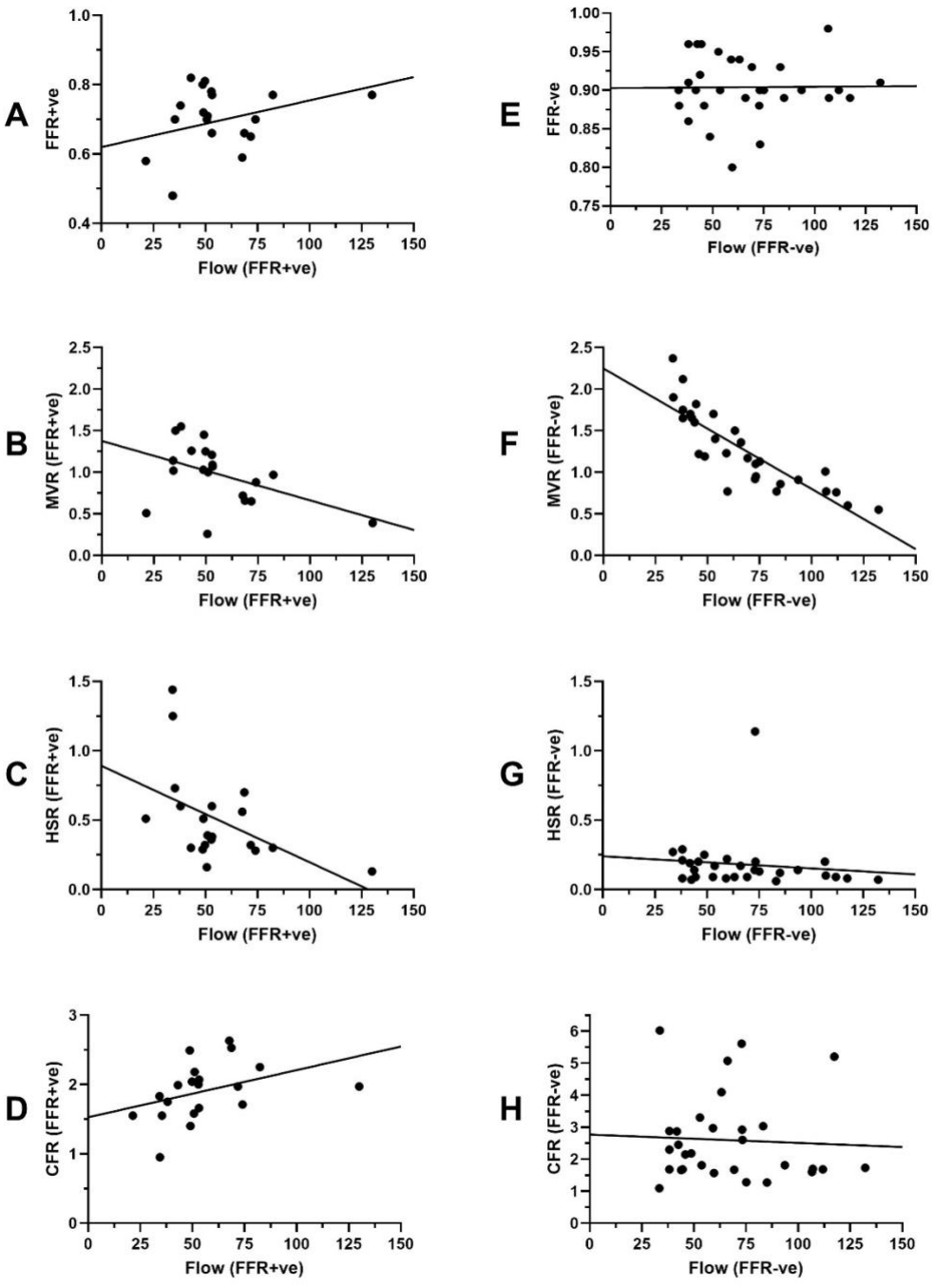


Figure 2.15 Correlation plots between coronary absolute flow and other coronary physiology metrics in FFR positive (left) and FFR negative (right) groups.

A) Flow and FFR+ve (p=0.17), B) flow and MVR (p<0.5), C) flow and HSR (p<0.05) and D) flow and MVR (p=0.09). E) Flow and FFR-ve (p=0.95), F) flow and MVR (p<0.01), G) flow and HSR (p=0.51) and H) flow and MVR (p=0.78).

2.4 Discussion

2.4.1 Summary of the results

In this chapter, which represents one component of the VIRTU-5 project, I have shown that computing coronary physiology metrics such as coronary absolute flow, HSR, MVR and CFR using the ICA and invasive pressure wire data is feasible both before and after PCI. This is currently not done in everyday clinical practice. This was achieved in 75/78 vessels with a modelling success rate of 96% including severe, moderate, mild lesions and post-PCI assessment. The relationships between wire-based FFR and vFFR with other coronary physiology metrics in the presence of flow limiting disease were shown to follow certain patterns. This was shown in the negative correlation with HSR ($p<0.01$) in FFR and vFFR. A positive relationship was observed between wire-based FFR and coronary flow, and it was even stronger with vFFR ($p=0.17$ and $p<0.01$, respectively). This relationship was observed between CFR with FFR and vFFR as well. However, MVR did not show any significant pattern in that respect. Additionally, all coronary metrics significantly changed post-PCI at the ($p=0.01$) level, except for CFR ($p=0.75$). The change in HSR and MVR in response to PCI had the largest effect on coronary absolute flow compared to other metrics ($p<0.01$, $p<0.01$, respectively). Additionally, when vessels with a positive FFR were compared to vessels with a negative FFR, MVR and CFR were significantly higher in the latter ($p<0.05$, $p<0.05$) and HSR was significantly lower ($p<0.01$). Computed flow was numerically higher in the negative group, but this was not statistically significant ($p=0.13$). Summary of the main findings is shown in figure 2.16.

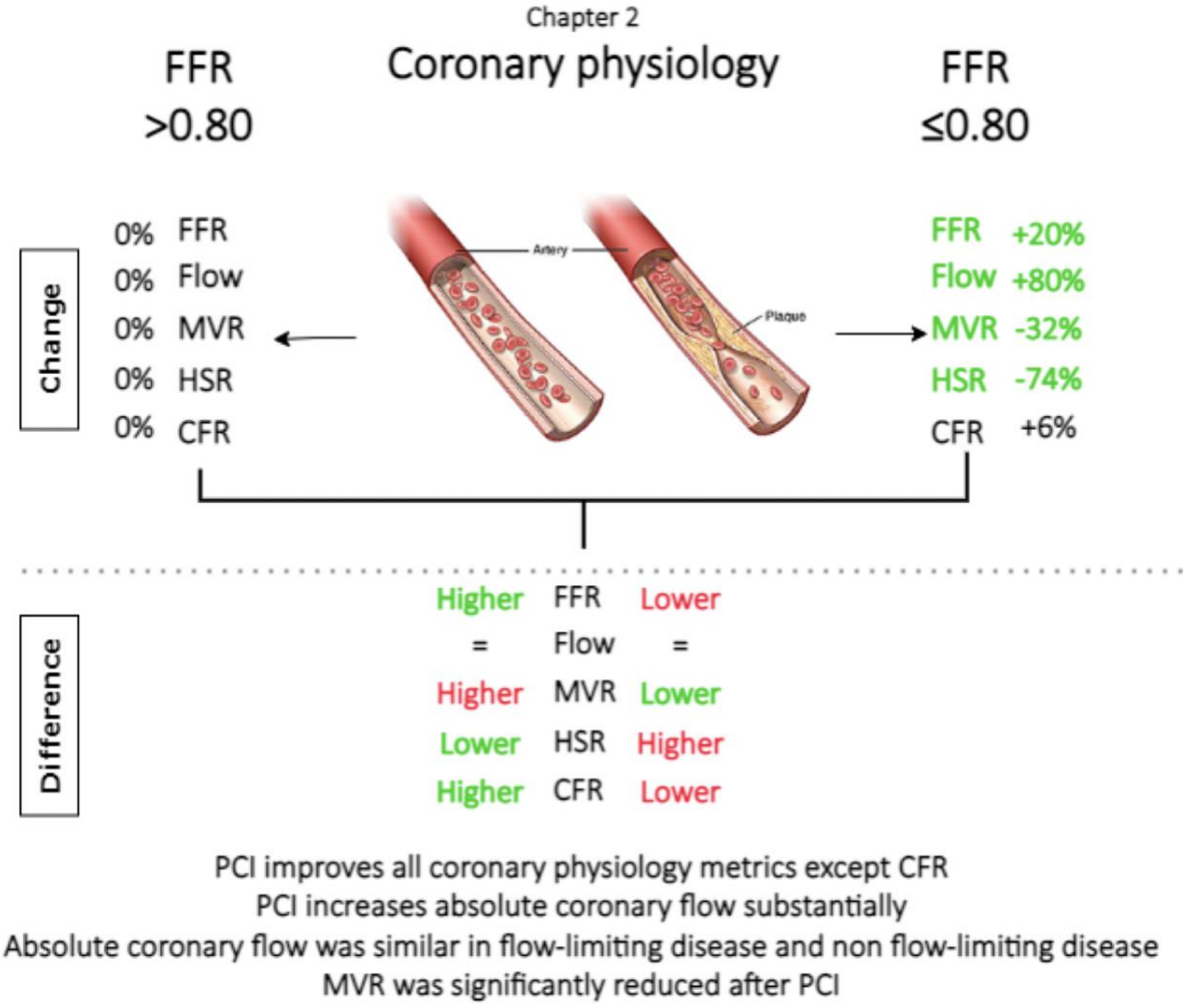


Figure 2.16 Schematic summary of the findings from chapter two

2.4.2 Modelling coronary physiology

Conventional methods for assessing functional severity are mainly pressure-derived, such as FFR and other resting indices. However, FFR provides a percentage of coronary flow reduction compared with a similar hypothetically healthy artery. In concept, FFR is a representation to the ratio of pressure drop across the artery in a response to increase in epicardial resistance (stenosis). Despite FFR being superior to the angiogram in guiding PCI, and the current gold standard for ischemia discrimination, pressure in this context is used as a surrogate to flow, yet the exact flow

value remains unidentified. FFR as it stands has provided excellent value to the current practice, yet quantifiable specific coronary metrics may enrich our assessment. This computational method provides a comprehensive exploration of coronary physiology and potentially an assessment method that aids in quantifying the ischemic burden of a given lesion, especially that this work was done in real-world patients.

The current methods to derive coronary flow and the subsequent metrics such as resistances (HSR, IMR and MVR) are limited to coronary Doppler ultrasound and thermodilution. However, these modalities are very limited in clinical practice due to operator experience, high levels of variability, expense, time, wire handling and proneness to errors. Recent findings (Morris *et al.*, 2021) demonstrated that virtuQ flow modelling system was able to predict flow and was in agreement with ultrasound Doppler *in-vitro and in-vivo*. It was also reported that computed flow was associated with low levels of variability compared to Doppler derived flow. Additionally, computed CFR using virtuQ was closely correlated with pressure-derived CFR. Therefore, believing that this system is able to produce validated flow, it is safe to assume that computed resistances which are derived from flow based on hydraulic equivalent Ohm's laws ($Q=\Delta P/R$), could carry a high level of reliability. It is crucial to highlight the role of segmentation and 3D reconstruction that was used in this method of calculating flow. The VIRTUheart system has been shown to be accurate in predicting FFR with a diagnostic accuracy >90%. In this chapter, I have shown that there was no significant difference between mFFR and vFFR ($p=0.31$) and they were closely correlated ($r=0.90$) with strong inter-observer agreement (ICC 0.89, $r=0.80$). Therefore, the computed flow and derived metrics may be assumed to be acceptable.

2.4.3 The relationship between FFR and other coronary physiology metrics

Fractional flow reserve and coronary absolute flow

In this chapter, I investigated the relationship between FFR in both its invasively measured and virtually generated forms using CFD simulation with other coronary physiology parameters in chronic coronary syndrome patients. Acceptable levels of correlations were observed pre-PCI for all patients (figure 2.6) and for the flow limiting disease subgroup in particular (figure 2.9).

Furthermore, coronary absolute flow and FFR were poorly correlated when assessed at the full cohort level, however, this was not the case in flow limiting disease. The relationship failed to gain statistical significance on the latter; yet a stronger correlation was observed. This relationship was strong and significant when assessed against vFFR in flow limiting disease. Note that vFFR failed to show a significant correlation with flow when assessed in the whole cohort, similar to mFFR; yet there was a significant relationship in the flow-limited group, unlike mFFR. This is an important finding because it highlights the sensitivity of this flow model to the geometry more than the pressure drop, since mFFR and vFFR showed good agreement as discussed earlier and did not differ significantly. Flow around the uncertainty zone (FFR of 0.78-0.82) was more scattered and away from the fitted trend line (Figure 2.9A) which agrees with the literature that this range of FFR might be not representative of actual flow reduction in 20% of the measurements and could result in change of management (Petraco *et al.*, 2013). Due to the small sample size of flow limiting disease (20 vessels), I was not able stratify the data into groups to compare the uncertainty zone with more severe cases. Furthermore, understanding the degree of relationship between FFR and flow in this range might be of a great value. Absolute flow and FFR seem to correlate better at lower values. This was also demonstrated when FFR negative vessels were compared to FFR positive (figure 2.13). The diminished relationship at higher values of FFR may indicate that coronary flow cannot be generalised and in fact should always be treated as vessel-dependent and patient-dependent. For example, hyperemic coronary absolute flow of 70 ml/min is not necessarily better than 40 ml/min, because the latter might be enough to meet the myocardial demand whereas the former may be insufficient for some. This may be useful in personalised decision making, and in developing systemic and coronary vascular models.

FFR and HSR

HSR was the most closely related metric to FFR and vFFR alike in both analyses compared to others. HSR remained strongly correlated with FFR, in which a high FFR was associated with a low HSR, and vice versa. This finding aligns with Poiseuille's principle, which states that vessel resistance is inversely proportional to r^4 (De Bruyne and Sarma, 2008). Furthermore, small changes in vessel diameter, which imitate epicardial resistance, should reflect on flow and, therefore, significantly

on FFR. This was also demonstrated when the change in resistance was assessed against percentage of change in flow (table 2.4); and changes in FFR and flow were most sensitive to changes in HSR after PCI (r=-60, $p<0.05$, and r=-61, $p<0.01$) respectively. Moreover, HSR had a strong correlation with FFR in different analyses (full cohort, flow-limiting disease only and post-PCI). The reported correlation between FFR and HSR for the full cohort agrees with the findings of others (Van De Hoef *et al.*, 2014). This finding also agrees with optical coherence tomography derived stenosis resistance in 21 patients in a cohort of negative and positive FFRs (Guagliumi *et al.*, 2013).

FFR and MVR

Calculating hyperemic MVR non-invasively is one of the most important outputs of this CFD model. Different groups have been successful in generating angio-IMR derived from QFR by incorporating aortic pressure and an estimation of the mean transit time (Tebaldi *et al.*, 2020; Mejia-Renteria *et al.*, 2021; Scarsini *et al.*, 2021). One main difference between the QFR based method and the vFFR based method is that, in the latter, the boundary conditions are precisely entered into the model, ensuring personalisation of the model. Incorporating microcirculatory information while interpreting FFR can be of a great value, since FFR is calculated with the assumption of neglecting MVR. This chapter's results suggested that there is a moderate positive relationship between MVR and mFFR (r=0.34, <0.05), MVR and vFFR (r=0.39, <0.05) when MVR was assessed in the full cohort. However, in the flow limiting disease subgroup, this relationship was not significant and, interestingly, it was reversed between FFR and vFFR (r=0.22, p=0.4 and r=-0.34, p=0.13) respectively. Increased hyperemic MVR with increased stenosis severity (low FFR) has been reported previously (Van De Hoef *et al.*, 2014; Nijjer *et al.*, 2016), however, I was able to show that only in one relationship analysis. The three other analyses showed that hyperemic MVR increases with reduced severity (high FFR). This controversial finding might be attributed to the probability of microvascular dysfunction in the FFR positive group. When groups were compared in the basis of FFR in section 2.3.6, MVR was significantly higher in the negative group 1.28±0.46 compared to 0.98±0.35 in the positive group ($p<0.05$). This shows that high MVR values were clustered in the negative group (n=30) compared to the positive group (n=20). A possible explanation to the

inverse relationship in flow limiting disease could be the high sensitivity of the MVR generated by the model to the vFFR, which resulted in redistribution of the MVR values based upon vFFR, although the difference between FFR and vFFR was not significant. However, further investigations are warranted to ascertain the nature of the relationship, and sensitivity analysis might be helpful to identify which parameters are most affected by such differences.

FFR and CFR

CFR provides a ratio that can measure the entire coronary circulation, because the microvasculature is accounted for in addition to any epicardial stenosis. Therefore, I tried to assess its relationship with FFR, which evaluates the severity of the stenosis neutral to microvasculature (in concept). When the relationships between CFR, FFR and vFFR were assessed for the full cohort, results agreed with earlier work (Lee *et al.*, 2016), which reported a very modest positive correlation (r=0.20), similarly to my analysis (r=0.24 for FFR and r=0.23 for vFFR). Also, a comparable correlation between FFR and CFR (r=0.34) was reported earlier where a CFD model of the coronary circulation was used to predict the relationship between FFR and CFR in 438 cases (Johnson, Kirkeeide and Gould, 2012). This chapter's results suggested an even stronger relationship in the subgroup of flow-limiting disease only (FFR r=0.37, vFFR r=0.57), indicating that low FFR is associated with low CFR. However, this modest correlation may add to the fact that CFR alone might not be a suitable index of stenosis severity due to some limiting factors, most importantly, its dependence on baseline coronary flow which carry a high probably of variation due to HR discrepancy, myocardial performance and metabolism (Heusch, 2010). In addition, this modest relationship might explain the previously reported discordance between FFR and CFR relative to identified cut-off values. Furthermore, the sub analysis of FFR positive and FFR negative groups showed that the mean CFR value for each group (1.90±0.41 vs 2.6±1.34, $p<0.05$) respectively, agrees with the current acceptable CFR cut off value (≤2.0). Despite the mean of the FFR negative group being in the normal range, it is important to note that the standard deviation is relatively large, which could be attributed to the high MVR that was discussed earlier.

2.4.4 Coronary physiology changes in response to PCI

The physiological and angiographic outcomes after stent deployment can be of a significant value to assess procedural success and prognosis. The importance of post-PCI FFR has been addressed before, but it was not extensively investigated compared to pre-PCI FFR. It has been reported in different studies that higher post-PCI FFR values are associated with fewer cardiac events following PCI, with a range of estimated cut-off values for better outcomes of 0.88-0.92. In this chapter, the mean post-PCI FFR was 0.87±0.04. Although this value was below the prognostic cut-off, the increase in FFR was significant (ΔFFR=0.18), which equates to an increase of 28% ($p<0.01$). A linear relationship was observed in the change in FFR, and (self evidently) lower values increased the most (figure 2.11). Moreover, FFR and coronary absolute flow increased in 100% of the treated vessels. The associated increase in absolute flow was substantial (80%) with a mean increase of 49.97±32.61 ml/min ($p<0.01$), suggesting that myocardial blood supply was almost doubled immediately after PCI. A similar mean increase in flow (52.8 ml/min, $p<0.01$) was reported by (Kanaji *et al.*, 2017) and the same group reported a similar modest relationship between the change in FFR and absolute flow in a later work (Hamaya *et al.*, 2019). Furthermore, HSR and MVR dropped significantly after stent(s) deployment as well. These findings agree with earlier work by (Murai *et al.*, 2017) where IMR was significantly reduced and coronary absolute flow (measured by thermodilution) has significantly increased. The study suggested that the change in flow was strongly correlated with pre-PCI IMR, which aligns with the significance found on the correlation matrix in table 2.4 which shows that FFR and MVR are strong markers in change in absolute flow ($p<0.05$ and $p<0.01$) respectively. Nijjer et al have demonstrated similar outcomes in JUSTIFY-PCI study signifying that treating significant stenosis (FFR<0.80) was associated with significant increase in coronary flow (measured by Doppler flow) and significant decrease in HSR and MVR (Nijjer *et al.*, 2015). Patients in the later study were stratified according to FFR values, which resulted in interesting correlations between lower FFR values and higher levels of changes. I was not able to perform similar analysis due to my small sample size (n=17). In the contrary, decrease in the microvasculature post-PCI was challenged by other studies which reported that it was independent from epicardial stenosis or remained constant after correcting for collaterals by incorporating coronary wedge pressure (Fearon *et al.*, 2003; Layland *et al.*, 2012). The change in

HSR and MVR showed weak relationship despite them both being significantly related to the change in flow. It would be interesting to study the prognostic value of post-PCI MVR as it was the strongest marker to change in flow. Conversely, CFR was increased slightly (6%) post-PCI, but this was not statistically significant, unlike what was reported by other studies. In the current study, seven vessels (41%) had decreased CFR post-PCI (figure 2.19). Matsuda et al, for example, reported a decrease in CFR in 28% of 220 studied lesions; however, the authors reported a significant correlation between ΔCFR and ΔFFR which was not shown in the current study (Matsuda *et al.*, 2022).

2.4.5 Differences in physiology in the presence and absence of flow limiting disease

The comparison between functionally significant stenoses (FFR<0.80) with non-significant stenoses (FFR>0.80) has shown significant differences in multiple parameters. Coronary absolute flow was numerically higher in the negative FFR group, although this was not statistically significant (55.47±23.3 vs 66.80±27, p=0.13). This was reported by others using a thermodilution microcatheter (Rayflow, France) (Laforgia *et al.*, 2020; Fournier *et al.*, 2021; Paradies *et al.*, 2021). However, unlike the findings in this chapter, the authors of the earlier works reported no difference in MVR between the groups (p=0.89), whereas in my subgroup analysis the MVR was higher in the negative group (p<0.05). It is important to highlight this difference in MVR between the groups as this reflected significantly on the absolute flow (figure 2.13). In Laforgia et al and Paradies et al works, all assessments were performed on LAD, whereas only 48% of my cases involved the LAD. Alternatively, other metrics such as HSR were lower in the FFR negative group, and the mean CFR was beyond the normal cut off value (2.6±1.3). In addition, the FFR negative group showed weak to no relationship between coronary flow, FFR and other metrics. Nevertheless, when the same relationships were assessed in flow limiting disease, the correlations were greater (figure 2.13). My analyses suggest that MVR was the dominant factor that controls coronary flow when the FFR is >0.80, independent of FFR, HSR and CFR. In the contrary, all metrics show mild to moderate relationships to flow in flow limiting disease. It is worth highlighting that using dichotomous cut-off value of FFR to analyse this wide-spread physiological metrics may undermine some aspects of the generated data. This cut-off value was mainly proposed on the

basis of treat or differ to aid decision making. However, FFR should be looked at more broadly since FFR values may tell us different messages based on different patients and vessels. However, with dichotomising, all values below 0.80 suggest the presence of flow limiting disease. Although I have performed this analysis based on the dichotomous cut off value, I have also presented a more comprehensive analysis including all physiology metrics and FFRs despite the significance as shown in figures 2.8. Yet, this dichotomised analysis remains important for two main reasons; the first is to understand physiology based on real-life practice and, the second is that it will be followed by similar analyses in the next chapters. Therefore, it is important to put these metrics in the context of the current method of assessing flow limiting disease.

2.4.5 Limitations

First, the number of studied vessels in the flow limiting disease group was small, with even fewer cases having a full set of pre and post PCI pressure wire data (17 vessels). As a result, I was not able to undertake further analysis based upon FFR strata and how coronary physiology was affected in response to pressure drop and different FFR values including the grey and uncertainty zones. Second, there was high distribution of increased MVR in the FFR negative group, which may led to unintentional bias, especially considering that MVR was a predominant factor in determining coronary flow. This may have resulted in reduced flow in the FFR negative group, although coronary flow remained higher than FFR positive group. Third, this CFD analysis neglects side branches, as reported earlier by (Morris *et al.*, 2021), and consequently underestimating flow in proximal segments.

2.5 Conclusion

In this chapter, I studied the physiology of coronary artery disease in the presence and the absence of significant stenosis. The virtuQ modelling system is capable of generating coronary physiology metrics using invasive pressure data reliably, but is highly dependent upon the segmentation. The relationship between FFR and other metrics suggests that HSR is the most significant predictor of FFR. In addition, the absence of a significant stenosis does not necessarily mean a high flow; but once the FFR is reduced below certain levels, flow can be explained by FFR. Additionally, elective PCI guided by FFR can guarantee significant increase in coronary flow (80%), significant decrease

in HSR (-74%) and MVR (-34%) even though prognostic post PCI cut-off was not achieved. Finally, decrease in MVR post-PCI was the strongest predictor to high levels of coronary absolute flow restoration. These novel concepts may have a role in more precise assessment of ischaemia and predicting the likely improvements following revascularisation.

Chapter three: Myocardial ischemic burden.

3.1 Introduction

The key role of coronary arteries is to supply the myocardium with blood and thereby match its demand. Reduced or absent supply increases the risks of ischemic events. Moreover, the location of the lesion in the coronary artery, and the degree of narrowing, determines the myocardium at a risk. It has been established that stenting proximal LAD and LMS lesions result in symptomatic improvement and high event-free survival rates (Hueb *et al.*, 1995; Thiele *et al.*, 2009; Knuuti *et al.*, 2020). This emphasises on the importance of lesions location to prognosis, because it is prognosis is defined by the myocardium area at risk. This was proposed by the Bypass Angiography Revascularisation Investigation (BARI) trial, in which an index based upon anatomy was proposed to estimate the myocardium at risk (Alderman and Stadius, 1992; Bourassa *et al.*, 1995). Myocardial jeopardy index (MJI) provides a simple method to estimate myocardial area at risk that only requires invasive coronary angiogram. Furthermore, BARI-MJI has been shown to be predictive of mortality at one year in patients who were treated medically or with PCI and was also reliable at estimating area at risk when validated against CMR (Graham *et al.*, 2001; Moral *et al.*, 2012). However, we have learned from the FAME trial that ICA might misjudge the severity and FFR is superior in discriminating ischemia inducing stenosis (Tonino *et al.*, 2010). In addition, higher residual FFR after intervention is associated with better outcomes (Piroth *et al.*, 2017, 2022). Nevertheless, FFR remains vessel specific, and the measured value represents the pressure drop in a given vessel of a certain size. Therefore, FFR provides understanding of the physiology within a vessel and, combined with positional information, helps us estimate which territory of the myocardium is endangered (Watkins *et al.*, 2009). But it does not inform us about the precise extent of the myocardium at risk. Each major vessel perfuses different segments of the myocardium and, by estimating the flow reduction in all major vessels, we can hypothetically estimate the overall myocardial hypoperfusion and the amount (and severity) of myocardium at risk. In fact, this is not a completely new idea. The $_{3V}$FFR method was the first to propose a value, calculated by summing up three main vessels' FFRs. Its prognostic value was shown by (Lee *et al.*, 2018) who stratified the patients into two groups (high and low risk), based upon the median and reported significant negative correlation between $_{3V}$FFR and MACE rates at two years ($p<0.001$),

suggesting lower values to be associated with higher rate of events. MACE was mainly driven by revascularisation rates. The FAME investigators proposed a similar method ($_{GLOBAL}$FFR) which works by summing the FFR values as well to predict the long-term outcomes (Fournier *et al.*, 2020). Their study included patients with non-flow limiting disease or post-stent FFR values only. The authors stratified the patients into three risk groups (low, mid and high). Lower $_{GLOBAL}$FFR values were associated with higher events rates (high risk) and vice versa. MACE rates were mainly driven by revascularisation similar to $_{3V}$FFR method. The message from these studies is that it is possible to predict future outcomes based merely upon summing FFR in the three major coronary arteries. However, it could be argued that these methods neglect the coronary vasculature, which carry information about flow distribution, as discussed above. Prior to that, the FAME investigator proposed a score that combine physiology and anatomy, namely, functional SYNTAX score (FSS) (Nam *et al.*, 2011). The FSS method suggested adding the FFR in flow limiting lesions (FFR <0.80) to the score of SYNTAX to calculate the FSS. This method predicts MACE at one year based upon risk stratification ($p<0.01$), and is a better predictor of MACE compared with the purely anatomical SYNTAX score. However, it neglects other 'non-flow limiting' lesions, and therefore, limited to assess the coronary system objectively. In this chapter, I propose a novel method named FFR_{CUM} that incorporates anatomy and physiology in calculating an index value of myocardial ischemic burden, validate it and assess the change in response to coronary intervention.

3.2 Methods

3.2.1 Study population

Forty patients were recruited for this study, and 33 were included in this analysis. Patients screening and recruitment was described earlier (page 59). FFR measurement in at least on vessel pre or post PCI and complete ICA for all arteries and branches were the inclusion criteria for this analysis. Patients who underwent CABG, did not have any coronary physiology measures or had missing angiograms were excluded (n=7).

3.2.2 Angiographic estimate of myocardium at risk

Myocardial Jeopardy Index (BARI-MJI)

The BARI-MJI method of assessing left ventricular myocardial jeopardy was used in this study. It was first described by the Bypass Angioplasty Revascularization Investigation (BARI) (Alderman and Stadius, 1992; Bourassa *et al.*, 1995). The percentage of LV myocardium jeopardized by angiographic lesions ≥50% diameter stenosis was based upon the extent of distribution of the three main coronary arteries and all major branches. Different scores were given to each vessel ranging from absent, through non-significant, small, medium to large, based upon vessel length and its extent of branching. Coronary arteries ≥ 1.5 mm diameter were included in the scoring. The vessels Included were left anterior descending artery, diagonal and some septal branches, left circumflex, obtuse marginal branches, ramus intermedius (when it existed), right coronary artery, posterolateral and posterior descending arteries. A numerical score reflecting the size of LV territory supplied by each vessel was based upon the ratio of the length of the terminating artery to the LV base to apex distance. A numerical LV score for each terminating artery was assigned based upon extent of LV distribution (Table 3.1). The sum score of all terminal arteries (diseased and healthy) reflected the coronary distribution of the entire LV myocardium. The BARI MJI ratio was then calculated as follows:

$$BARI\ MJI = \frac{Total\ terminal\ arteries\ distal\ to\ lesions\ of\ interest}{Sum\ of\ left\ ventricle\ myocardium\ score}$$

Table 3.1 Terminal arteries segments' sizes and corresponding scores

Segment size	Definition	Scores
Insignificant	Branches that extend less than one fifth of the distance from base to apex of the left ventricle	0
Small	A small segment is subtended by a terminal vessel extending less than one third of the distance from base to apex of the left ventricle	1
Medium	A medium segment is subtended by a terminal vessel extending approximately one third to two thirds of the distance from base to apex of left ventricle	2
Large	Large segment is subtended by a terminal vessel extending approximately more than two thirds of the distance from base to apex of left ventricle	3

3.2.3 Calculating FFR as an index value for multiple vessels

There are several methods to calculate an index representing a total FFR across the main epicardial vessels. In this study, three methods were used to calculate an index value of total FFR, using both previously published methods and a novel method incorporating vessel specific weighted score based upon the BARI MJI protocol. This is described in detail in section (3.2.1).

A) The 3V FFR FRIENDS method

A method of calculating global FFR was described by Lee et al in the 3V FFR FRIENDS prospective study. The proposed method was to sum the FFR values of the three major epicardial vessels, and provide a metric index of total physiologic atherosclerotic burden, and its clinical relevance, with two year clinical outcomes. FFR was not measured in diminutive LCx or RCA; therefore, in those cases the mean value of the FFR in the two main vessels was multiplied by 3 to calculate $_{3V}$FFR. In d vessels, FFR is rarely measured due to the fact that the short length and small diameter (<2.0 mm). This is a prognostic method and only applied final FFR values, therefore, it includes post-stent values and untreated or healthy arteries. A median value of ≥ 2.72 (out of 3) was used to

identify patients into groups of low and high risk in the original work. Further details about the $_{3V}$FFR method have been published previously (Lee *et al.*, 2018).

If FFR were measured in all three major vessels:

$$_{3V}FFR = FFR_{LAD} + FFR_{LCx} + FFR_{RCA}$$

If FFR were measured in two vessels and a diminutive vessel was present:

$$_{3V}FFR = mean\ of\ (FFR_{main\ vessel\ 1} and\ FFR_{main\ vessel\ 2})\ x\ 3$$

B) Global FFR as described by Fournier et al

The method used by Fournier et al was of a similar design to the $_{3V}$FFR and was proposed by the FAME trials investigators. The authors suggested a sum of the three FFR values to calculate a single metric. In case of a missing FFR, but a vessel reported as angiographically 'normal', an FFR value of (1.0) was given; and if the missing FFR were post-PCI, a value of (0.90) was given. This was based upon the median value of post-PCI FFR in the FAME 1 and FAME 2 trials. The post PCI FFR values were used to calculate $_{GLOBAL}$FFR. Only FFR values higher than 0.8 were included in this method, and the five-year risk evaluation. Values ranged from 2.40 to 3.0, where 3.0 was considered as the maximal achievable value. Patient stratification was based upon $_{GLOBAL}$FFR tertiles; low ≤ 2.80, mid 2.81-2.87 and high ≥2.88 according to the original work. Further details about the $_{GLOBAL}$FFR method have been published previously (Fournier *et al.*, 2020).

If FFR was measured in three vessels:

$$_{GLOBAL}FFR = FFR_{LAD} + FFR_{LCx} + FFR_{RCA}$$

If FFR were measured in two vessels only and a post-PCI FFR value were missing:

$$_{GLOBAL}FFR = FFR_{Major\ vessel\ 1} + FFR_{Major\ vessel\ 2} + 0.9$$

If FFR were measured in two vessels and third vessel was angiographically normal:

$$_{GLOBAL}FFR = FFR_{Major\ vessel\ 1} + FFR_{Major\ vessel\ 2} + 1$$

C) Cumulative FFR: my proposed method

The objective was to create a single index which incorporated both pressure drop across the vessel represented by FFR and a vessel-specific weight derived from BARI MJI scoring protocol for terminal arteries. This index is named FFR_{CUM} to differentiate it from earlier indices. This metric was calculated before and after PCI, and comparison between post PCI and baselinewas made.

FFR values in the FFR_{CUM} method

FFR was measured during the procedure for vessels with visual stenosis of 30-90% whenever possible. Post-stent FFR was also measured if possible. Details of the VIRTU-5 procedural protocol including pressure wire assessment were described earlier in section 2.2.2. In the case of missing FFRs, I used the previously validated VIRTUheart™ software (University of Sheffield) to generate vFFR, such as those with minimal disease, vascular anatomy precluding safe pressure wire deployment, and other practical limitations. The method of generating vFFR has been described in section 2.2.3 and 2.2.4 (refer to pages 70-73). If a vessel were so severely diseased that pressure measurement was not possible or indicated, an FFR value of 0.6 was assigned. If a CTO were present, an FFR value of 0.5 was assigned.

Vessel anatomical weighed score

Each major coronary artery was given a score based upon the BARI-MJI protocol. The total sum of these scores equals 1.0; the total myocardial score. The score of a given artery depends upon its length and branches, thus, scores vary from one patient to another. The criteria for scoring is described in table 3.1.

Calculating FFR_{CUM}

To calculate FFR_{cum} an FFR either measured, simulated (vFFR), or even estimated should be available for all coronaries. Subsequently, vessel specific weighted score should be calculated for each vessel following the BARI-MJI method for assigning scores for each terminal artery based on its number of branches and length (Alderman and Stadius, 1992). Please note, only the vessel score is adapted into this method not the stenosis score. Once the two components are available for each major coronary artery, the score can be calculated by multiplying the FFR by the vessel specific weighted score for each artery. The sum of these values is then used as FFR_{cum} with a maximum achievable value of 1.0. This method can be applied for before intervention (with pre PCI FFR values) and after (with post PCI FFR values).

$$FFR_{CUM} = \sum_{i=1}^{3} (\text{FFR x vessel specific weighted score})$$

Where $i = 1$ Left anterior descending artery

$i = 2$ Left circumflex artery

$i = 3$ Right coronary artery

$$_{CUMULATIVE}FFR = LAD_{FFR\ x\ Vessel\ score} + LCx_{FFR\ x\ Vessel\ score} + RCA_{FFR\ x\ Vessel\ score}$$

The maximum possible value for FFR_{CUM} is 1.0 governed by FFR of 1.0 for all coronaries. However, the minimum is subjective to the lowest possible FFR. Therefore, a minimum value can not be stated similar to wire-based FFR.

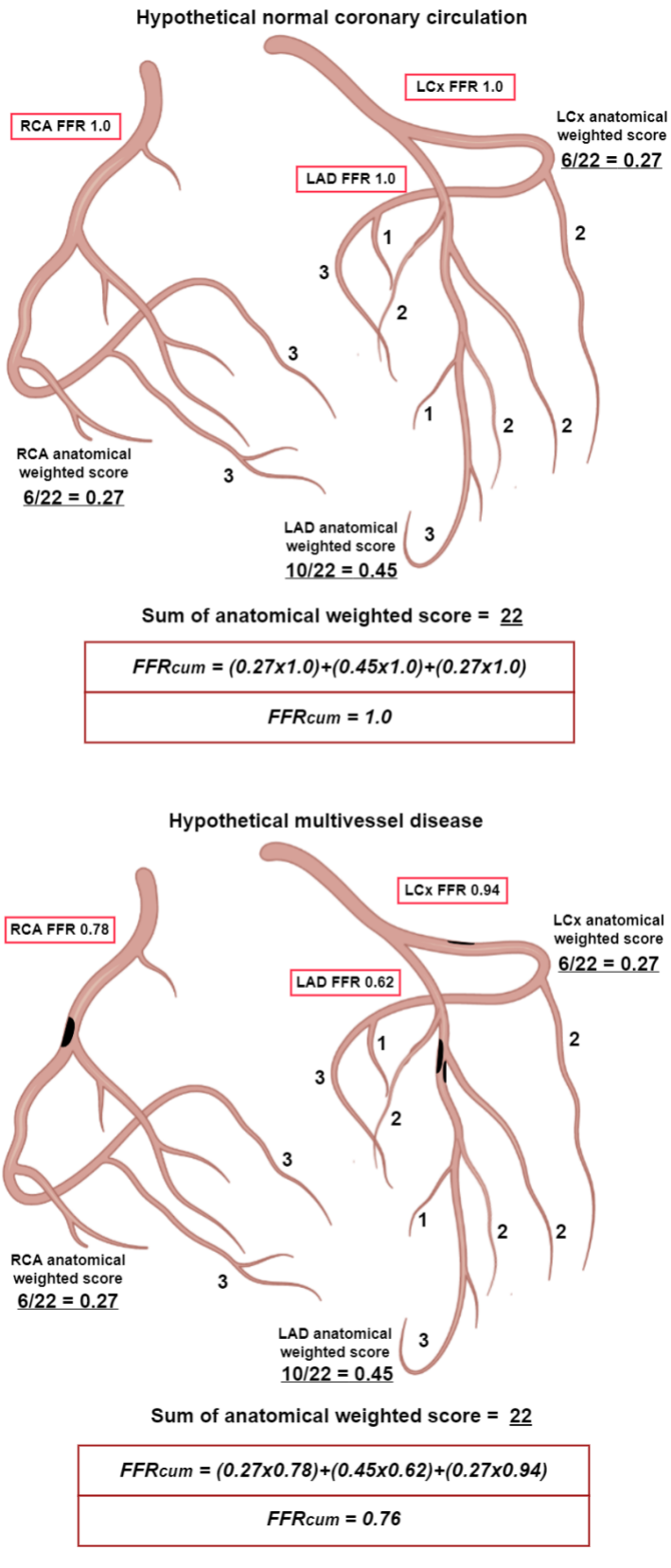


Figure 3.1 The method of calculating FFR_{CUM}.

In the top diagram, a normal coronary circulation is demonstrated, with each main artery and its branches being assigned a score based on its length. Each artery is given a weighted score based on the sum of main artery and its branches, and also given an FFR of 1.0. In the bottom diagram, a similar demonstration of the circulation but at the present of disease. Thus, hypothetical FFR values were assigned accordingly. FFR_{CUM} *is then calculated using the shown equation where each vessel anatomical weighted score is multiplied by its FFR and then summed up.*

Comparing FFR_{cum} with previous methods

In one hand, Interquartile ranges were used to divide the data into three risk groups; low, mid and high to compare it with (Fournier et al., 2020) originally reported risk groups based on IQRs. In the other hand, the median was used to divide the data into two risk groups (low and high) to compare it with (Lee et al., 2018) originally reported risk groups based on median.

3.2.4 Statistical analysis

Data were reported as means, standard deviations and percentages unless stated otherwise. Inter-observer variability was calculated using inter-class correlation and Pearson's after randomly assigning 10 cases for MJI experienced cardiologist. The cardiologist was blinded to the MJI scores that were already produced. Histograms were used to display frequency of variables and bar charts to demonstrate differences. For each patient, all indices were reported before and after PCI if applicable. A paired samples t-test was used to compare before and after PCI values, and an unpaired t test was used to compare the PCI and control groups. Pearson's correlation (r) was used to assess the linear relationship between $_{CUMLATIVE}$FFR values and other indices values. Kendall's coefficient of concordance (Kendall's W) was used to measure the agreement between FFR_{CUM} and other indices and Spearman's rank correlation (rho) was used to assess the strength of the agreement. GraphPad Prism (9.4.1) was used for statistical analysis.

3.3 Results

Thirty three patients were included in this analysis. Six patients were excluded for the following reasons; three were referred for CABG, one patient had missing RCA views on the angiogram DICOM file and two did not have any FFR measured. Twenty three patients underwent single (n=13) or double (n=10) vessels PCI. Details of the 33 patients are shown in table 3.2. All patients had at least one FFR measurement pre or post PCI. FFR was measured in 55 vessels pre-PCI, and 26 vessels post-PCI. vFFR was generated in 24 vessels pre-PCI, and nine vessels post PCI, that did not have wire-based FFR. FFR was estimated in high-risk vessels and CTOs in 20 cases, of which four were categorised as 'post-stent values' as there was no intervention. The sum of included values was 134 FFRs, including measured, virtual and estimated. A breakdown summary of the included vessels (n=134) is presented in table 3.3. Frequency histograms of FFR distributions for each vessel is demonstrated in figure 3.2. Individual FFRs per vessel per patients are shown in figure 3.3.

Table 3.2 Basic demographics for patients included in FFR_{CUM}

Patient characteristics	N = 33	Percentage	Mean (±SD)
Age			65 (±8)
Male	25	76	
Female	8	24	
Smoking status			
Current smokers	4	12	
Ex-smoker	21	64	
Non-smoker	8	24	
Risk factors			
Hypertension	21	64	
Hyperlipidaemia	11	33	
Type 2 Diabetes	5	15	
Procedural outcomes			
Underwent PCI			
Yes (PCI group)	23	70	
No (Control group)	10	30	

Table 3.3 Summary of all FFR values included in the analysis (measured, virtual 'simulated' and estimated)

		Baseline (n=33)		Post PCI (n=23)	
Wire-based FFR		N	%	N	%
FFR was measured in three vessels		5	15%	0	0%
FFR was measured in two vessels		14	42%	7	30%
FFR was measured in one vessel		12	36%	12	52%
FFR was not measured		2	6%	4	17%
Total number of mFFR		55	56%	26	67%
vFFR					
vFFR was generated for three vessels		0	0%	0	0%
vFFR was generated for two vessels		5	15%	2	9%
vFFR was generated for one vessel		14	42%	5	21%
vFFR was not generated		14	42%	16	70%
Total number of vFFR		24	24%	9	23%
Estimation of FFR (CTOs and high-risk stenoses)					
FFR was estimated in three vessels		0	0%	0	0%
FFR was estimated in two vessels		5	15%	0	0%
FFR was estimated in one vessel		10	30%	4	17%
FFR was not estimated		18	55%	19	82%
Total number of estimated values		20	20%	4	10%
FFR per vessel		Mean	±SD	Mean	±SD
	LAD	0.76	±0.14	0.85	±0.08
	LCx	0.81	±0.14	0.87	±0.11
	RCA	0.75	±0.18	0.85	±0.14

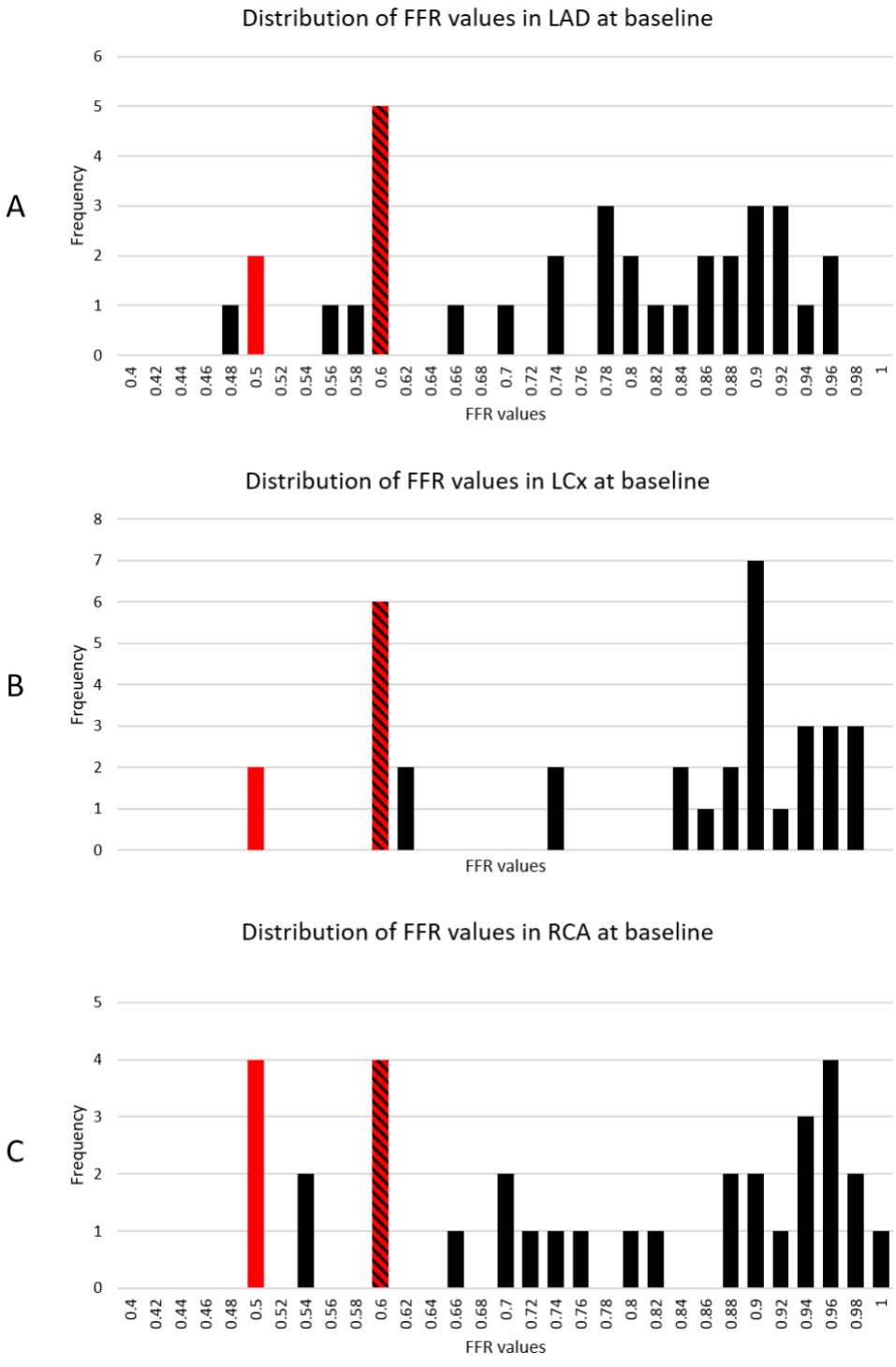


Figure 3.2 Frequency histograms showing the distribution of FFR values used in the analysis

- *Black coloured bars indicate mFFR and vFFR*
- *Red coloured bars indicate estimated FFR of 0.5 for CTO*
- *Red and black coloured bars indicate estimated FFR of 0.6*

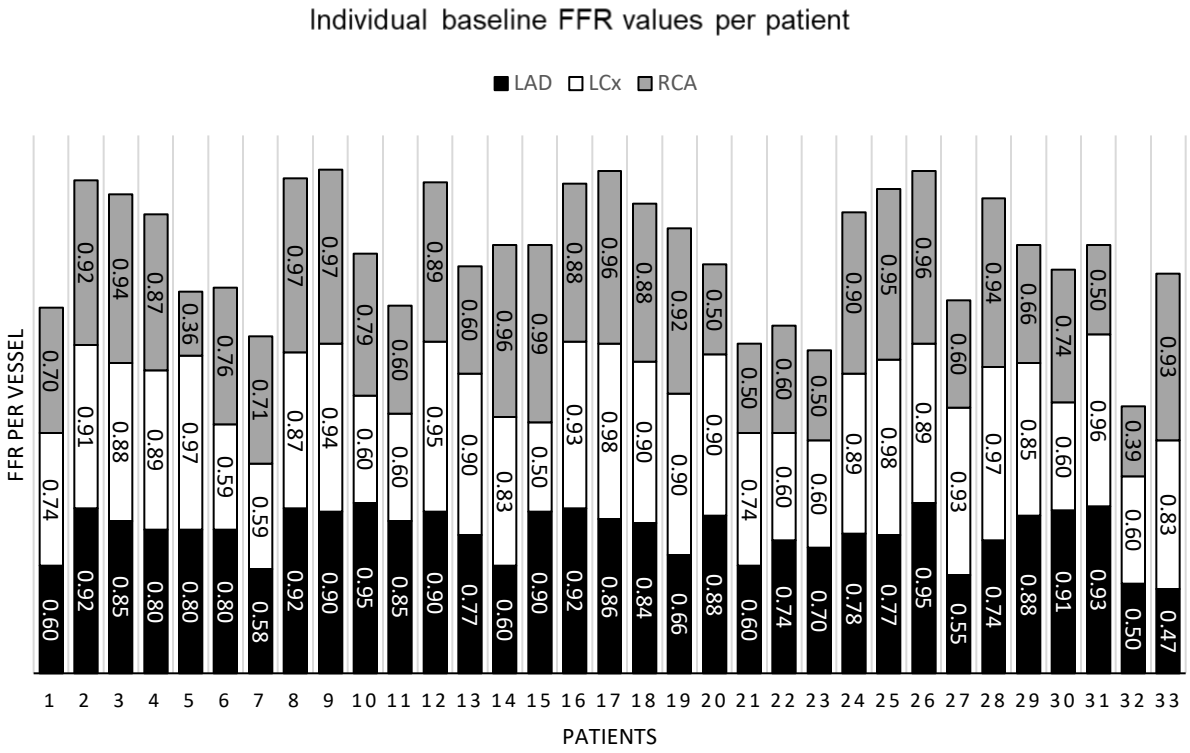


Figure 3.3 Individual baseline FFR values per patient

Values are presented as stacked bars, each bar represent FFR value in a given artery. Blue coloured bars are for LAD, orange coloured bars for LCx and grey coloured bars for RCA.

3.3.1. Visual assessment of myocardium at risk: the BARI MJI.

MJI was reported in 33 cases, of which 23 underwent PCI and 10 did not (the control group). The mean MJI score for the PCI group was 0.64±0.23 [range 0.17 to 1.0] and for the control group 0.22±16 [range 0 to 0.48] ($p<0.01$) (figure 3.3). The mean MJI score post-PCI was 0.25±019 [range 0 to 0.62]; a significant decrease ($p<0.01$), with a change of 65±22%. Individual changes and mean difference are shown in figure 3.4. A moderate relationship was observed between MJI scores pre and post PCI ($r=0.57$, $p<0.01$) (figure 3.5). A summary of MJI scores is presented in table 3.3

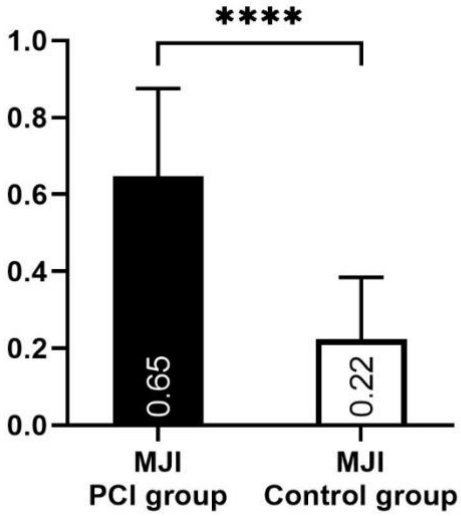


Figure 3.4 Histograms showing the difference in MJI between the PCI group and control group.

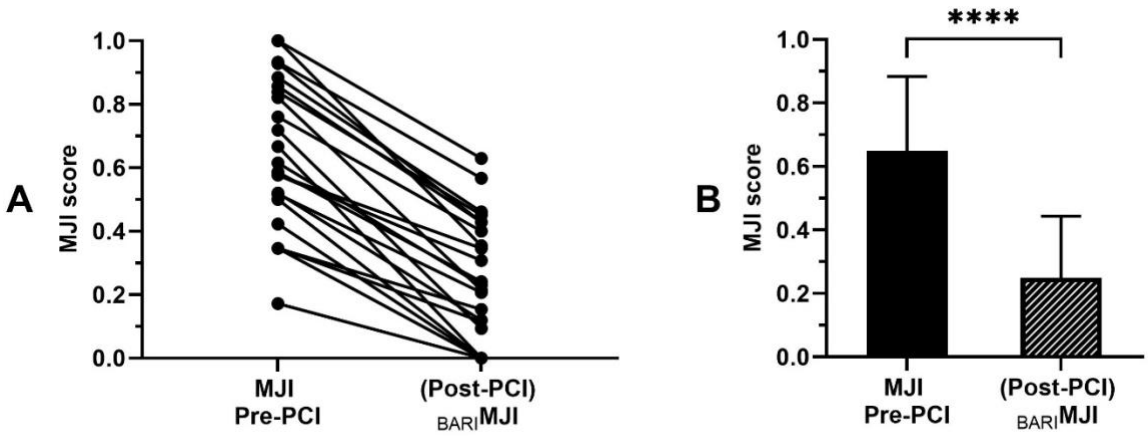


Figure 3.5 Changes in MJI in response to PCI

*(A) individual changes per patient, and (B) the difference between the means pre and post PCI. (****p<0.0001)*

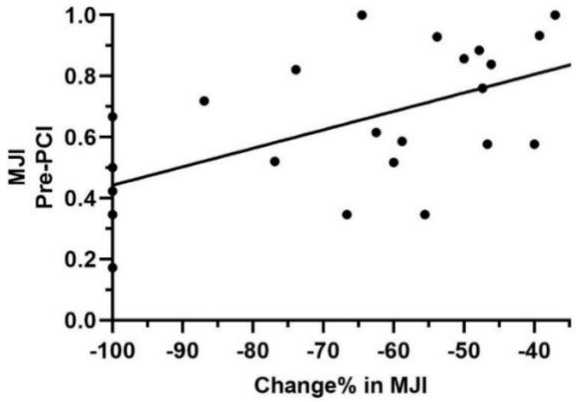


Figure 3.6 A correlation plot showing the percentage of change in MJI in relation to MJI values pre-PCI.

Table 3.4 Breakdown of MJI scores per vessels.

	PCI (n=23)		Control (n=10)		Full cohort (n=33)	
	Mean	±SD	Mean	±SD	Mean	±SD
Total possible score	27.5	±2.1	25.6	±1.9	26.9	±2.2
Total stenosis score	18	±7.1	5.8	±4.2	14.3	±8.5
MJI score	0.65	±0.2	0.22	±0.16	0.52	±0.3
Breakdown of MJI scores						
LAD possible score	11	±1.6	9	±1.2	10	±1.7
LAD stenosis score	7.73	±3.8	2.8	±2.6	6.2	±4.2
Percentage of myocardium jeopardised by LAD	39.5	±5%	35	±4%	37	±5%
LCx possible score	8.3	±2	8.1	±2.2	8.2	±2
LCx stenosis score	4.5	±4.2	0.3	±1	3.2	±4.1
Percentage of myocardium jeopardised by LCx	30	±7%	31	±9%	30	±7%
RCA possible score	7.8	±1.8	7.8	±2.1	7.8	±1.8
RCA stenosis score	5.4	±4.2	2.7	±4.3	4.6	±4
Percentage of myocardium jeopardised by RCA	29.5	±6%	30	±7%	29	±6%
Dominance						
Right	65%		80%		70%	
Left	26%		20%		24%	
Codominance	8%		0%		6%	

MJ= myocardial jeopardy index, LAD= left anterior descending artery, LCx= left circumflex, and RCA= right coronary artery.

Inter-observer variability of BARI-MJI scoring

The mean MJI for the first assessor was 0.61±0.30 and 0.63±0.24 for the second (p=ns), and the agreement between observers was strong (r= 0.83, ICC= 0.90, p<0.01). Bland-Altman and correlation plots are shown in figure 3.7.

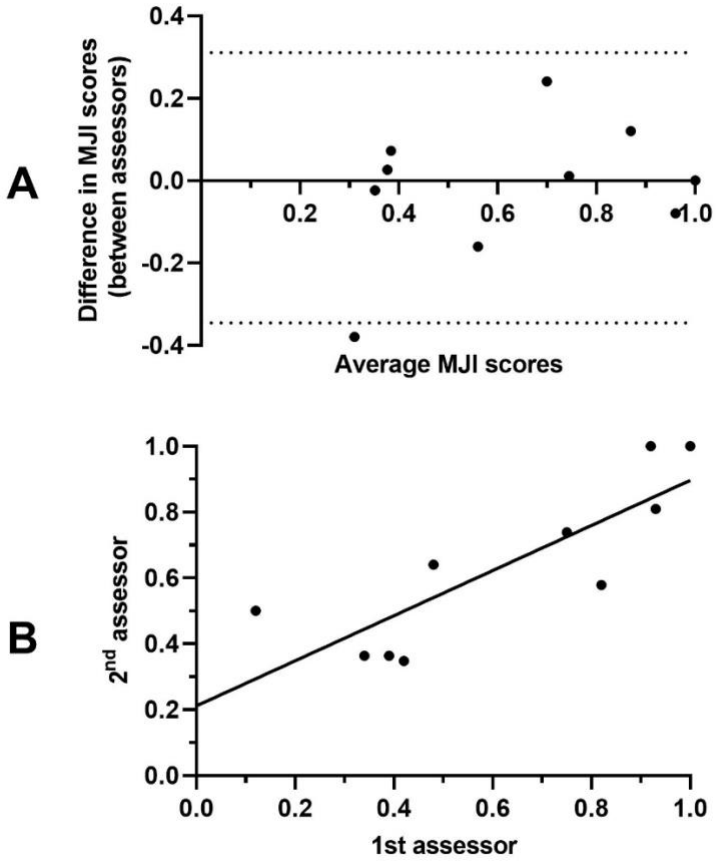


Figure 3.7 BARI MJI agreement plots.

(A) Bland-Altman plot demonstrating agreement and differences in scoring BARI-MJI between two assessors. The upper and lower limits of agreement are shown with the interrupted line (-0.34 to 0.31), and (B) Pearson's correlation for inter-observer variability (r=0.83, p<0.01).

3.3.2. Calculating a single FFR value for multiple vessels: The FFR_{CUM} index.

The FFR_{CUM} was successfully calculated for all the patients (n=33). The mean FFR_{CUM} at baseline was 0.76±0.1 [range 0.51 to 0.93]. The distribution of values at baseline is shown in figure 3.8. The mean FFR_{CUM} in the PCI group pre-PCI was 0.72±0.1 and in the control (non-PCI) group 0.84±0.07. Post-PCI FFR_{CUM} was 0.83±0.08, $p<0.01$. Pre- and post PCI values were closely correlated ($r=0.83$). The mean percentage of change in response to PCI was 16.6±10%. A strong negative relationship was found between the change in FFR_{CUM} and pre-PCI values ($r=-70$, $p<0.01$). Individual changes and the correlation between change and pre PCI are demonstrated in figure 3.9. There was no significant difference between the post-PCI values and those of the control group ($p=0.78$). The differences between all groups are demonstrated in figure 3.10. I have conducted a preliminary analysis of vessels contribution to the myocardium at risk (table 3.5). In single vessel intervention, the LCx was associated with the highest increase in FFR_{CUM} (0.14±0.01) compared to 0.08±0.4 for interventions on LAD and on RCA alike. Two vessel PCI resulted in the greatest increase in FFR_{CUM} (0.24±0.02), and this was in LCx and RCA. The relative increases in response to single and double vessel interventions were 0.09±0.04 and 0.14±0.06, respectively.

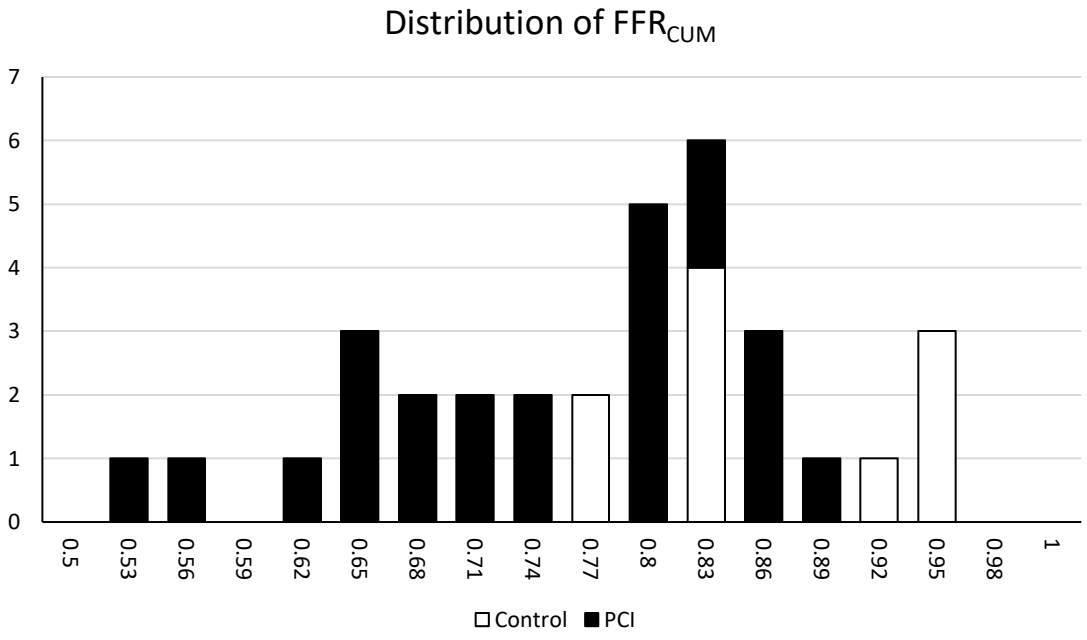


Figure 3.8 Distribution of FFR_{CUM} values at baseline in increments of 0.03.

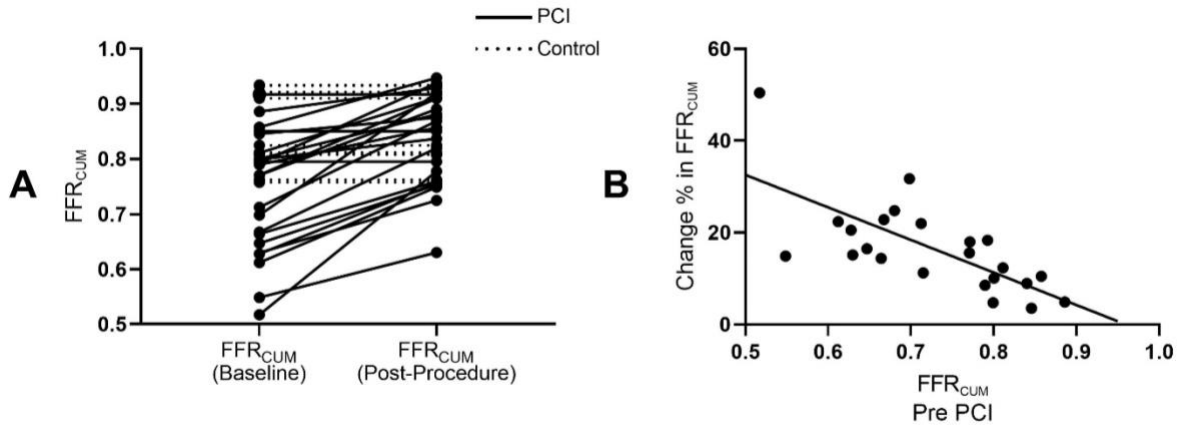


Figure 3.9 Changes in FFR_{CUM} in response to PCI

(A) Individual changes per patient, and (B) A correlation plot demonstrating the percentage of change in FFR_{CUM} in relation to FFR_{CUM} values pre-PCI (r=-0.70, p<0.01). Dotted lines showing no change in the control patients.

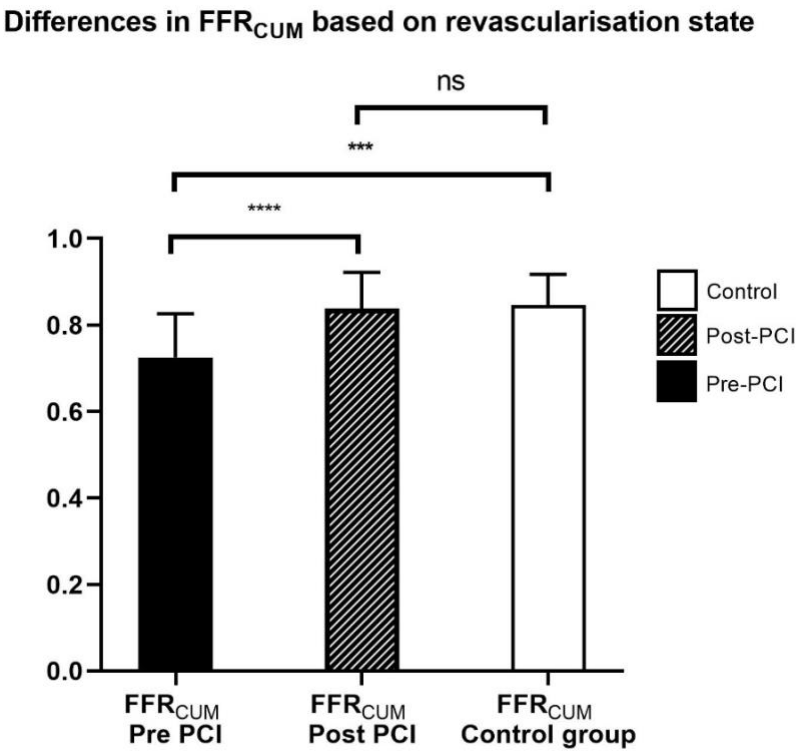


Figure 3.10 Histograms showing the FFR_{CUM} values for each group

Histograms showing the difference between Pre PCI FFR_{CUM} and control group FFR_{CUM}, Pre PCI FFR_{CUM} and post PCI FFR_{CUM}, and (C) Post PCI FFR_{CUM} and control group FFR_{CUM}
****p<0.001, ****p<0.0001.*

Table 3.5 Contribution of individual vessel revascularisation to FFR_{CUM}

Revascularisation	n	%	Relative increase in FFR_{CUM}	
			Mean	SD
One vessel only intervention	13	57%	0.09	±0.04
LAD	9	70%	0.08	±0.04
LCx	2	15%	0.14	±0.01
RCA	2	15%	0.08	±0.04
Two vessels intervention	10	43%	0.14	±0.06
LAD and RCA	5	50%	0.12	±0.03
LAD and LCx	3	30%	0.10	±0.03
RCA and LCx	2	20%	0.24	±0.02
Total	23		0.11	±0.05

3.3.3 Validation of FFR_{CUM}

3.3.3.1 Accuracy of the calculation

First, I compared FFR_{CUM} with BARI-MJI to estimate the myocardium at risk in baseline and post PCI. There was a significant and strong negative correlation between the two methods ($r=-0.73$, $p<0.01$) at baseline and with post-PCI only values ($r=-0.61$, $p<0.01$). Second, I compared the final single FFR, which includes post-PCI and control values, similar to what was reported by Fourier et al and Lee et al. This was applicable in all cases (n=33) for $_{3V}$FFR and in 25 case for $_{GLOBAL}$FFR. FFR_{CUM} scores demonstrated moderate to strong and statistically significant correlation with $_{3V}$FFR and $_{GLOBAL}$FFR scores ($r=0.73$, $p<0.01$ and $r=0.57$, $p<0.01$) respectively. Correlation plots are demonstrated in figure 3.11.

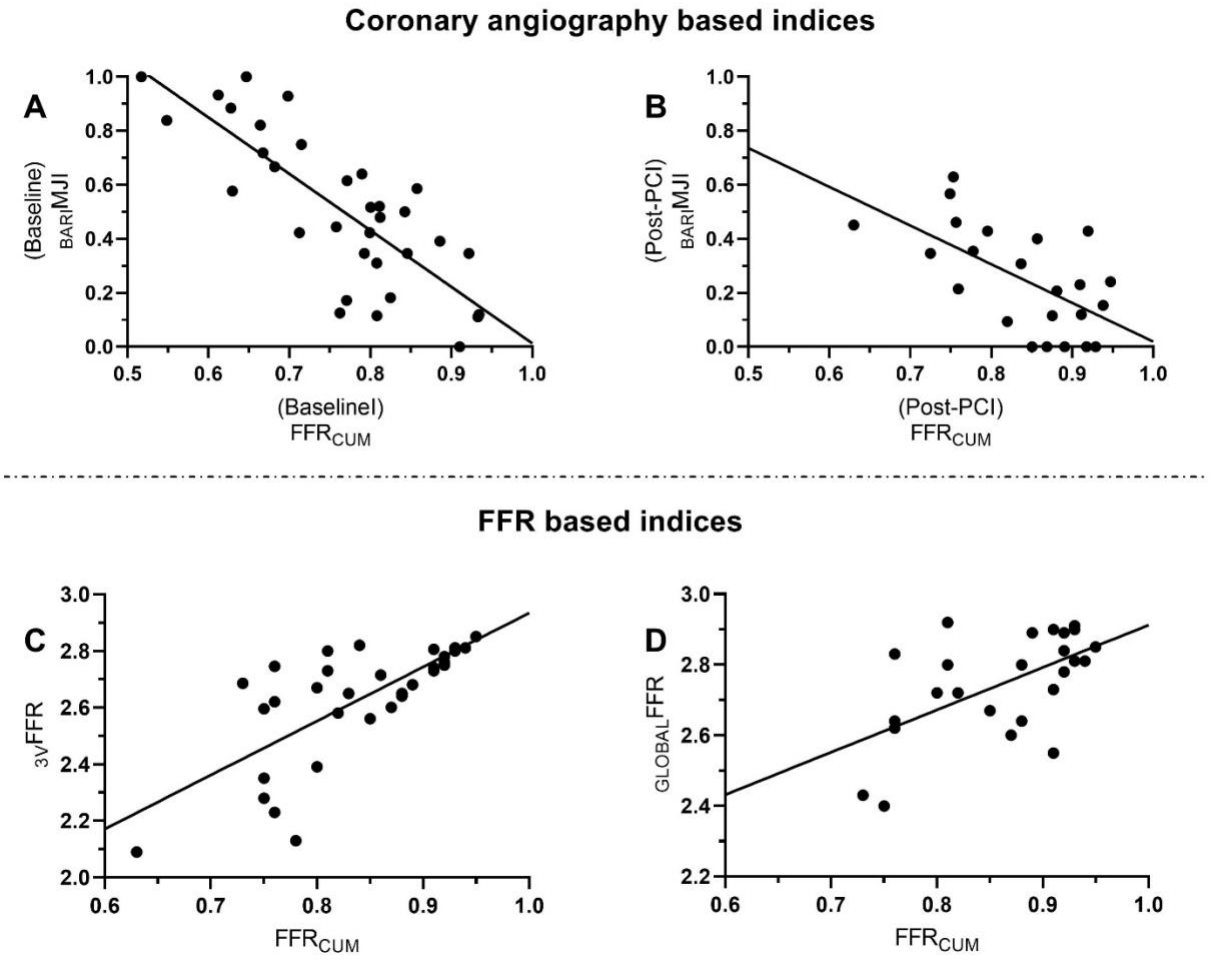


Figure 3.11 Correlation plots demonstrating the relation between FFR_{CUM} values and the other methods.

(A) Correlation between baseline values (n=33) of FFR_{CUM} *and BARI-MJI (r=-0.73, p<0.01), (B) Correlation between post-PCI values (n=23) of* FFR_{CUM} *and BARI-MJI (r=-0.61, p<0.01), (C) Correlation between* FFR_{CUM} *and* $_{3V}FFR$ *values (n=33) (r=0.73, p<0.01) and (D) Correlation between* FFR_{CUM} *and* $_{3V}FFR$ *values (n=25) (r=0.73, p<0.01).*

3.3.3.2 Agreement in classifying total physiological ischemic burden after invasive coronary angiogram ±PCI: A comparison with established values.

I used ranges to divide the patients (n=33) into three groups; low (≤0.78), mid (>0.78 to ≤0.91) and high (>0.91) FFR_{cum} and compared it with Fournier et al's originally reported tertiles of $_{GLOBAL}FFR$; low (≤2.80), mid (>2.80 to ≤2.88) and high (>2.88) (figure 3.12). Eight cases were excluded from the analysis because they did not meet the eligibility criteria for $_{GLOBAL}FFR$. The agreement between FFR_{CUM} and $_{GLOBAL}FFR$ (n=25), as tested using Kendall's coefficient of concordance, was acceptable (W=0.74, p=0.06). There was a moderate positive relationship between the classifications of the two methods (r=0.57, p<0.01). Individual values and classification is shown in table 3.6.

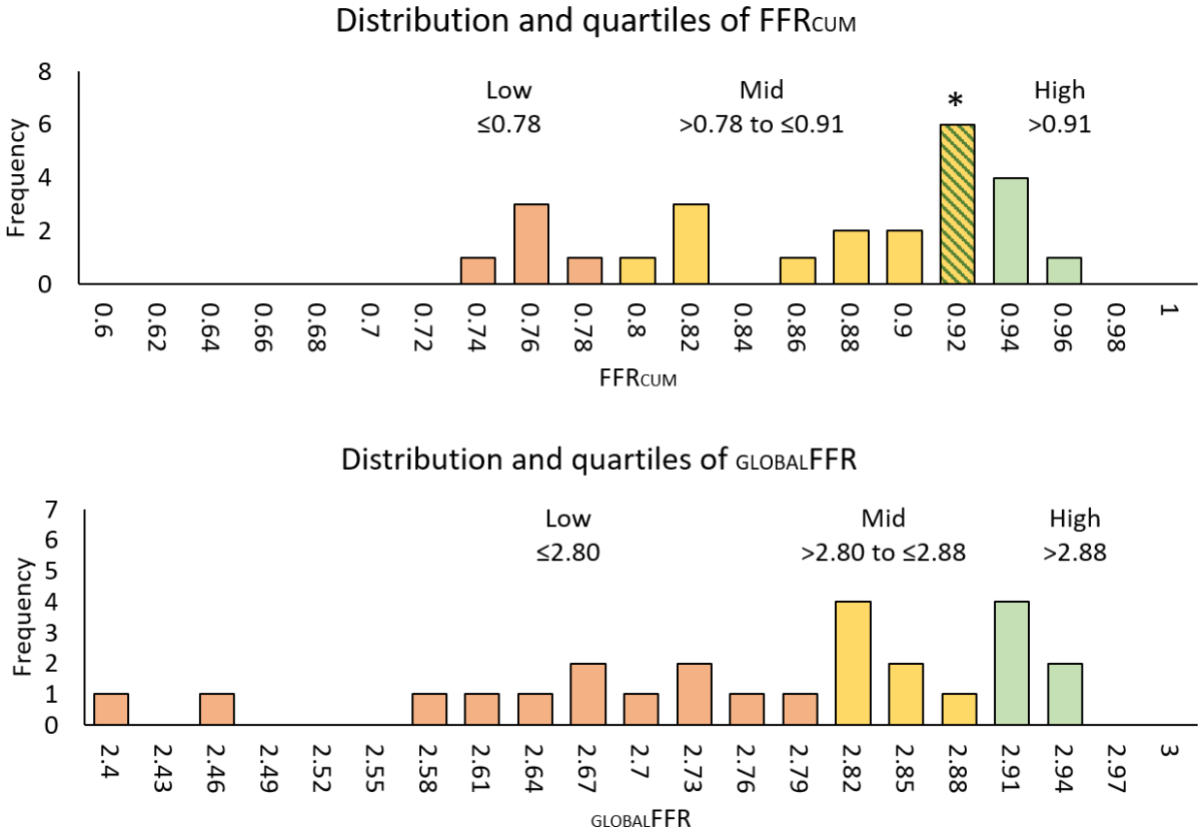


Figure 3.12 Distribution of FFR_{CUM} and $_{GLOBAL}FFR$ values.

Bars are coloured according to their classifications; Red represents low values, yellow represents mid values and green represents high values.
**Green and yellow represents intertwine of both classes at this bar.*

Table 3.6 Comparing the agreement between FFR_{CUM} and $_{GLOBAL}FFR$

Patients N=25		FFR_{CUM}	Classification	$_{GLOBAL}FFR$	Classification
1	Post-PCI	0.82	Mid	2.72	Low
2	Post-PCI	0.92	High	2.84	Mid
3	Post-PCI	0.80	Mid	2.72	Low
4	Post-PCI	0.85	Mid	2.67	Low
5	Post-PCI	0.76	Low	2.83	Mid
6	Post-PCI	0.76	Low	2.64	Low
7	Control	0.92	High	2.89	High
8	Control	0.93	High	2.9	High
9	Post-PCI	0.92	High	2.78	Low
10	Control	0.91	High	2.9	High
11	Post-PCI	0.89	Mid	2.89	High
12	Post-PCI	0.94	High	2.81	Mid
13	Control	0.81	Mid	2.92	High
14	Control	0.81	Mid	2.8	Mid
15	Control	0.76	Low	2.62	Low
16	Post-PCI	0.91	Mid	2.73	Low
17	Post-PCI	0.75	Low	2.4	Low
18	Post-PCI	0.88	Mid	2.64	Low
19	Post-PCI	0.93	High	2.81	Mid
20	Control	0.93	High	2.91	High
21	Post-PCI	0.73	Low	2.43	Low
22	Post-PCI	0.95	High	2.85	Mid
23	Post-PCI	0.88	Mid	2.8	Mid
24	Post-PCI	0.91	Mid	2.55	Low
25	Post-PCI	0.87	Mid	2.6	Low
Classification		**n**	**%**	**n**	**%**
	Low	5	20%	12	48%
	Mid	11	44%	7	28%
	High	9	36%	6	24%
		Agreement			P-value
	Correlation (Spearman's)			r= 0.55	<0.01
	Concordance (Kendall's)			W= 0.74	0.06

The same analysis was performed against the $_{3V}$FFR (n=33) method to assess agreement. Groups were divided into high and low scores according to the original median reported by Lee et al (2.72); for the FFR_{CUM}, the median was (0.85) (figure 3.13). Values therefore were classified as high when ≥2.72 and ≥0.85, or low when less than those. The agreement between FFR_{CUM} and $_{3V}$FFR was good (w=0.74, p<0.05) and the relationship between the classifications of the methods was moderate (r= 0.45, p<0.01). Individual values and classification are shown in table 3.7.

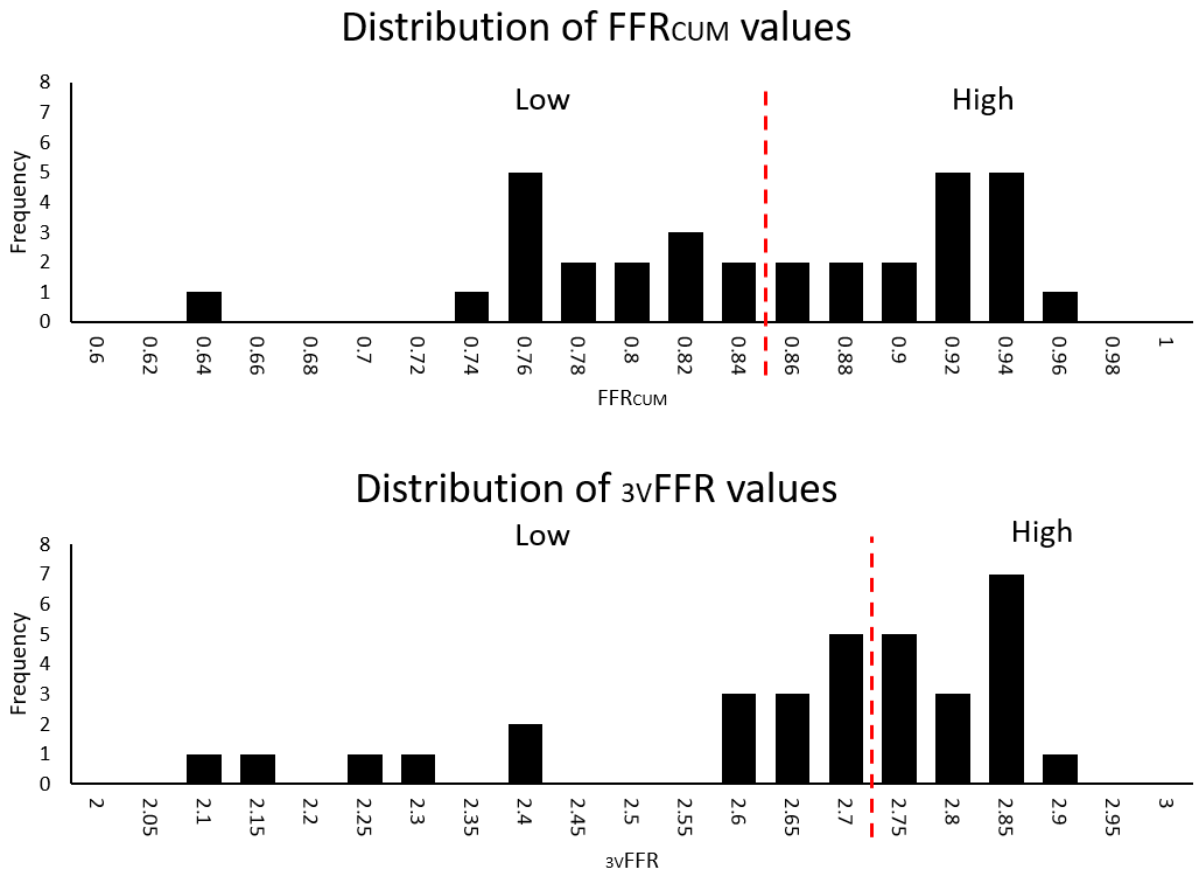


Figure 3.13 Distribution of FFR_{CUM} and $_{3V}$FFR values.

The red dotted line represents the median in both methods.

Table 3.7 Comparing the agreement between FFR_{CUM} and $_{3V}FFR$:

Patients (N=33)		FFR_{CUM}	Classification	$_{3V}FFR$	Classification
1	Post-PCI	0.82	Low	2.58	Low
2	Post-PCI	0.92	High	2.75	High
3	Post-PCI	0.80	Low	2.67	Low
4	Post-PCI	0.85	High	2.56	Low
5	Control	0.83	Low	2.65	Low
6	Post-PCI	0.76	Low	2.745	High
7	Post-PCI	0.76	Low	2.23	Low
9	Control	0.92	High	2.76	High
10	Control	0.93	High	2.81	High
11	Post-PCI	0.84	Low	2.82	High
12	Post-PCI	0.92	High	2.78	High
13	Control	0.91	High	2.74	High
14	Post-PCI	0.86	High	2.715	High
15	Post-PCI	0.89	High	2.68	Low
16	Post-PCI	0.94	High	2.81	High
17	Control	0.81	Low	2.73	High
18	Control	0.81	Low	2.8	High
19	Control	0.76	Low	2.62	Low
20	Post-PCI	0.91	High	2.73	High
21	Control	0.75	Low	2.28	Low
22	Post-PCI	0.75	Low	2.595	Low
23	Post-PCI	0.75	Low	2.35	Low
24	Post-PCI	0.63	Low	2.09	Low
25	Post-PCI	0.88	High	2.64	Low
26	Post-PCI	0.93	High	2.81	High
27	Control	0.93	High	2.8	High
28	Post-PCI	0.73	Low	2.685	Low
29	Post-PCI	0.95	High	2.85	High
30	Post-PCI	0.88	High	2.65	Low
31	Post-PCI	0.91	High	2.805	High
32	Control	0.80	Low	2.39	Low
33	Post-PCI	0.78	Low	2.13	Low

Classification	N	%	n	%
Low	16	49%	17	51%
High	17	51%	16	49%

Agreement		P-value
Correlation (Spearman's)	r= 0.46	<0.01
Concordance (Kendall's W)	W= 0.72	<0.05

3.4 Discussion

3.4.1 Summary of the results

In this chapter, I have described and validated a novel index (FFR_{CUM}) of determining myocardium at risk by quantifying the total ischemic burden prior and after coronary intervention, which may in future be used for its diagnostic and prognostic value to assess the value of different treatment strategies. In my method, anatomical complexity is accounted for as well as physiological severity to provide a patient specific value. I have demonstrated that FFR_{CUM} (0.72±0.1) was able to predict myocardium at risk in different disease severity when it was compared to myocardial jeopardy index before intervention. The FFR_{CUM} increased in this cohort by a mean 17% after coronary intervention (from 0.72±0.1 to 0.83±0.08). Acceptable agreement was demonstrated with existing risk stratification methods, namely $_{3V}$FFR and $_{GLOBAL}$FFR, in 33 and 25 patients respectively. Summary of the main findings is shown in figure 3.14.

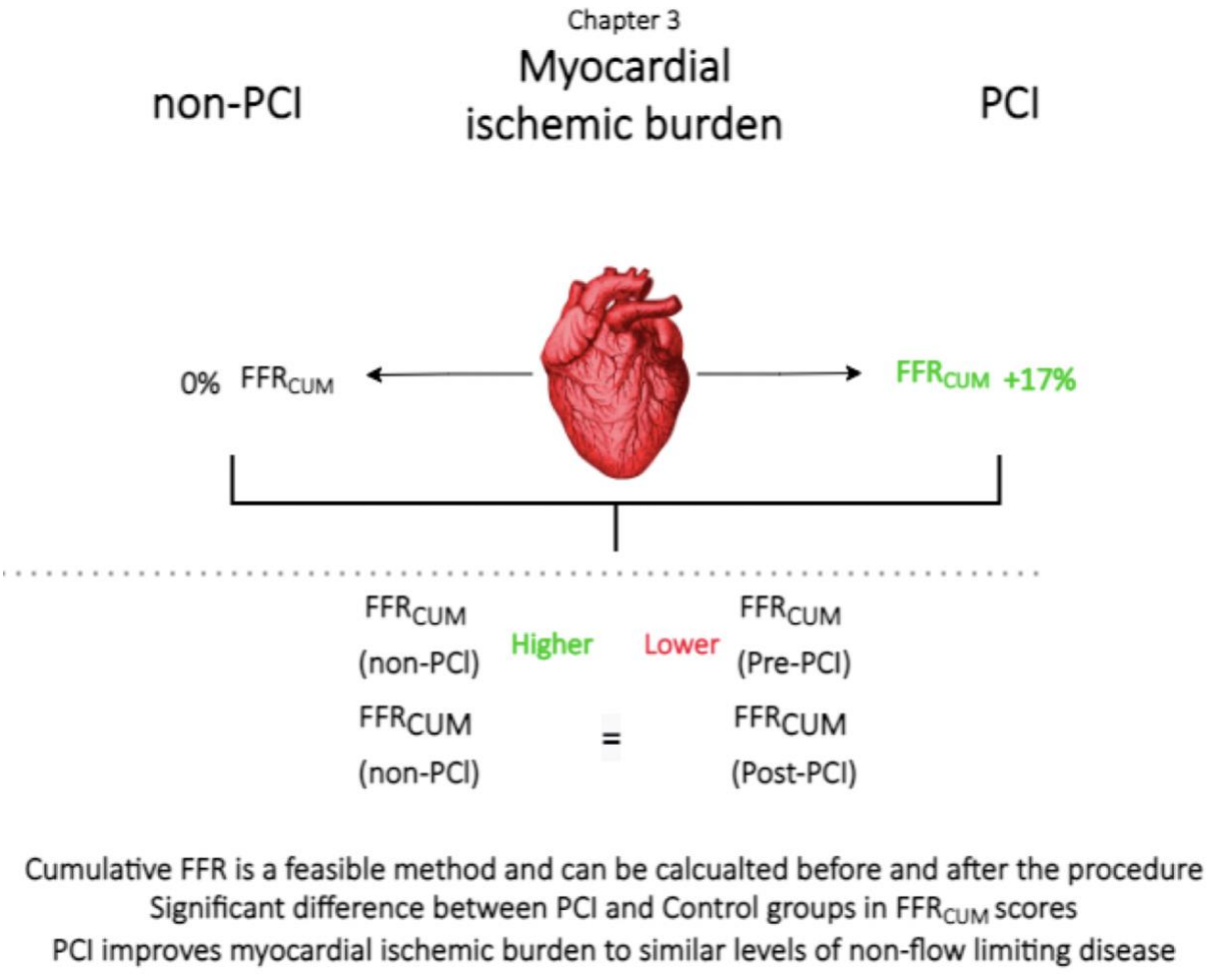


Figure 3.14 Schematic summary of the findings from chapter three

3.4.2 Method development

The FFR_{CUM} consists of two components which are physiology and anatomy. Generally, it is a functional method to provide a single FFR value with respect to anatomy. The functional SYNTAX score was the first to include functional assessment with anatomy. Moreover, thirty-two percent of patients were moved to low-risk classification after applying FFR measures to their initial SYNAX scores. Thus, it is apparent that adding physiology to anatomical assessment inform us more about CAD. However, the SYNTAX score was designed to assess the complexity of coronary artery disease, and was applied retrospectively in the SYNTAX study, where a relationship was found

between this measure and long term outcomes after coronary intervention (Mohr *et al.*, 2013). Yet, it does not account for visually non-significant stenosis, which makes it incomplete to some extent. Following from that, two functional methods were proposed ($_{GLOBAL}$FFR and $_{3V}$FFR), in which a simple sum of the three FFR values for the major vessels was derived. These methods overcome the limitation of FSS by including physiologically non-significant lesions. However, these two methods do not account for anatomy and were designed to be used after left heart catheterisation (±PCI) to assess prognosis. They were not intended for pre-PCI assessment of myocardium in any form. The other component of FFR_{CUM} is personalising the FFR values relative to the coronary specific anatomical weighted score based on BARI-MJI criteria of identifying anatomical score for each terminal artery. In this system, individual vessel scores are calculated for each major terminal artery based on the length, calibre and branches (Alderman and Stadius, 1992). An estimate of the total LV supply is calculated as the sum of these scores. Therefore, by assigning each vessel score (as percentage) to the FFR, a relative fractional value is obtained and the sum of these three values result in FFR_{CUM}. The inclusion of a vessel weighted score is the main difference between my method and the other methods, which treat FFR as an independent value.

Ideally, FFR_{CUM} requires FFR measurement in all major vessels, but this is not practical, and is challenging for routine practice, because FFR is only indicated in intermediate lesions and FFR is costly and invasive. Thus, an alternative vFFR can be used to replace any missing FFR. VIRTUheart™, which was used to produce vFFR in this work, has demonstrated excellent diagnostic accuracy (>90%) compared with wire-based FFR (see section 2.3.2). The only remaining obstacles to calculate FFR_{CUM} are CTOs and high-risk stenosis in which passing a pressure wire might impose a risk. By this means, an estimation using vFFR is reasonable to produce this index value in clinical routine cases. Different FFR values for CTO (also known as FFR_{myo}) have been reported in the literature, with values ranged from 0.45 to 0.50 (Zimarino *et al.*, 2006; Sachdeva *et al.*, 2014; Lee *et al.*, 2017). In this study, I therefore used an FFR of 0.50 for cases with CTO. Similarly, an FFR of 0.60 was used for lesions in which passing the FFR wire was not safe, and in which using VIRTUheart™ was not successful for technical reasons including very extremely narrowed lesions or severe left main stem lesions which can not be segmented using the software. Moreover, extremely narrowed lesions will result in failure of processing in some cases.

Variability between FFR_{CUM} assessors

The mathematical principles behind cumulative FFR, is not complicated and can be performed using simple equations. However, the components of the technique may carry some levels of operator subjectivity, particularly, in modelling vFFR and vessel weighted scoring. Ideally, this method should be calculated with pressure-wire derived FFR, however, this is rarely available in all three major vessels unless for research purposes. Additionally, the BARI-MJI vessel scoring method is subjective, and requires a detailed visualising of the coronary angiogram and appropriate levels of understanding of the coronary anatomy. The BARI criteria to define and score anatomy is not recent, in fact it has been published and used for almost three decades. These challenges, that may impose some levels of variability are not limited to the FFR_{CUM} method and similar limitations have been proposed before with other operator-dependent methods. To minimise such risk of assessors' variability, some measures can be taken including inter-observer variability in both components separately to avoid cumulative error in calculation. This was performed in this work, as shown in sections 2.3.2 and 3.3.1, for both vFFR modelling and BARI scoring respectively. Inter-observer variability analysis is encouraged at the validation stage of this technique. Automated methods can be later introduced, including anatomical scoring because it follows a simple concept which is based on the length of arteries and branches from the base to apex. In concept, if the myocardium length and the distance that a given artery covers measured manually, a ratio or a score can be automatically generated. This preliminary proposal can reduce the variability in anatomical vessel scoring, but it has yet to be developed and investigated.

Advantages of FFRcum

FFR_{CUM} can be used to estimate overall disease severity, incorporating a more sophisticated measure of myocardium at risk than is currently used (or not used) following a simple mathematical calculation. Moreover, this system can be used ahead of the LHC to provide an initial estimation of the disease's burden and plan accordingly. Prognostic value can be also gained if calculated post-PCI since the technique allows the calculation with FFR negative and positive vessels unlike other methods. Therefore, the calculation may be deployed in cases with visually non-significant disease, which is an advance.

3.4.3 Myocardium at risk assessed by FFR_{CUM}

I have used the BARI-MJI in this chapter which follows a similar concept to estimate myocardium at risk and to validate my method (Graham *et al.*, 2001). The BARI-MJI has been validated against CMR and found to be a reliable estimate of myocardial at risk in STEMI patients (Ortiz-Pérez *et al.*, 2007; Moral *et al.*, 2012). A further analysis of the MJI suggested that it has an inverse relationship with FFR, meaning that the higher the percentage of jeopardised myocardium, the lower the FFR values ($r=-0.40$, $p<0.01$) (Leone *et al.*, 2013). In this chapter, I have shown that pre-PCI MJI was significantly higher than the post PCI group ($p<0.01$), and higher than the control group ($p<0.01$) suggesting that lesions in the PCI group don't only have functionally significant disease but a larger area at risk as well based on the findings of previous works. The relationship between BARI-MJI and FFR_{CUM} was significant and inversely correlated which aligns with Leone et al work. Nonetheless, the correlation was stronger in my method compared to individual FFR values only ($r=-0.73$ vs $r=-0.40$). This is understandable because MJI estimates the area at risk by dividing the sum of branches distal to the index lesion by the total LV score. Thus, providing a single FFR value will only apply to one vessel or lesion whereas MJI accounts for all vessels and lesions with narrowings >50% diameter, even if not functionally significant.

FFR_{CUM} was significantly lower in the PCI group (0.72±0.1) compared to the control group (0.84±0.07), which is perhaps not surprising, but was also lower than post PCI values (0.83±0.08). These findings suggest that PCI reduces, but certainly does not normalise, the myocardium at risk. This is an unpalatable finding, but accords with common interventional practice, in which residual FFR, even after a single vessel PCI, is not always measured, and seldom achieves normality. Interestingly, the change in FFR_{CUM} post PCI was inversely correlated with FFR_{CUM} pre PCI ($r=-0.70$, $p<0.01$), implying that more severe cases (lower values) benefit from intervention the most in terms of reducing the area at risk. A similar finding was found in chapter two, where lower FFR values had the largest increase ($p<0.01$). In the preliminary analysis of vessels' contribution to the myocardium at risk (table 3.5), the findings suggested that, in single vessel intervention, PCI to LCx resulted in the highest increase in FFR_{CUM}. In double-vessel intervention, PCI to LCx and RCA, resulted in the greatest increase in FFR_{CUM}. In our study, only large calibre or dominant LCx were treated, which may explain this finding. However, the sample size of the analysis was modest, with

13 single and 10 double vessel interventions. In addition, about 73% of the cases involved an intervention on the LAD either alone (n=9) or with another artery (n=8). Yet, this seems an interesting area to explore in future work to better estimate outcomes.

3.4.4 Comparing FFR_{CUM} with similar methods

The $_{GLOBAL}$FFR method is used for prognosis and is calculated at the end of the procedure. Thus, it only includes vessels with wire-based FFR >0.80 (a non-significant stenosis) or post-PCI (FFR which is usually >0.80). Therefore, the lowest achievable value is always (2.40/3). Additionally, the $_{GLOBAL}$FFR method assumes a value of 1.0 if the artery is angiographically 'normal' and a value of 0.90 if post-PCI FFR was missing, whilst FFR_{CUM} includes all values from severe to very mild, including CTOs and missing FFRs (by using vFFR); in the case of CTO, an FFR value of 0.50 was given (n=3), and an extremely severe stenosis left untreated was given a value of 0.60 (n=4). It is clear that both methods (cumulative and global) have some levels of assumptions in their calculation which is understandable as measuring FFR in all epicardial vessels after intervention is not always feasible. Nonetheless, $_{GLOBAL}$FFR tends to overestimate the calculation by assuming an FFR of 1.0 for angiographically normal arteries. Theoretically, there should not be a significant pressure drop across a healthy coronary artery and the FFR should be 1.0. However, these indices are likely to be used in patients with CAD, so an assumed FFR of 1.0 is unlikely to be correct. In the FFR_{CUM} method, vessels with missing FFR and those which cannot be segmented (CTOs, ostial location, calcification or severe LMS disease) or those which failed at the simulation process (extremely narrowed) were given estimated values as well.

The $_{3V}$FFR method, on the other hand, which is also calculated at the end of the PCI, includes all measured vessels, whether functionally significant or not. That will of course provide a wider range of values than the $_{GLOBAL}$FFR method; and as a result, lower $_{3V}$FFR values may be produced. The $_{3V}$FFR method assumes the calculation to be invalid in case of a missing FFR, so measuring FFR in all major arteries is obligatory. However, FFR was not measured in diminutive RCA or LCx, in which case the mean of the FFR values in the other two vessels is multiplied by three and used as the total value. In terms of obtaining FFR in all vessels, this is indeed ideal, and the ultimate objective

in all methods that aim to calculate similar value, but this is rarely possible in a routine practice, thereby limiting the method to research only in very few cases. The authors used this method as a dichotomous index in which any value below <2.72 has a higher risk of 2-years MACE and a high total physiologic burden. That means all FFR values that are included in the calculation of $_{3V}$FFR should be at least 0.90-0.91 to obtain a value >2.72, and therefore, low risk of 2-years MACE. It can be understood from the work of *lee et al* that $_{3V}$FFR method is another evidence of the value of post-stent FFR of >0.90 in showing favourable outcomes (Pijls *et al.*, 2002; Diletti *et al.*, 2021; Piroth *et al.*, 2022).

A primary difference between my method and the previous methods is the applicability prior to the procedure. With FFR_{CUM} an estimation of the myocardium at risk because of the diseased arteries can be, and encouraged to be calculated. This is useful to be used in diagnostic angiography settings, because vFFR can be applied to all vessels, without a pressure wire. An early assessment of myocardium at risk may be of use in planning the management, and in quantifying the change post procedure.

In general, all of the methods are in agreement about summing three FFR values for the major arteries to produce a single prognostic index value. However, what distinguishes FFR_{CUM} is that it incorporates the distribution of the lesions. Coronary arteries vary in their sizes (length and diameter) and number of branches, based upon patient size, dominance, race and gender. Furthermore, size variation is not only limited to different patients, but within a patient's coronary bed as well. For example, an FFR of 0.75 in an RCA of a right dominant system does not represent equal flow reduction compared with a normal sized LCx with FFR of 0.75 in the same patient. The flow is indeed significantly reduced in both, but FFR remains a pressure ratio-based tool and the measured value is percentage rather than an absolute flow reduction. Therefore, the relative size and extent should be considered when trying to assess a global flow reduction and its effect on the myocardium. In my method, anatomical vessel specific score is given for each major artery and the FFR values are cumulatively added together relative to vessels distribution. The vessel weighted score method is adapted from the well described BARI-MJI angiographic definitions protocol (Alderman and Stadius, 1992).

3.4.5 Method validation

To validate the reliability of FFR_{CUM} values in matching different severity degrees, correlation of the numeric values were performed to ensure the consistency between my method and previous methods. First, FFR_{CUM} and BARI-MJI showed significantly strong negative correlation at baseline and in post-PCI only cases (r=-0.73 and r=-0.61). This suggests that the higher the FFR_{CUM} value, the less the myocardium is jeopardised. It could be argued that BARI-MJI scoring method was partially used to calculate my method and therefore, values are expected to correlate. Nevertheless, the BARI-MJI scores neglect diameter stenosis less than 50%, and this can be seen in the seven cases shown in (figure 3.11B) with a total BARI-MJI score of zero. In contrast, in my method, I only use the vessel weighted score not the stenosis score. The former is a score that is used to describe the size, length and branches of the artery, whilst the latter is for the myocardium beyond the lesion. Thus, FFR_{CUM} adopts the vessel scoring method but not the calculation. Despite this major difference in calculation methods, the two indices were closely correlated. Second, functional methods ($_{GLOBAL}$FFR and $_{3V}$FFR) values were compared with FFR_{CUM}. Moderate to strong and statistically significant correlations were observed with $_{GLOBAL}$FFR (r=0.57, p<0.01) and $_{3V}$FFR (r=0.71, p<0.01). Clearly, my values correlated better with $_{3V}$FFR and this can be attributed to the $_{GLOBAL}$FFR protocol of requiring any missing FFR that appear angiographically normal to be counted as 1.0 which might overestimate the FFR values when I compare it with virtually generated FFR. Another factor is that there were fewer variables included in the analysis, because the eligible cases were fewer in $_{GLOBAL}$FFR (n=25) compared to $_{3V}$FFR (n=33). Of note, as the $_{3V}$FFR method requires all vessels to be measured and does not propose an estimation method for missing values, I used vFFR to replace missing angiographically normal arteries or missing post-stent values. It is worth nothing that all methods seem to correlate better in higher values (less functionally diseased), and vary considerably around 0.75-0.85 in the FFR_{CUM} scale (figure 3.11C and D). Most importantly, I validated the ability of my method to classify patients into risk groups. I used previously reported values from the $_{GLOBAL}$FFR and $_{3V}$FFR original work generated corresponding values using my data set to assess the agreement between the methods. The authors of the $_{GLOBAL}$FFR method used tertiles to divide the patients into three groups, indicating that higher values are associated with better outcomes at five years. I performed a similar analysis of my

dataset. Using Kendall's coefficient of concordance, the agreement was acceptable (W=0.74, p=0.06). It is clear from table 3.6 that the discordance was mainly observed in lower values, because almost half of $_{GLOBAL}$FFR values were considered in the low group compared to 20% in FFR_{CUM}. Of course, ranges quoted in $_{GLOBAL}$FFR are more reliable due to the large population that was used (>2000 patients), yet I was able to demonstrate a close to statistical significance agreement and showed a significant Spearman's correlation (r=0.55, p<0.01). Likewise, I used the original method to report risk group in $_{3V}$FFR method where values higher than or equal to the median had better outcomes. The agreement was acceptable and statistically significant (W=0.72, p<0.05), and the classes of risk were moderately correlated (r=0.46, p<0.01). There was more cases (n=33) in this comparison compared to the earlier (n=25). Based upon these findings, it can be concluded that FFR_{CUM} can classify patients into risk groups at comparable rates to previously validated methods.

3.4.6 Limitations

First, this is an hypothesis-generating work with a modest sample size (n=33). These are preliminary findings, so the reported median and IQRs should be updated with a larger dataset. Second, this method neglects demographic characteristics and clinical risk predictors (i.e. hyperlipidaemia and diabetes). However, none of the other similar methods (BARI-MJI, $_{GLOBAL}$FFR and $_{3V}$FFR) were able to address this limitation either. Third, because of the time limitation, I was not able to perform quantifiable perfusion analysis to elaborate more on the diagnostic value of FFR_{CUM}. This can be achieved with the already collected perfusion scans for some of the study participants. The acquired data can be used to generate quantitative perfusion maps following the 16 segments AHA model and a percentage of reduced perfusion can be produced. Furthermore, by comparing these values with the already produced FFR_{cum}, the first step to appropriately validate this scoring method could be established. This is a key area for future work if this method should be fully validated and potentially applied at larger dataset. Fourth, FFR_{CUM} carries a level of subjective measures, particularly in the weighted score step, and training for BARI-MJI scoring protocol is essential, and inter-class variability should always be considered if this method to be used in research.

3.5 Conclusion

Calculating FFR_{CUM} before and after coronary revascularisation is feasible and carries important information about myocardium at risk and ischemic burden. This novel method might be useful in reclassifying risk stratification in middle or lower values compared to currently available methods of single FFR for multiple vessels. Further work is needed to validate this method's ability to predict reduced myocardial perfusion. It may be useful in predicting a patient's response to treatment (see Chapters four and five)

Chapter four: Living with CCS

4.1 Introduction

Episodes of angina typically are triggered by exertion, and therefore people who suffer from angina perform fewer activities, or conduct them with caution. PCI has been shown to improve angina symptoms and physical activity as assessed by exercise time. The ACME trial, for example, reported a significant increase in exercise time (2.1 vs 0.5) minutes after PCI vs OMT alone ($p<0.01$) (Parisi *et al.,* 1992). It has been widely accepted by cardiologists that PCI results in considerable improvement in exercise time. However, the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial, which was the first truly blinded, placebo-controlled, randomised study of PCI (+OMT) vs OMT, reported otherwise (Al-Lamee *et al.*, 2018). The findings of ORBITA were that, despite successfully treated coronary stenoses, exercise time and angina did not improve significantly in comparison to placebo intervention combined with OMT.

The ORBITA trial was the first to apply true blinding in patients undergoing PCI. Although blinding was shown to be effective and safe in invasive and surgical settings before (Bhatt *et al.*, 2014). The PCI effect on mortality rates in CCS patients, with and without adjacent physiological tools has been heavily investigated in the past two decades, however, the true effect size of PCI, or simply the magnitude of the difference between the two compared arms, in exercise and angina was not tested before ORBITA. The trial has shown that placebo controlled studies on PCI are safe and feasible. However, it is also worth mentioning that the follow up time was relatively short (six weeks), but this might be attributed to the difficulty of blinding the patients for longer period if they had truly ischemic stenoses. The findings of ORBITA were indeed surprising, which resulted in conflicting responses to the trial outcomes. The belief that revascularisation results in significant improvement in both symptoms and exercise capacity arose from previous trials, and from the pathophysiological principles of CAD which states that coronary stenosis results in flow impairment, thereby, reducing blood supply to myocardium resulting in angina and physical limitations. However, the current guidelines are still in favour of treating patients with stable ischemic disease with PCI to improve angina if angiographically or physiologically indicated,

despite the outcomes of ORBITA. Moreover, angina relief is a principal outcome in the management of CCS, and achieving that with optimised medications for a long period or the rest of life might be challenging and impractical in real-life settings. In addition, it is still not clear whether these findings apply to MVD or not. The absence of a meaningful change in exercise test duration, as shown in ORBITA, inspired the design of this component of VIRTU-5, but in free-living conditions. In this chapter, physical activity is assessed through complementary methods, with the objective of evaluating the change in response to PCI, in a more systematic and personalised way than is common in everyday practice.

Wearable devices have been available for 15 years, and are becoming used to objectively measure daily activities such as step count and time spent in different state of activities (sedentary, light and vigorous). However, activity monitoring has been mainly directed towards rehabilitation in CAD patients, particularly, evaluating home-based rehabilitation. However this technology has not been used for the assessment of activity after revascularisation in comparison to baseline (Reid *et al.*, 2006; Houle *et al.*, 2011; Frederix *et al.*, 2015). Exercise testing, usually in the form of maximal exercising on a treadmill or bicycle, has long been employed both to diagnose ischaemia (McNeer *et al.*, 1978; Belardinelli *et al.*, 2003) and, to a lesser extent, assess the success or otherwise of revascularisation (Bengtson *et al.*, 1990; Rosanio et al., 1998). The problem with these forms of assessment is their artificial nature compared with what the patient is used to in everyday life. In contrast, the , six-minute walk test, which is a 'submaximal' test, more relevant to the patient's experience, and which is well validated as a clinical tool to measure activity and functional capacity, was used in this work. It has been previously utilised in cardiovascular disease before and after intervention to assess the response (Gremeaux *et al.*, 2011; Beatty., et al, 2012; Stewart *et al.*, 2018).

The aim of this chapter is to evaluate and assess physical activity in CCS patients before and after coronary revascularisation using contemporary methods, which are relevant to the patient's experience.

4.2 Methods

4.2.1 Study population

Patient screening and recruitment was described earlier (section 2.2.1). In brief, patients had a CCS and were on the waiting list for ICA with a view to PCI. They must have internet connection at home, a sufficient period of monitoring at baseline (>one month), and after LHC±PCI (>three months) in order to be included in this analysis. Patients who underwent CABG shortly after their LHC were excluded. It is important to note that the selection criteria for this study was based on the ability of the participants to be mobilised due to the nature of the study which requires physical activity monitoring. Thus, patients who had severe mobility limitations where excluded during the initial selection phase. Additionally, access to internet was preferable, however, this did not influence the selection criteria as this information is difficult to be obtained before participant's contact or visit. However, only three participants did not have wi-fi access at home.

4.2.2 Activity monitoring

4.2.2.1Fitbit™ Charge 4

A commercially available Fitbit™ Charge 4 wrist-worn fitness tracker (Healthy Metrics Research Inc. California, US) was used for this study to monitor physical activity in free-living conditions. The watch uses Fitbit Operating System (OS) and Fitbit cloud storage to transfer and export data. Activity and sleep data can be tracked and exported, as well as heart rate. All daytime activities including steps, distance and 'active zone' minutes can also be acquired on daily basis. The Charge 4 contains several sensors, including accelerometers, a vibration motor sensor and an optical heart rate sensor. A micro-electromechanical system (MEMS) tri-axial accelerometer is used for motion tracking and specifically step counting. The mechanism of this built-in sensor is to translate mechanical movement into electrical signals to measure dynamic acceleration (Albarbar and Teay, 2017). Photoplethysmography (PPG), a non-invasive and simple optical sensor, is used to detect HR. PPG uses a photodetector and light source to measure volumetric changes in radial and ulnar arteries (Figure 4.1).

Figure 4.1 Basic explanation of HR detection technique in Fitbit™ Charge 4 watch.

A) Fitbit charge 4 watch and user screen, with a magnified PPG sensor device B) The principle of heart rate detection via PPG.

4.2.2.2 Data collection

The watch provides simultaneous data synchronisation to the Fitbit official website through a Bluetooth pairing with a network-connected smartphone. If a patient's mobile phone was outdated, a smartphone was supplied, to ensure data synchronisation. Each patient had a unique Fitbit account, and a unique password to ensure data safety and confidentiality. Strict measures of data anonymisation were taken, each participant had a unique code consisted from letters and numbers, with no identifiable or personal information on the account to ensure data protection

and safety as all data were uploaded directly to Fitbit website. Only the research team had access to account details. Raw activity data were exported periodically, either monthly or weekly, according to the number of participants being monitored at the same time.

Data collection started one day after giving the patients their watches. Watches were given on the day of recruitment and were kept with the patient for up to six months after their LHC±PCI. The period from recruitment to procedure was considered the baseline activity period. This time depended upon the hospital waiting list (which was prolonged during the COVID pandemic of 2020-22), aiming for at least one month of activity data before the procedure day. Once the procedure was done, both groups of patients (PCI and control) were asked to continue wearing the watches for up to six months. Patients were not asked or encouraged to do any extra activity. Instead, all notifications and reminders to undertake activity were disabled to avoid bias resulting from motivational notifications. The intensity classifications are defined and coded in the Fitbit device. These are based on the metabolic equivalent task (MET) calculations. The definition of each category is presented in table 4.1. The main exported data, measured per day, were the number of steps, 'fairly active' minutes and 'very active' minutes. The sum of the last two metrics was used to generate 'moderate to vigorous' physical activity minutes, which have previously been used to assess changes in intensity efforts associated with intervention. Daily heart rate data were only able to be viewed in the database as averaged data points, which were plotted graphically and used for analysis.

Table 4.1 Definitions of activities intensity

Intensity category	Definition of threshold according to Fitbit system
Sedentary	Activities registering <1 MET.
Lightly active	Activities registering between 1 to 3 METs.
Fairly active	Activities registering between 3 and 6 METSs.
Very active	Activities registering ≥6 METs or greater than or equal to 145 steps per minute in at least 10-minute bouts.
Moderate to vigorous physical activity	Activities registering ≥3 METs in at least 10-minute bouts (a combination of the fairly active and very active categories)

These definitions are reproduced from (Semanik *et al.*, 2020)*. Extracted with permission from John Wiley and Sons via copyright clearance (5476531089345)*

4.2.2.3 Quality assurance and wearing time

Patients were instructed how to recharge their watches by demonstration. Each watch was linked to the patient's smartphone or, if not available, a Samsung Galaxy™ A10, which was given to the patient for the period of the study. Common troubleshooting methods were explained to patients, or the research fellow would visit the patient's home to fix any technical issues. A 'valid day' was explained to the patient as one in which the watch was constantly worn while sleeping, while awake, or a cumulative wear time that exceeded 10 hours. Daily data were checked for quality assurance, the Fitbit™ heart rate algorithm being the first option to check number of hours or gaps during the day. A valid day also required all exported daily metrics to be error-free and a day with any missing metric was excluded (figure 4.2).

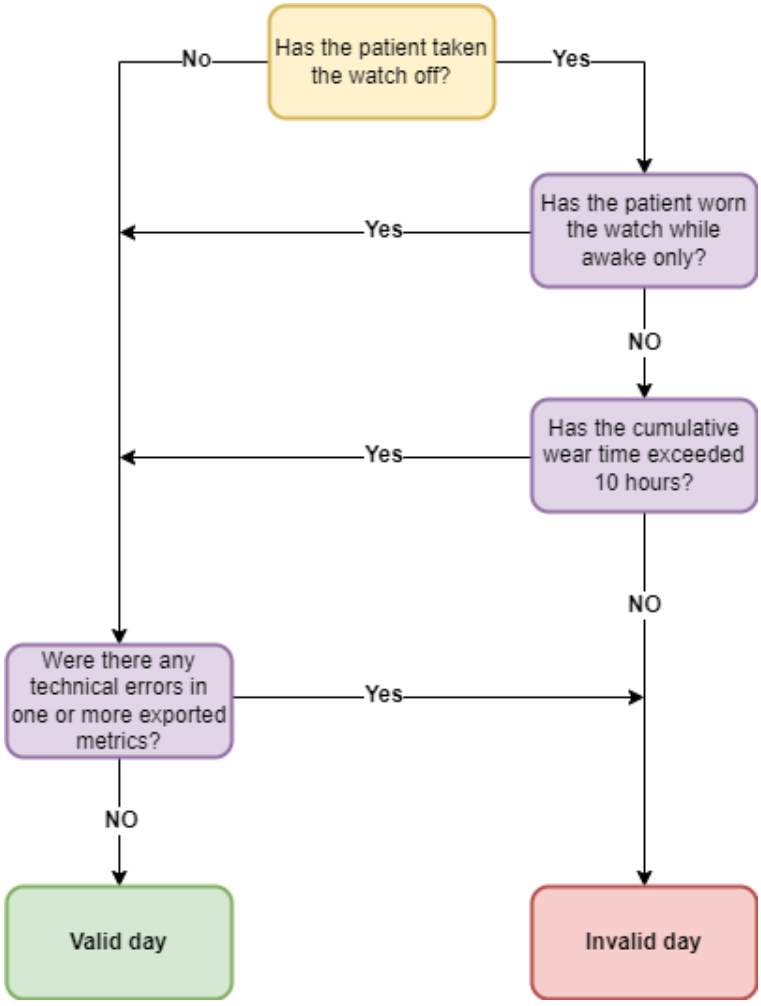


Figure 4.2 Flowchart demonstrating the method of Fitbits wear-time and data quality assurance.

4.2.3 Six-Minute Walk test (6MWT)

4.2.3.1 Procedure protocol

The test was performed according to the standardised protocol and guidelines of American Thoracic Society (Enright, 2003; Holland *et al.*, 2014). The test was conducted in a quiet, flat, obstacle-free corridor at Sheffield Northern General Hospital. Before the test, study participants were instructed to rest for 15 minutes, during which baseline assessment, comprising oxygen saturation, heart rate, and blood pressure were measured. Test instructions were given to the participant as follows; to walk as far as possible, back and forth along a 20m course for 6 minutes. Participants were also instructed to walk around the cones at each end of the course, keeping them always towards their right. The research fellow demonstrated one lap. Participants were made aware that they could stop for rest if necessary, and continue to walk as soon as they felt able to. If no further walking could be done, the test was terminated, and the reasons recorded, along with the distance walked. To avoid influence on walking speed, patients walked unaccompanied and were asked not to talk unless there was a problem or a question. Participants were asked to inform the research team if they experienced chest pain or dizziness. A final reminder was given that the objective was to walk as far as possible and to avoid running or jogging. During the test, a standard encouragement was called out every minute, also giving an indication of the time remaining (i.e. 'Keep up the good work; you only have two minutes left'). If a participant stopped during the test, the stop watch was kept running and a chair was brought if needed. The research fellow advised the participant to resume walking if they felt better. When the six minutes were over, participants were asked to stop and stay where they were. A trundle wheel was used to measure the distance walked in the last lap. The total distance walked, HR, BP were recorded while sitting on a chair. A resting period of 15 minutes following the completion of the test was provided.

4.2.3.2 Safety during the walk test

All walk tests were conducted in a clinical area under the supervision of two research fellows. A portable oxygen cylinder, a suitable face mask and cardiac arrest trolley were all located in the next ward. Any clinical concern regarding participant safety resulted in test termination.

4.2.3.3 Scoring

The 6MWT walked distance (in meters) was reported for each test. This was performed at baseline and at follow up. Each participant performed the 6MWT twice at every visit, both walk distances were documented, and the second walk was reported for analysis. This practice was conducted to eliminate the training effect as was reported earlier (Wu., 2003). The absolute increase in walked distance was reported and the percentage of change was calculated. Additionally, the reported cut off value of 25m was used to differentiate minimal clinically important difference (MCID) for CAD patients (Gremeaux *et al.*, 2011). Symptoms or clinical events were recorded as well.

4.2.4 Change in physiology

The change in three months physical activity was calculated as an averaged change of the three months following the procedure.

Change in FFR was calculated as:

If no intervention, a value of 0% was given

If one vessel: $\frac{\Delta FFR}{Pre-PCI\ FFR}x100$ If two vessels: $\frac{\frac{\Delta FFR}{Pre-PCI\ FFR}+\frac{\Delta FFR}{Pre-PCI\ FFR}}{2}x100$

Change in FFR_{CUM} was calculated as: $\frac{\Delta FFR_{CUM}}{Pre-PCI\ FFR_{CUM}}x100$

4.2.5 Statistical analysis

Data were reported as means, standard deviations and percentages unless stated otherwise. Histograms were used to display frequency of variables and bar charts to demonstrate differences. Unpaired t tests were used to compare the metrics of the PCI and control groups, and paired t tests were used to compare the change in all measured metrics in individual patients after LHC±PCI. One-way ANOVA was used to assess statistical difference between control, single vessel and two vessel interventions Pearson's correlation was used to investigate the relationship between disease severity and physical activity and trends in changes at follow up. GraphPad Prism (9.4.1) was used for statistical analysis.

4.3 Results

4.3.1 Physical activity assessment in CCS patients using fitness tracker.

Patients' characteristics

Forty patients who were planned to undergo elective LHC±PCI were recruited in this study. Thirty-two patients were included in this analysis. Eight patients were excluded for the following reasons; two underwent CABG, three did not have Wi-Fi at home to set up the devices, and three did not have enough data after their procedure for useful analysis. All 32 patients underwent LHC, of which 21 had PCI in one (n=12) or two (n=9) vessels. The patients without revascularisation (n=11) comprised the 'control' group, because they received all the assessments, and an invasive procedure, including pressure wire measurements in all relevant vessels, but without stent implantation. Patients' characteristics are shown in table 4.2.

Table 4.2 Baseline characteristics and procedural outcomes.

Patient characteristics	N = 32	Percentage	Mean (±SD)
Age			65 (±8)
Male	24	75	
Female	8	25	
Smoking status			
Current smokers	3	9	
Ex-smoker	20	63	
Non-smoker	9	28	
Risk factors			
Hypertension	22	69	
Hyperlipidaemia	11	34	
Type 2 Diabetes	5	16	
Anti-anginal medications			
Beta blockers	22	69	
Long acting nitrates	15	47	
Calcium channel blockers	15	47	
Ranolazine	3	9	
Procedural outcomes			
Underwent PCI			
Yes (PCI group)	21	66	
No (Control group)	11	34	
Single vessel intervention	12	57	
Double vessel intervention	9	43	

4.3.2 Assessment of physical activity in patients planned to undergo LHC±PCI

The mean daily step count for the full cohort at baseline was 8190±4279 steps [range 3057 to 20921 steps] and the mean daily minutes of moderately vigorous physical activity was 40±35 minutes [range 3 to 145] (figure 4.3). Physical activity at the third month did not significantly differ from the baseline, with a mean daily step count of 8553±4275 [range 3329 to 22972 steps] and a mean daily minutes of MVPA of 44.69 [range 4.9 to 175 minutes]. The difference was not statistically significant when the two time points were compared, (p=0.33 and p=0.21) but they were closely correlated (r=0.88 and r=0.88) for step count and minutes of MVPA respectively. Additionally, anti-anginal medications remained the same for all except for one in the control group. Summary of the medications is shown in table 4.3

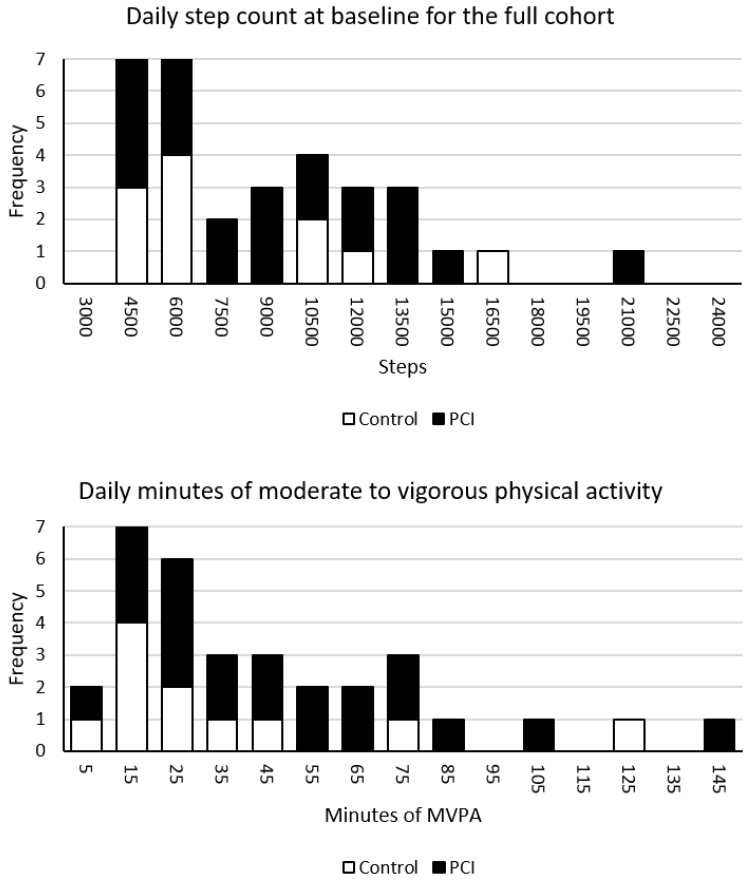


Figure 4.3 Full cohort frequency distribution demonstrating physical activity metrics at baseline

(A) Frequency of mean daily step count in increments of 1500 steps and (B) the mean minutes of MVPA are presented in increments of 10 minutes.

Table 4.3 Summary of anti-anginal medications before and after procedure

		PCI		Control	
		N=21	Percentage	N=11	Percentage
Anti-anginal medications					
Beta-blockers	Pre	15	71%	7	64%
	Post	15	71%	6	55%
Long acting nitrates	Pre	10	48%	5	45%
	Post	10	48%	5	45%
Calcium-channel blockers	Pre	11	52%	4	36%
	Post	11	52%	4	36%
Ranolazine	Pre	3	4%	0	0%
	Post	3	4%	0	0%

There was no significant difference in the mean daily step count at baseline between the PCI group (8699±4413) and the control group (7216±4030) (p=0.36). The difference remained statistically non-significant between the groups up to three months (p=0.27, p=0.25 and p=0.21) at first, second and third months, respectively. Monthly changes following the procedure were assessed in both groups. For the PCI group, the mean daily step count was less than what was measured in the three months averaged baseline by 204 steps (p=0.58) and the performed minutes of MVPA were less by 0.5 minutes (p=0.88) at the first month. However, in the second month, patients gained an extra 638 steps and 6 minutes of MVPA a day on average (p=0.13 and p=0.10) respectively. At three months, patients gained an extra 545 steps and 6.8 minutes of MVPA a day on average (p=0.30 and p=0.08) respectively. Similarly, the analysis was done for the control group. After one month, daily step count was less by 321 steps and time spent in MVPA was reduced by 8 minutes (p=0.52 and p=0.23) respectively. After two months, patients walked extra 279 steps a day in average and minutes of MVPA remained reduced compared to baseline by 4.5 minutes (p=0.56 and p=0.38). At the third month, walked distance was similar to baseline, with an extra 16 steps, and the minutes of MVPA were reduced by 1.9 minutes (p=0.97 and p=0.77). Monthly differences are demonstrated in figure 4.4 for both groups, and a summary is shown in tables 4.4 and 4.5. Trends of daily steps and MVPA following the procedure are shown in figure 4.5.

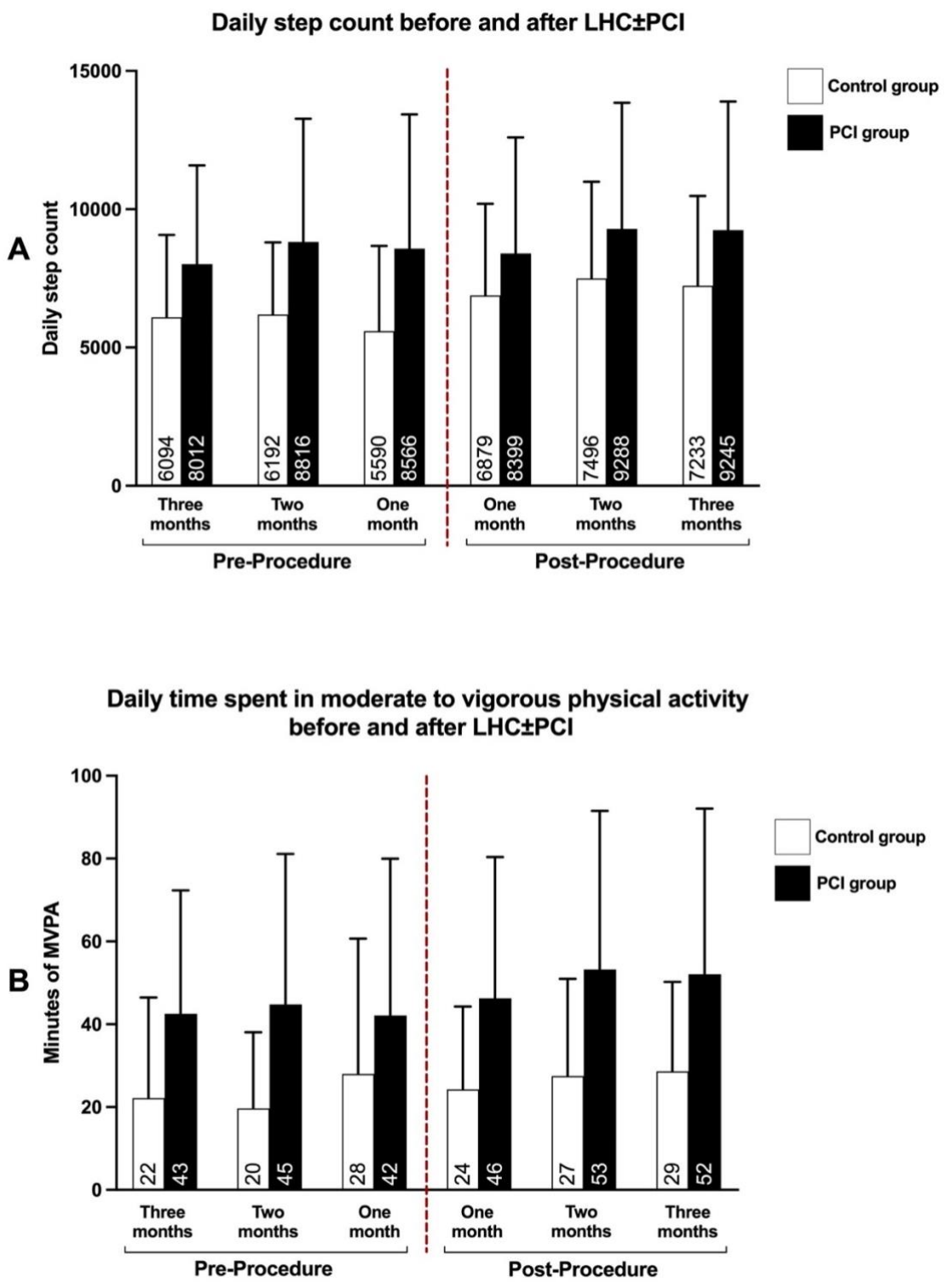


Figure 4.4 Physical activity metrics before and after LHC±PCI.
In (A) mean values for daily step count for each group are placed at the same time point. Similarly, for (B) but in minutes of MVPA. Black bars represent the PCI group and white bars the control group. The red dotted line is a representation of the time of the procedure.

Table 4.4 Summary of daily step count for both groups up to three months before and after LHC±PCI

Daily step count	PCI (n=21)		Control (n=11)		p-value
	Mean	±SD	Mean	±SD	
Pre procedure					
Three months	8012	±3575	6094	±2976	0.21
Two months	8816	±4451	6192	±2607	0.13
One month	8566	±4858	5590	±3087	0.07
Post procedure					
One month	8399	±4104	6879	±3309	0.27
Two months	9288	±4561	7496	±3495	0.25
Three months	9245	±4646	7233	±2370	0.21
Change in step count					
Change at first month	3	±25%	1	±29%	0.91
Change at second month	12	±27%	11	±35%	0.90
Change at third month	11	±30%	8	±29%	0.77
Overall change after three months	9	±23%	7	±30%	0.83

PCI=percutaneous coronary intervention

Table 4.5 Summary of daily time spent in moderate to vigorous physical activity in both groups up to three months before and after LHC±PCI

Minutes of MVPA	PCI (n=21)		Control (n=11)		p-value
	Mean	±SD	Mean	±SD	
Pre procedure					
Three months	42	±30	22	±24	0.12
Two months	45	±36	20	±18	0.08
One month	42	±37	28	±38	0.30
Post procedure					
One month	46	±35	24	±20	0.08
Two months	53	±39	28	±24	0.08
Three months	54	±40	29	±21	0.11
Change in minutes of MVPA					
Change at first month	4	±31%	1	±34%	0.81
Change at second month	27	±43%	-4	±33%	0.06
Change at third month	28	±42%	34	±52%	0.72
Overall change after three months	20	±31%	10	±33%	0.46

PCI=percutaneous coronary intervention, MVPA= moderate to vigorous physical activity.

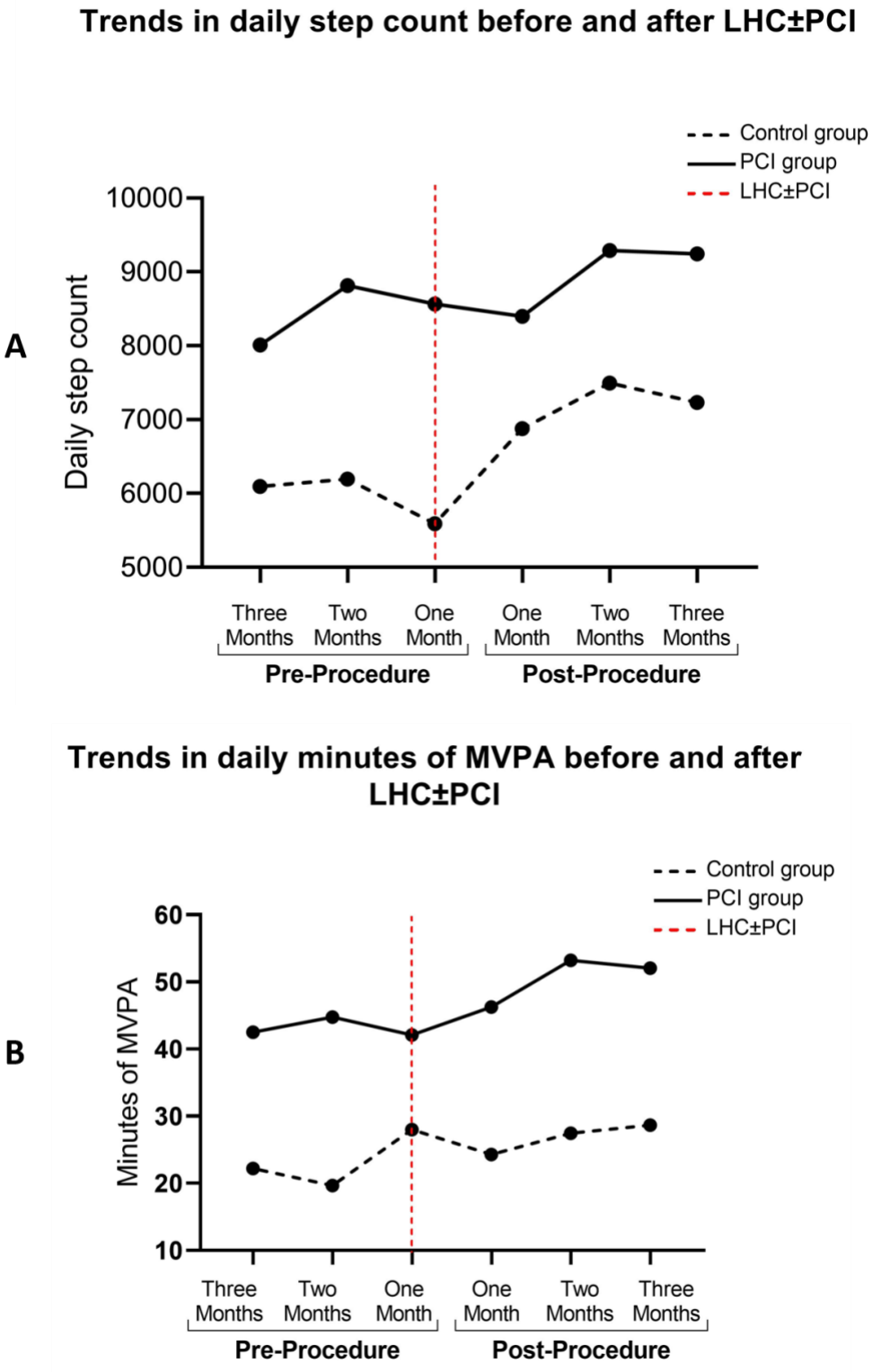


Figure 4.5 Trends in daily physical activity reported as monthly means prior and after the procedure

The red dotted line illustrated the procedure (the starting and ending point for each phase). The PCI group trend is shown with black line and the control group with black dotted line.

4.3.3 Relationship between disease severity and physical activity

Number of treated vessels: sub group analysis

The mean daily step count for patients who underwent PCI to one vessel (n=12) was 8856±3673 steps at baseline, 8315±3210 steps at one month, 9295±s3825 steps at two months and 8823±3863 steps at three months. The difference between each month's daily step count after PCI and baseline did not significantly differ ($p>0.05$). The mean change in daily step after three months following the intervention was 2±20%. For patients who had stents in two vessels (n=9), the daily step count was 8491±5482 steps at baseline, 8734±5275 steps at one month, 9394±5646 steps at two months and 9807±5729 steps at three months. The difference between the first two months and baseline was non-significant ($p>0.05$), the number of daily steps was significantly higher in the third month compared to the baseline ($p=0.03$) and the mean change was 17±24%. Same analysis was done for minutes of MVPA. The mean daily performed minutes of MVPA for single-vessel PCI patients was 48±28 minutes at baseline, 49±24 minutes at one month, 57±30 minutes at two months and 55±31 minutes at three months. There was no statistically significant difference between baseline and the other three months following the intervention. The mean change in minutes of MVPA after three months following the intervention was 21±29%. Daily minutes of MVPA for patients with two-vessels PCI was 44±46 minutes at baseline, 41±49 minutes at one month, 45±52 minutes at two months and 50±54 minutes at three months. Similarly, no significant difference in performed MVPA was observed. The mean change in minutes of MVPA after three months following the intervention was 18±35%. Comparison between baseline and following months for each metric and group are presented in figure 4.6. There was no significant difference observed in all studied PA metrics at baseline, three months and percentage of change between patients with single-vessel and two-vessel interventions (Table 4.6 and 4.7).

Table 4.6 Summary breakdown of daily step count subgroup analysis based on number of treated vessels.

Daily step count	Control N=11		Single vessel PCI N=12		Two vessel PCI N=9		p-value
	Mean	±SD	Mean	±SD	Mean	±SD	
Pre-procedure							
Three months	6094	±2976	8987	±3583	6721	±3420	0.21
Two months	6192	±2607	8741	±3218	8945	±6357	0.33
One month	5590	±3087	8837	±4211	8205	±5860	0.20
Post procedure							
One month	6879	±3309	8315	±3210	8734	±5275	0.54
Two months	7496	±3495	9295	±3825	9394	±5646	0.52
Three months	7233	±2370	8823	±3863	9807	±5729	0.40
Change in step count post procedure							
Change at first month	1	±29%	-4	±18%	11	±32%	0.44
Change at second month	11	±35%	8	±25%	17	±30%	0.77
Change at third month	8	±29%	3	±28%	23	±29%	0.28
Overall change after three months	7	±30%	2	±20%	17	±24%	0.40

Table 4.7 Summary breakdown of daily step count subgroup analysis based on number of treated vessels.

Daily minutes of MVPA*	Control N=11		Single vessel PCI N=12		Two vessel PCI N=9		p-value
	Mean	±SD	Mean	±SD	Mean	±SD	
Pre-procedure							
Three months	22.2	±24	51.6	±32	30.4	±23	0.11
Two months	19.7	±18	43.6	±27	46.8	±51	0.11
One month	28	±38	46.5	±30	36.2	±47	0.48
Post procedure							
One month	25	±20	49.5	±24	41.2	±49	0.19
Two months	28	±24	57.5	±30	45.6	±53	0.17
Three months	31	±21	55.5	±31	50.6	±53	0.26
Change in minutes of MVPA post procedure							
Change at first month	1	±34%	9	±31%	-3	±34%	0.69
Change at second month	-4	±33%	29	±43%	24	±33%	0.16
Change at third month	34	±52%	24	±42%	33	±52%	0.13
Overall change after three months	10	±31%	21	±30%	18	±34%	0.74

MVPA= moderate to vigorous physical activity

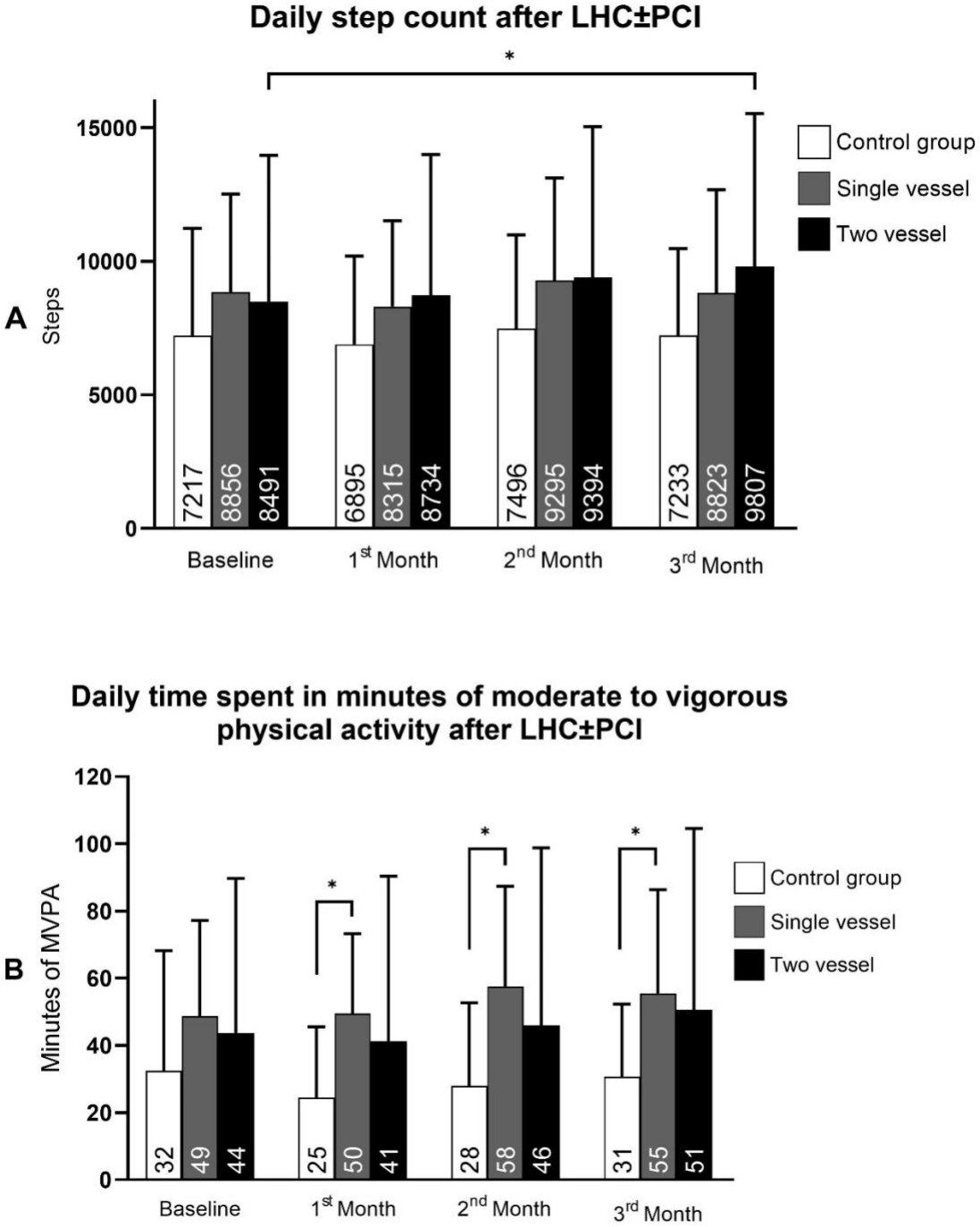


Figure 4.6 Differences in physical activity in response to PCI based upon the number of treated vessels.

In (A) the averaged three months prior to the procedure (baseline) daily step count are compared with each subsequent month in patients with single-vessel, two vessel intervention and control. Likewise in (B) but comparing minutes of MVPA with baseline. Each group is compared to the other groups at all time points in both (A) and (B) figures. All comparisons were statistically non-significant (p>0.05) except the labelled ones. p<0.05.*

Relationship between CAD severity and the change in physical activity: subgroup analyses

1) Change in FFR and averaged change in physical activity up to three months

Twenty-eight patients were included in this analysis, of whom 17 had PCI and 11 did not. The averaged change in FFR was compared to the average change of the three months period post procedure. For the control group (n=11) there was no change in FFR and therefore a value of '0' was given. The 'change' in FFR failed to show a meaningful relationship with the change in PA metrics. The correlation between daily step count and the change in FFR was weak (r=-0.10, p=0.58), and diminished for minutes of MVPA (r=-0.01, r=0.98). The same analysis was conducted for the PCI group only. The change in daily step count remained independent from the change in FFR, but there was better correlation (r=-0.28, p=0.27). Similarly, the relationship remained weak between the change in FFR and minutes of MVPA (r=0.13, p=0.62). Correlation plots are shown in figure 4.7.

2) FFR_{cum} and three months change in physical activity

Twenty patients were included in this analysis, and one patient was excluded due to missing RCA views and therefore inability to calculate FFR_{cum}. Moreover, pre-PCI FFR_{cum} showed no correlation with daily step count (r=0.01, p=0.99) and weak correlation with time spent in MVPA (r=0.33, p=0.16) at baseline. This was not changed when post-PCI FFR_{cum} values were compared with third month's findings (r=0.10, p=0.68) and (r=0.32, p=0.18) for step count and minutes of MVPA respectively. The change in FFR_{cum} did not explain the change in other PA metrics suggesting weak correlations with the change in both daily step count (r=0.04, p=0.84) and minutes of MVPA (r=-0.01, p=0.71). Correlation plots are shown in figure 4.8.

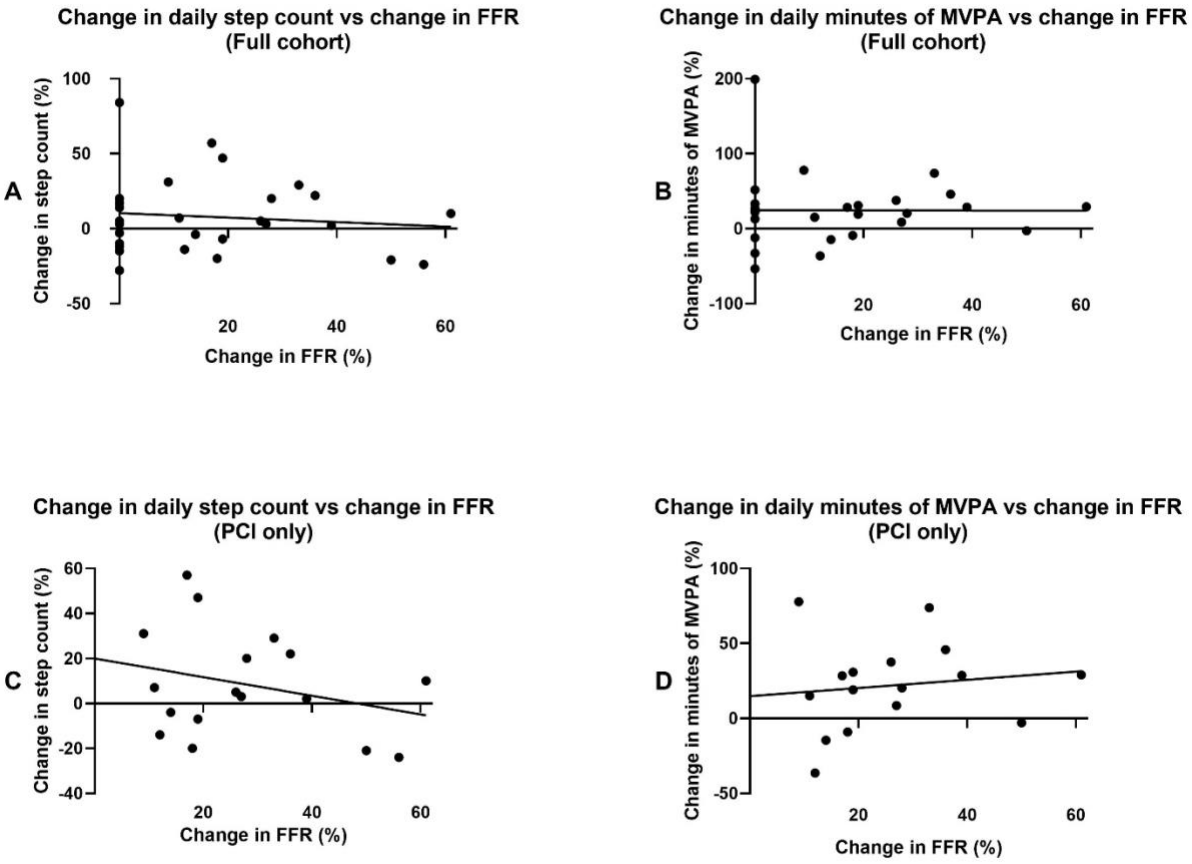


Figure 4.7 Relationship between the change in FFR and the change in physical activity.

The overall change represented as averaged percentage of the change in the three months post LHC±PCI are plotted against the change in FFR in (A) daily step count and (B) minutes of MVPA for the full cohort. Similar analysis was done but only including PCI patients (C) daily step count and (D) minutes of MVPA.

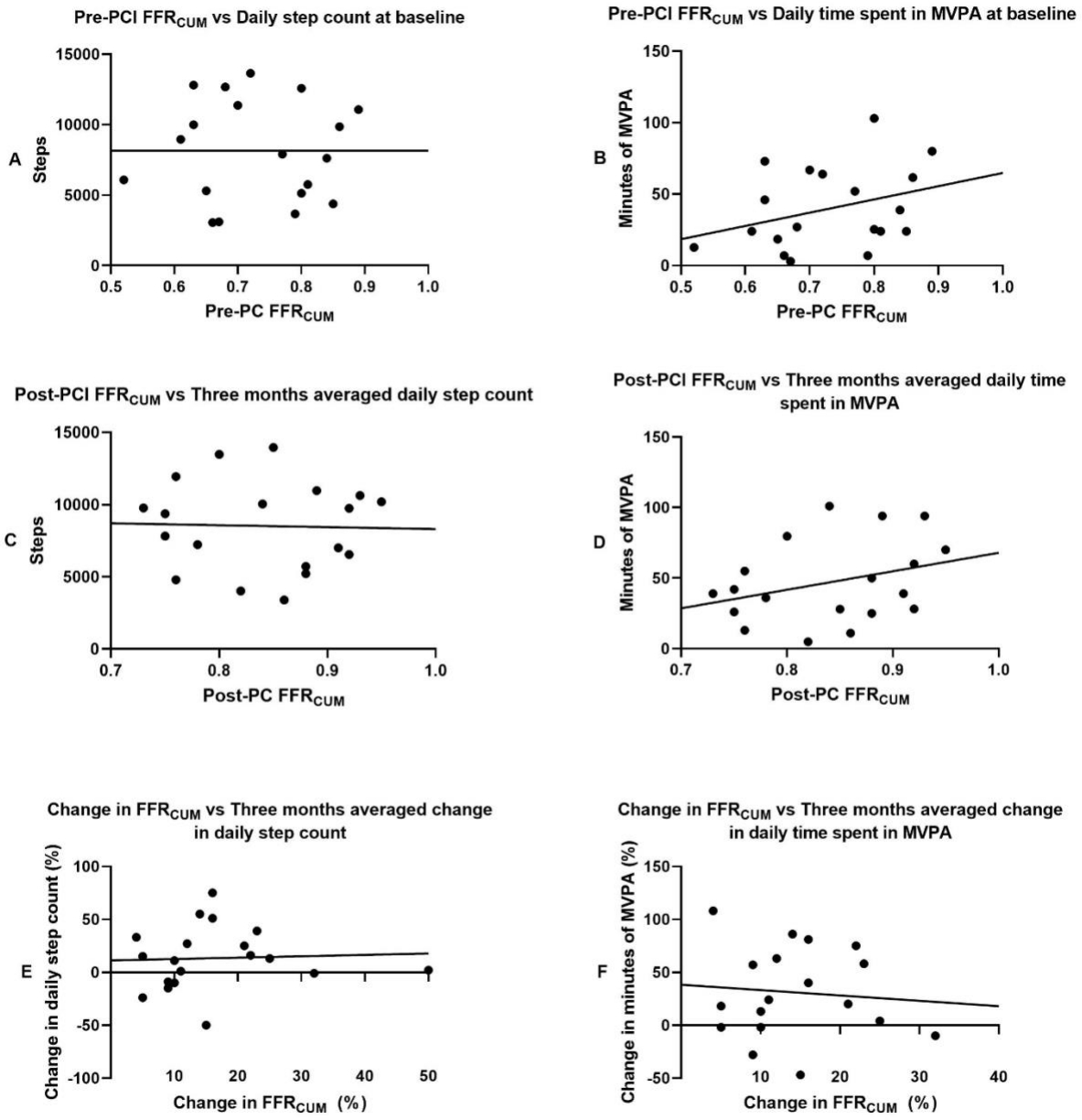


Figure 4.8 Relationship between FFR_{CUM} before or after PCI and associated change in physical activity.

The overall change represented as percentage after three months are plotted against pre-PCI FFR_{CUM} in (A) daily step count and (B) minutes of MVPA. Same values are then plotted against post-PCI FFR_{CUM} in (C) daily step count and (D) minutes of MVPA. The change in FFR_{CUM} after intervention is plotted against the overall change in (E) daily step count and (F) minutes of MVPA.

4.3.4 Six-minute walk test: assessment functional capacity and the change following elective PCI

Out of the forty patients recruited for the study, 34 patients had at least one six-minute walk test, of which 26 had 6MWT before LHC±PCI and three months after. Two patients had baseline assessment only and six had three months assessment only. Only patients with complete assessment (before and after) were included in this analysis. Baseline characteristics for the included patients are as follows; 22 (81%) were male, 17 (63%) had hypertension, eight (30%) had hyperlipidaemia and three (11%) had 2DM. The mean walked distance at baseline for the full cohort (n=26) was 457±85 m [range 299 to 636], and 482±69 m [range 340 to 664] at three months (figure 4.9). The mean difference was 25±39 m and the overall change was 6±7%.

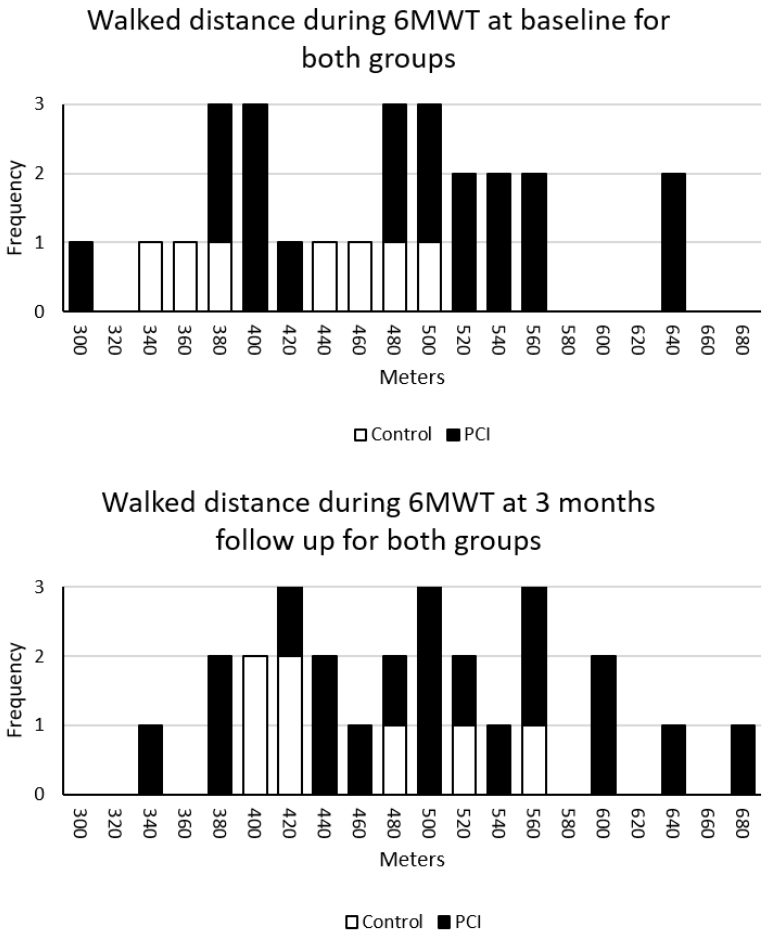


Figure 4.9 Full cohort frequency distribution of six-minute walked distance for each patient

Frequency of walked distance (in meters) are shown in (A) baseline and (B) after three months.

Effect of PCI upon functional capacity

Nineteen patients underwent PCI in one or more vessel following their baseline 6MWT assessment (PCI group), and seven did not (control group). There was no statistical significant difference in the walked distance between both groups, 474±91 m and 411±59 m, p=0.10 for PCI and control respectively. The difference remained statistically non-significant at three-months between the PCI group (496±90m) and the control group (447±56m), p=0.19. When each group was analysed separately, a statistically significant increase in walked distance was observed ($p<0.05$) in both groups at three-month follow up figure 4.10. The mean change in walked distance for the PCI group was 5±9% and 9±7% for the control group. A mild, non-significant, negative correlation was observed between the walked distance and the percentage of change (r=-0.37, p=0.12) in the PCI group, and a mild, non-significant, negative correlation was observed in the control group (r=-0.52, p=0.23). A full cohort analysis suggested a statistically significant moderate negative correlation between distance walked and percentage of change (r=-0.43, p=0.03). Correlation plots are demonstrated in figure 4.11. Minimal clinically important difference after PCI was observed in 47% of the patients (9/19). No difference was observed when patients were stratified according to the number of treated vessels. 6MWD summary breakdown based on this stratification is shown in table 4.8.

Table 4.8 Summary of the differences between single-vessel and double-vessel PCI

	Control N=7		Single vessel PCI N=9		Double vessel PCI N=10		p-value
	Mean	±SD	Mean	±SD	Mean	±SD	
Baseline walked distance	411	±59	502	±101	450	±80	0.11
Follow up walked distance	447	±56	519	±82	476	±97	0.23
Difference	35.3	±26.5	17	±41	26	±48	0.67
Percentage of change	9	±7%	4	±9%	6	±10%	0.54
	(n)	%	(n)	%	(n)	%	
Minimal clinical important difference	4	57%	4	44%	5	56%	

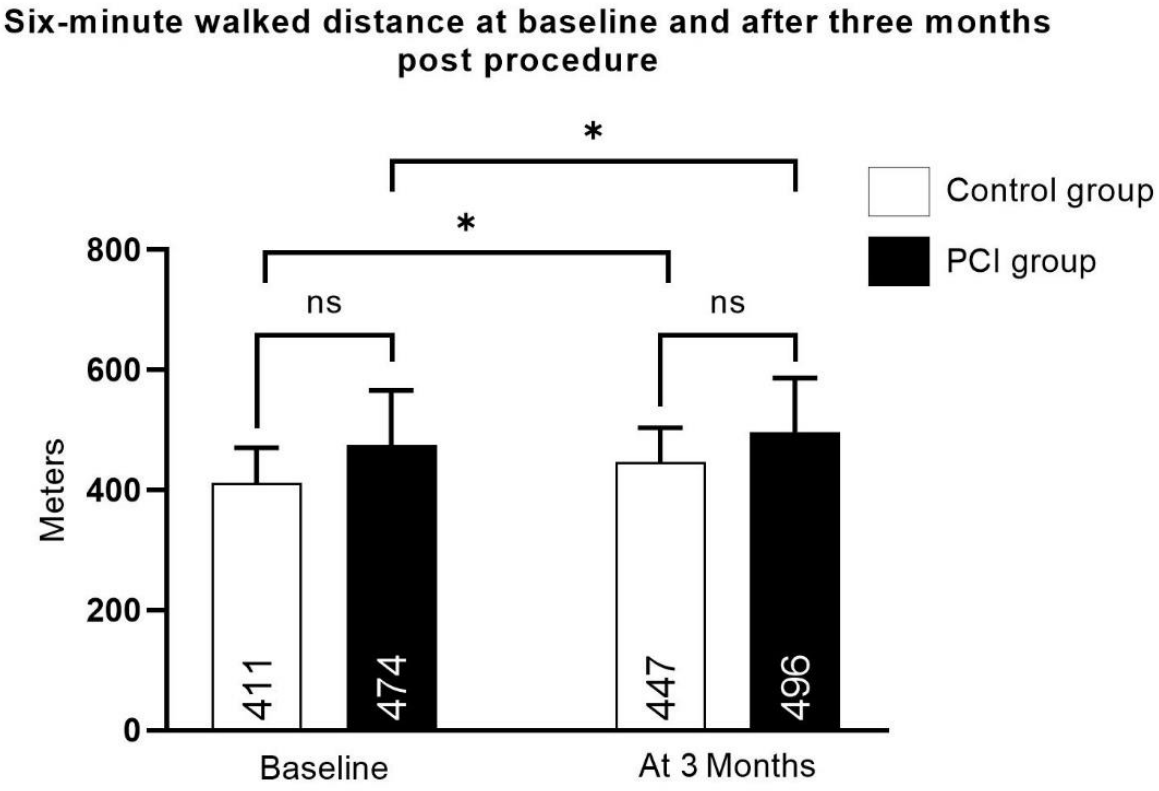


Figure 4.10 Comparison of the six-minute walked distance following LHC±PCI in PCI and control groups

The histograms demonstrate the non-significant difference in the six-minute walk distance (meters) at baseline (p=0.10) and after three months (p=0.19) between the PCI and control groups. The change in response to LHC±PCI is shown in top two pairwise comparisons for the control (p=0.01) and PCI (p=0.05) groups.

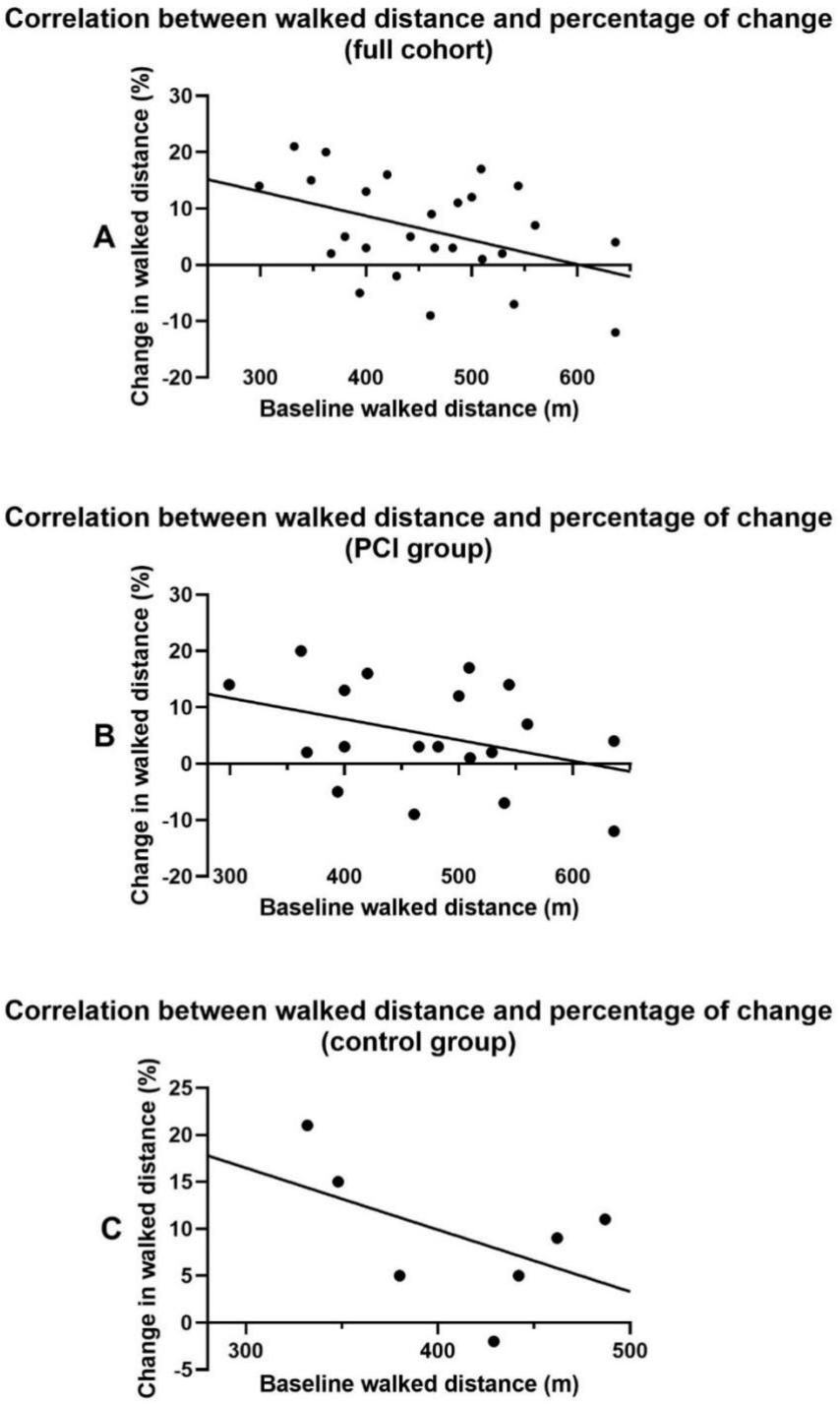


Figure 4.11 Relationship between baseline six-minute walked distance and the change after PCI

The change in walked distance after three months reported as percentage is plotted against the baseline walked distance for (A) full cohort (r=-0.43. p<0.05), (B) PCI group (r=-0.37, p=0.12), and (C) control group(r=-52, p=0.23).

Relationship between 6MWT and FFR_{cum}

The total number of patients who underwent PCI with complete 6MWT at baseline and at follow up in addition to FFR_{cum} was 14 patients. The 6MWD at baseline was compared with pre-PCI FFR_{cum} and showed a weak correlation (r=0.12, p=0.67). Similarly, the correlation was weak when investigated for follow up 6MWD and post-PCI FFR_{cum} (r=0.14, p=0.62). Finally, no correlation was observed between the change in the walked distance and the change in FFR_{cum} both calculated as percentage (r=-0.03, p=0.90). Correlation plots are shown in figure 4.12.

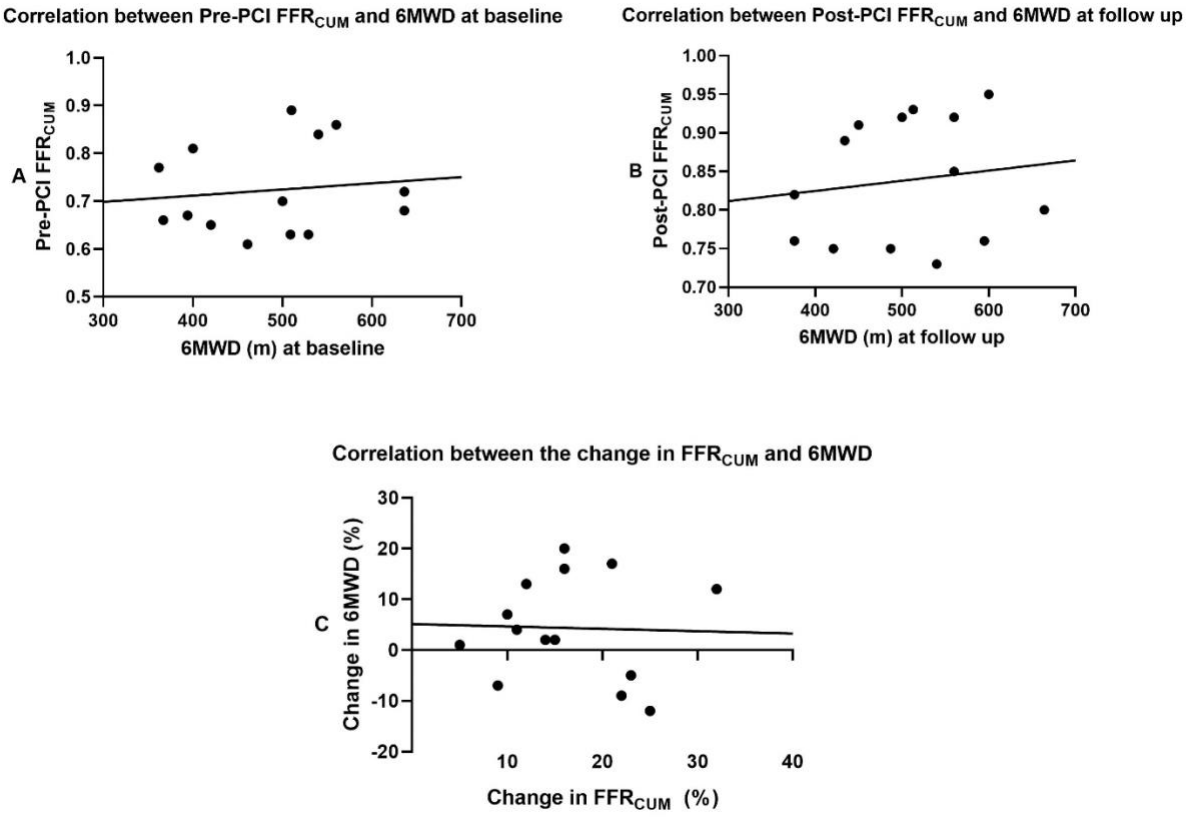


Figure 4.12 Correlation plots demonstrating the relationship between FFR_{CUM} and 6MWD

Correlation between 6MWD (m) and FFR_{CUM} at (A) baseline (r=0.12, p=0.67) and at (B) follow up (r=0.14, p=0.62) and the percentage of change between the two values (r=-0.03, p=0.90).

Relationship between 6MWT and other PA metrics: a subgroup analysis

Twenty three patients had complete dataset with 6MWT performed at baseline and after three months, in addition to three months PA monitoring. The 6MWD and daily step count at baseline was moderately correlated (r=0.67, p<0.01), and similarly with daily minutes of MVPA (r=0.48, p=0.02). At follow up, the correlation between 6MWD and daily step count did not change (r=0.67, p<0.01), but was higher than baseline for the minutes of MVPA (r=0.58, p<0.01). Correlation plots are shown in figure 4.13.

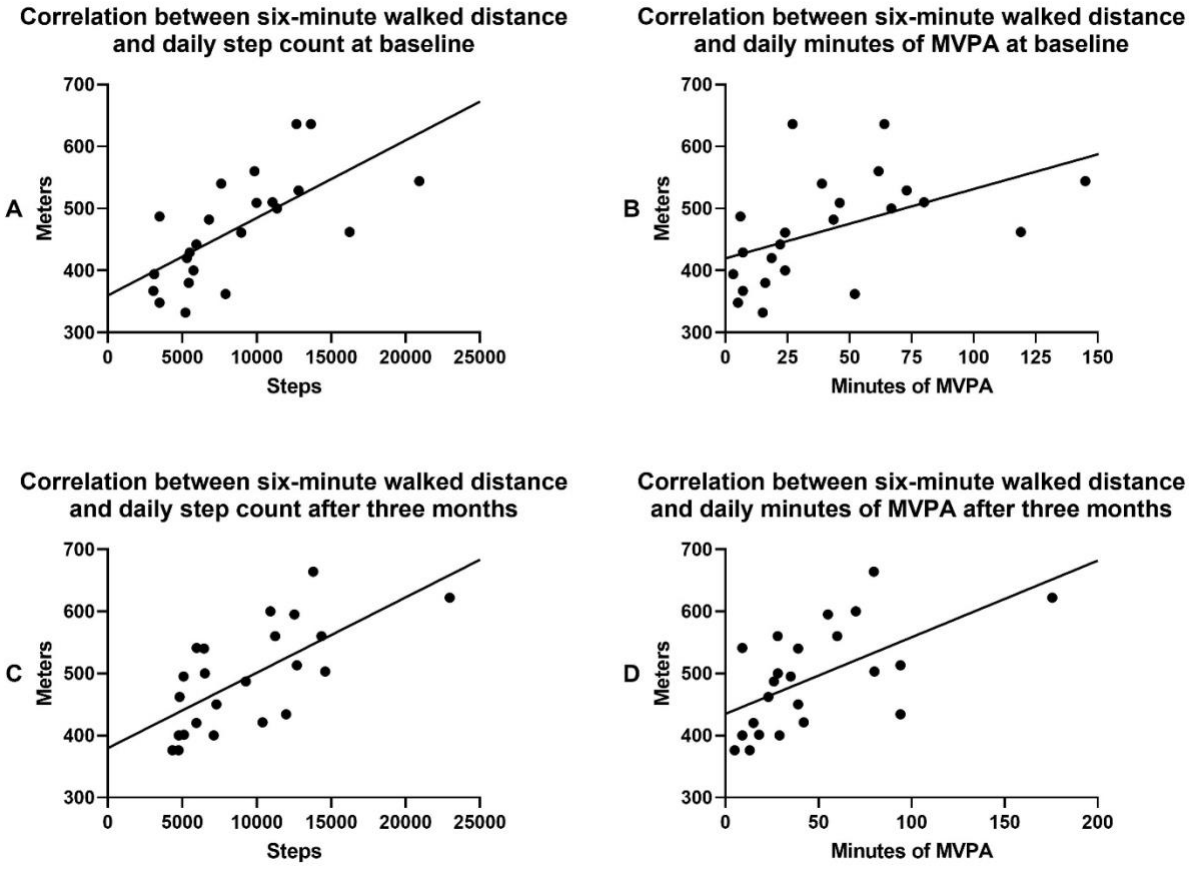


Figure 4.13 The relationship between 6MWT and other daily PA metrics.

(A) Correlation between 6MWD and daily step count at baseline (r=0.67, p<0.01), (B) 6MWD and minutes of MVPA at baseline (r=0.48, p=0.02), (C) 6MWD and daily step count at follow up (r=0.67, p<0.01), and (D) 6MWD and minutes of MVPA at follow up (r=0.58, p<0.01).

4.4 Discussion

In this chapter, the physical activity and functional capacity of patients who were planned to undergo revascularisation were assessed before and after the procedure. In summary, the findings were as follows. First, the findings suggested no statistically significant difference in daily step count (8699 vs 7216), minutes of MVPA (47 vs 32) and six-minute walked distance (474m vs 411m) at baseline between patients who underwent PCI and those who did not. However, the PCI group had numerically higher values, albeit non-significant, in all measured components. Second, the difference in these metrics (step count; 9244 vs 7233, MVPA minutes; 54 vs 29, and walked distance; 496m vs 447m) remained statistically non-significantly different between the PCI and control groups up to three months after the procedure. Third, there was a significant increase in walked distance after procedure in PCI and control groups, but this was not observed in other daily physical activity metrics. Fourth, the change in wire-based FFR and FFR_{CUM} were associated with weak and non-significant correlations with change in PA. Finally, patients who received stents in two vessels had higher overall change in daily step count (17% vs 2%) and performed slightly better in 6MWT at follow up (6% vs 4%) than one vessel intervention. Summary of the main findings is shown in figure 4.14.

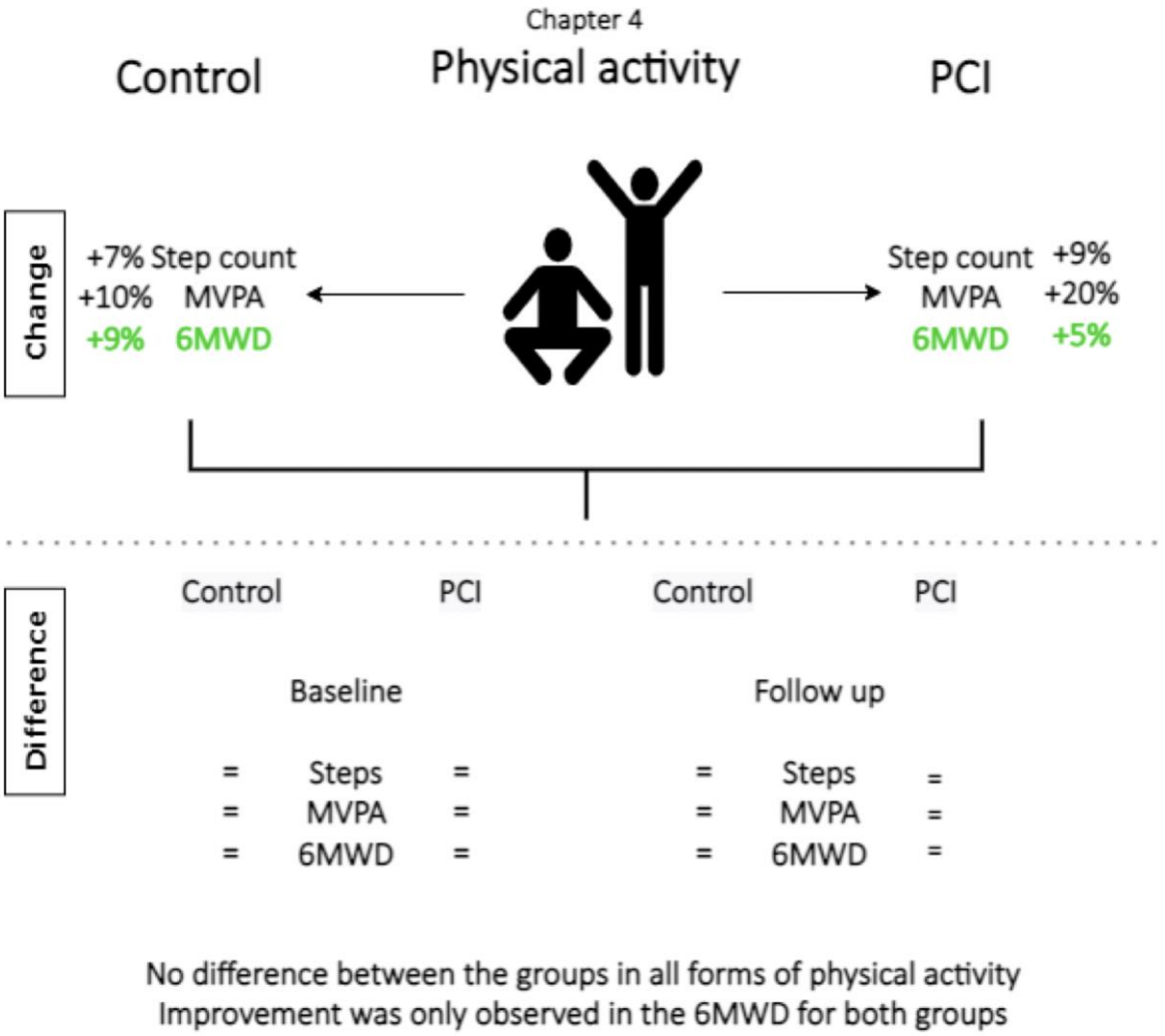


Figure 4.14 Schematic summary of the findings from chapter four

4.4.1 Physical activity monitoring in CCS patients

To the best of my knowledge, this is the first study to evaluate and objectively measure daily activities with wearable technology following LHC±PCI for a prolonged period. In this work, 24 patients were monitored for three months or more prior to their procedure but a maximum of 90 days were included in the monitoring period (2.6±0.75 months). This provides both extensive, reliable and representative baseline information about the patient's activity levels. Baseline data should be treated carefully in these settings especially concerning analysis of the response to

intervention. Inadequate baseline data may result in an inaccurate or misrepresentative evaluation of the change if the baseline monitoring period were too brief. Moreover, following the procedure, despite including only three months, most patients were monitored for up to six months (6.6±1 months), which also highlights the feasibility of PA monitoring in CAD patients. Generally, patients were compliant with the instructions given and wore their Fitbit™ for most of the time. A major issue was 'data hygiene', which is particularly necessary in this type of work. This term includes aspects such as checking wearing time and artefact free days. It was time consuming to ensure data hygiene, but it ensured that only days with error free >10 hours of wearing time are included in the analysis as described in the quality assurance section. See *figure 4.2* for more details. It is clear that using commercially available fitness tracker such as a Fitbit™ for monitoring is feasible and an objective way of quantifying physical activity for prolonged periods. Furthermore, using activity tracker was well received by the patients, and some patients have stated that they will buy their own trackers once they end their participation in the study.

Device selection

In this study, I used the well validated fitness trackers (Fitbit™). The Fitbit trackers have been proven to be feasible for monitoring in multiple studies and in different conditions (Evenson et al., 2015; Vetrovsky et al., 2020; St Fleur et al., 2021). One of the main reasons to elect this tracker was its battery life, which can last for one week with one charge only. This provides more reliable data collection due to the increased wear-time and also more convenience for the study participants. Another reason is its simplicity, the trackers are designed as wrist-band that only shows time unless the user intentionally reach for the advanced settings. Due to this simple design, these trackers are limited on the collecting and downloading vital signs time-series data (i.e. HR), but only allow a view of HR intervals over the course of 24 hours. In addition, it fails to measure blood pressure, or detect arrhythmias, although these might not be very relevant for this study.

4.4.2 Quantifiable differences between PCI and control groups

The mean daily step count was numerically higher in the PCI group compared to controls for the averaged period since recruitment until the procedure (8699 vs 7216 steps), but this 20% difference was not statistically significant. The PCI group mean daily step count lay beyond the suggested daily step count threshold (7500 steps) which is associated with reduced cardiovascular events (Houle *et al.*, 2013; Lee *et al.*, 2019). The difference remained non-significant at the end of the analysis period (9245 vs 7233 steps at three months) but the difference between the groups increased every month, starting from a difference of 1483 steps (p=0.36) at baseline to 2011 steps (p=0.21) after three months. See *table 4.4* for more details. It may be therefore, that the different may have become significant with the passage of more time. Similar to the above, the difference in daily minutes of moderate to vigorous physical activities was not significant between groups either at baseline (47 vs 32 minutes) or after three months (54 vs 29 minutes). Nonetheless, the gap between the groups tended to increase over the months, from 15 minutes between the groups at baseline to 25 minutes at three months. Although the difference was not significant, a trend can be seen towards increased activity in the PCI group in both metrics. Furthermore, light activities such as walking might be less transformed by PCI, whereas patients may benefit more in high-intensity activities, hence the close to significance p-value in time spent in MVPA post PCI. Both groups achieved a similar 6MWD at baseline (p=0.10) and follow up (p=0.19) and no significant difference was observed between the groups' functional capacities, although both groups achieved a greater distance, on average, at follow up (+22 vs +35m) for PCI and control group respectively. Therefore, whilst intervention may result in some improvement in functional capacity, this may be non-significant (Chen *et al.*, 2018; Stewart *et al.*, 2018). In addition, the increase in walked distance in both groups may be explained by the 'learning effect' which has been observed in several disease states (Wu et al, 2003; Bellet et al, 2012). It can be argued that cardiac rehabilitation may have influenced the outcomes of physical activity analysis following the procedure, since it can be routinely prescribed following cardiac catheterisation procedures. However, cardiac rehabilitation is mainly performed following acute cases (STEMI and NSTEMI). Yet, it can be recommended either by the cardiologist or the general practitioner for chronic patients similar to the studied cohort in VIRTU-5. Though, due to COVID-19 pandemic, cardiac

rehabilitation appointment either took longer than the study involvement period or did not take a place at all. Therefore, it is safe to assume that the 6MWT and physical activity performance were not influenced post-procedure for this particular sample of patients.

4.4.3 The change in physical activity following coronary revascularisation

Until recently, it has been widely accepted that PCI results in an improvement in physical activity levels in CCS patients, as assessed by exercise time or domains in questionnaires (Parisi *et al.*, 1992; Weintraub *et al.*, 2008). Conversely, daily monitoring of physical activity in this work failed to demonstrate any significant increase in activity levels up to three months following PCI, whether in daily step count or in time spent in high intensity activities. This is an interesting finding, despite invasive intervention and demonstrably improved (albeit hyperaemic) coronary blood supply to the myocardium. The absence of a meaningful change following PCI agrees with the ORBITA trial findings (Al-Lamee, *et al.*, 2018). In ORBITA, participants were blinded to their procedure, and no difference was reported in either (treadmill) exercise time ($p=0.20$), nor Duke treadmill score ($p=0.10$) at six-week follow up. Despite the difference in the assessment tools between our study and ORBITA, a similar message is emerging. This was also observed in the control group, which maintained similar levels of activities despite the fact that those patients became aware that the narrowings in their arteries are not significant and were assessed with gold-standard technologies. It is worth highlighting that these findings address PA in particular, and are independent from angina symptoms. Thereby, the non-significant increase in PA does not particularly constitute failure to improve, because if similar activities can be achieved post-PCI without triggering an angina episode, then a main reason for undertaking the procedure has succeeded. Further analysis about the relationship between PROMs and PA will be discussed in the next chapter. Furthermore, angina medications did not change for the PCI and control groups except for one patient in the latter group. Therefore, these findings in this chapter can be regarded as independent from any medication changes and the PA results are not influenced by the change in anti-anginal medications. For the 6MWT, a significantly increase post procedure was observed in the PCI group (+5%, $p=0.046$) and control group (+9%, $p=0.1$), yet no meaningful difference in the walked distance between the groups was observed at baseline or at follow up ($p>0.5$). When patients

were stratified into three groups of control, one vessel and two vessel interventions, all groups walked similar distances (p>0.5) and had similar levels of change (+9% vs +4% vs +6%, p=0.54). The divergent findings in daily monitoring and 6MWT may possibly be explained by the effect of a 'controlled environment' activity test (i.e. 6MWT rather than steps at home). Also, it might be the case that patients believe that they should perform better because they have had an intervention or are not at high risk if they were told they do not need an intervention. Blinding the patients to outcomes, as done in ORBITA, may have overcome this uncertainty. Another justification is the learning (training) effect as mentioned in the previous section, by the time the 6MWT was completed at follow up, a total of four tests were conducted which made patients more familiar with test allowing them to perform better. In previous work, it has been reported that even in healthy volunteers, significant levels of increased walked distance were reported between same visit 6MWT (p<0.001) and at baseline vs two-month follow up tests (p<0.05) (Wu., 2003).

4.4.4 The relationship between disease severity and physical activity

In this chapter, the number of treated vessel (control vs single vs double) was used as a method of stratifying the patients in addition to FFR, FFR_{CUM} and the change in FFR. On the one hand, the physical activity in daily living did not differ significantly between the groups, whether in regards to daily extra steps after intervention, or in time spent in MVPA. However, it is perhaps worth noting that when compared with averaged three months pre procedure (baseline) the number of daily steps remained exactly the same three months post procedure in the control (7%) and one vessel (2%) groups whereas it increased by 1316 (23%) in the two vessel group (p=0.03). This was the only significant improvement in daily activity metrics in all of the analyses in this study. The single vessel group spent more time in minutes of MVPA compared to the control group (p<0.05) in each month post PCI, but this was not observed between one vs two vessel intervention nor in control vs two vessel intervention. Alternatively, the 6MWD did not significantly differ between the groups at baseline, or at follow up, with similarly minimal change (9% vs 4% vs 6%) for control, single and double vessel interventions, respectively. Although the difference in the walked distances between the groups was not significantly different at baseline (p=0.11) and at follow up (p=0.23), the single vessel group walked an extra 52m at baseline compared to the two vessel

group and an extra 91m compared to the control group. Both FFR and FFR_{CUM} failed to explain any trends in the activity measures. Correlations were weak or diminished except for the change in FFR for the PCI group and the change in daily step count. Although the finding was not statistically significant, a trend towards larger changes in daily step count in association with small changes in FFR (r=-0.28, p=0.27) was observed. However, conclusion cannot be drawn, yet it might be an interesting area to explore. Perhaps an FFR of > or <0.80, as one might expect (being a hyperaemic measurement), has more relevance to maximal effort, such as that seen on a treadmill, than to daily living, such as the number of steps undertaken or a distance walked (rather than run). In a society in which maximum exercise is a rarity, perhaps the interventionist's concept of the physiological threshold does not accord with real life. This hypothesis may accord with ORBITA, in which the results of exercise testing did not show increase in time as a response to PCI more than the placebo procedure.

4.4.5 Limitations

The main limitation of this study is that the targeted population was of limited size. This is particularly important because the magnitude of the parameters measured varied greatly between individuals. For example, two patients of a similar age, who both needed stents in two vessels, had a baseline daily step count of 6079 and 20921 steps a day, respectively. It is also possible that the group were in some way unrepresentative of the group of patients with CCS as a whole. As in the ORBITA study, it could also be possible that the frequency and quality of physicianly input by the research fellow to both groups, and throughout, may have eroded any measurable differences either between groups, or over time. Additionally, the selection criteria was restricted in principle due to the need of participants' mobility in order to assess changes in daily physical activity. However, this could be understandable as the total recruited patients for the study was modest. Yet, a more generalised study including participants with mobility aids may be needed to understand the change in all types of CCS patients. Another weakness was that the control group were not truly 'blinded' to their procedure. Although they underwent a procedure which was 90% similar to the PCI patients (premedication, the same catheterisation laboratory, arterial catheter insertion, angiography, pressure wire insertion, adenosine administration,

aftercare), they were aware whether or not they had received a stent. However, if this had been an important influence, one would have expected the PCI group (or perhaps both groups) to show evidence of post-procedural improvement, which they did not. As regards general applicability of the methods, some older patients do not have an internet connection at home, and these could not be included, which may have biased the sample. Furthermore, some participants were not familiar with the technology used. This problem, however, was solved by multiple visits for troubleshooting, which is clearly not practical for large scale studies. Additionally, some 6MWTs were cancelled due to restrictions during the COVID-19 pandemic, which coincided with this work.

4.5 Conclusion

Daily physical activity for patients who suffer from CCS with flow-limiting disease, according to the standard definition of FFR<0.80, does not appear to significantly improve after receiving one or more stents. This was also observed in patients who underwent for LHC without PCI. Moreover, no difference was observed when both groups were compared in terms of change over three months. Additionally, disease severity does not seem to have an explanatory role in understanding the levels of change after treatment. Finally, only a subgroup of patients who had stents in two vessels showed significant and gradual improvement towards the third month. Further analysis to explore the relationship between physical activity, angina and quality of life after intervention will be conducted in chapter five.

Chapter five: Patient reported outcomes measures (PROMs) in CCS patients

5.1 Introduction

CCS is associated with MACE rates which are substantially lower compared with ACS. In a meta-analysis that included 5457 patients, it was shown that CCS patients have lower rates of all-cause mortality, recurrent MI and revascularisation after deferral compared with ACS patients, on the basis of an FFR-guided revascularisation strategy (Liou *et al.*, 2019). Therefore one of the main reasons to undertake PCI in CCS patients is to relieve angina symptoms and, subsequently, improve quality of life, rather than prevent adverse events. Different measures are being used to assess symptoms, quality of life and health state in general, and these can be either patient reported (e.g. the Seattle Angina Questionnaire) or physician reported (e.g. Canadian Cardiovascular Society classification system for angina).

In this work, three patient reported outcomes measures (PROMs) were used, namely EuroQoL (EQ-5D), Short-Form-12 (SF-12) and Seattle Angina Questionnaire (SAQ). The EQ-5D is one of the most used health status instruments in research, and has been translated into more than 170 languages. It consists of five dimensions that all together can be scored and health status can be identified. These domains are mobility, self-care, usual activity, pain and discomfort, and anxiety and depression. The main objective that EQ5D was been built to fulfil was to value and describe the health-related quality of life by developing a generic measurement (Devlin and Brooks, 2017). The SF-36 was first introduced in the early 1990s to be used in clinical practice, general population surveys and research (Brazier *et al.*, 1992). However, a shorter version was later developed consisting of 12 questions with an objective of reproducing similar outcomes of the 36 questions instrument, with less questions, and therefore shorter completion time. Two specific summaries can be produced by completing these questions, which are physical component summary (PCS) score and mental component summary (MCS) score (Ware, Kosinski and Keller, 1996). The post infarction care study reported a strong correlation between the SF-12 and SF-36 in CAD patients, ($r=0.96$, $p<0.001$) for both PCS and MCS, and was responsive to change (Müller-Nordhorn, Roll and Willich, 2004). The SAQ is considered the most commonly used questionnaire in cardiology

research. A unique and important characteristic of this PROM is its disease specificity for CAD. Moreover, SAQ is a self-administered instrument that consists of 19 questions to quantify relevant domains to chest pain chest tightness and shortness of breath. SAQ domains include physical limitation, angina frequency, angina stability, treatment satisfaction and quality of life, all in relation to angina. This instrument can quantify relevant treatment objectives in CAD which makes it an appropriate endpoint for clinical investigations. The earliest study showed correlation between the five dimensions and the patient's function, and it was sensitive to both dramatic and subtle clinical changes as seen in angioplasty and outpatients, respectively (Spertus *et al.*, 1995). Furthermore, a UK version of SAQ was introduced, and tested among different GPs in North East England to assess validity, reliability and responsiveness. Both EQ-5D and SF-12 were used to validate SAQ, and the findings suggested moderated to strong correlation in all domains (Garratt, Hutchinson and Russell, 2001).

All three questionnaires have been used in landmark CCS trials. For instance, the FAME-2 trial used EQ-5D and demonstrated a significant improvement in quality of life in the FFR-guided PCI group compared with standard care. The RITA-2 trial used SF-36, and showed a higher PCS score improvement in the PCI group compared with the medical therapy group. Other trials have used both generic and disease specific metrics. The COURAGE trial is an example in which both SF-36 and SAQ were utilised. Similar to the previous trials, greater improvement in both symptoms and physical limitation were reported in the PCI group compared with the medical therapy group. The ORBITA trial, which was of a different design (double blinded, as well as randomised and placebo-controlled), used SAQ and EQ-5D, and was the first to assess the placebo-effect of a procedure (PCI or sham). ORBITA, however, did not report an improvement in the PCI group compared with the placebo group (Al-Lamee *et al.*, 2018). Although freedom from angina was more common in the PCI group compared to the placebo group (one in five at follow up), other domains in SAQ and EQ-5D were not significantly different between the groups with respect to the change from pre-randomisation to six weeks after the procedure ($p>0.05$). The lessons learned from ORBITA are important for the interventional cardiology community. The first is that improvement in response to PCI is not as great as expected; and in fact it was not statistically significantly different between the PCI and placebo groups, despite the reported improvement in coronary physiology metrics.

The second was the re-evaluation of our understanding about the relief of angina symptoms, because angina appears to be more complex than simple relief of physical symptoms. In this chapter, I aim to investigate the change in generic and disease specific PROMs in response to PCI and to evaluate health state and angina symptoms with disease severity in CCS patients.

5.2 Methods

5.2.1 Study population

Patient screening and recruitment was described earlier (see section 2.2.1). In brief, patients had a CCS and were on the waiting list for coronary angiography with a view to PCI. Patients who had CABG were excluded, as did those who did not complete all questionnaires.

5.2.1 Patient reported outcome measures (PROMS)

Each patient completed a combination of generic and disease specific questionnaires during a home visit intended for recruitment (baseline). After three months of having their procedure, repeat questionnaires were completed during a hospital visit to the first follow up. Patients were also invited for another visit six months post-procedure to complete a second follow up and end study participation. However, only the first follow up questionnaires were used in this analysis due to time limitation. Furthermore, the second follow up questionnaires will be used in future analysis looking at longer-term (six months) changes following LHC±PCI. At each time point, the EuroQoL™ (EQ-5D-5L) and the Optum™ (Medical Outcomes Short Form SF-12v2®) generic health questionnaires were completed. Additionally, the Seattle Angina Questionnaire (SAQ) [United Kingdom version], provided by CV Outcomes Instruments, LLC was completed to measure disease-specific patient reported outcomes. All three questionnaires address quality of life, physical limitation and mental health based upon different perspectives and scoring methods. Each domain utilised the recommended scoring method provided by EuroQoL, Optum and Outcomes Instruments. Licences were obtained specifically for this study (Appendix 3).

5.2.2 Measurement of general health status

EQ-5D

Patients were asked to report their general quality of life by describing their health on the specific day of completing the questionnaire, in five domains (mobility, usual-activity, self-care, pain or discomfort and anxiety or depression) and five levels of severity (no problems, slight, moderate, severe and unable or extreme). An additional visual analogue scale (VAS) was also provided as a numerical representation of patient's own view. The scale ranges from 0 labelled 'the worst health you can imagine' to 100 labelled 'the best health you can imagine' (See Appendix 3.A).

Scoring EQ-5D

Two main scores were generated from EQ-5D. The first was the VAS score which constitutes the patients' general view of how they feel. The second was the England index value which was generated based upon patients' response to each domain (Devlin *et al.*, 2018). The scoring method is based upon a 20-parameter model which weighs each answer to each dimension differently. The maximum achievable value is 1.0 and the minimum is -0.285 depending upon status profiles that were built based on responses. The model described by Devlin *et al* weighs the pain as the highest influencing factor on the index value followed by the mental state. Set values for each response is shown in table 5.1

Table 5.1 EQ-5D England index value model of domains and responses

	No problems	Slight	Moderate	Severe	Unable
Mobility	0	0.058	0.076	0.207	0.274
Self-care	0	0.050	0.080	0.164	0.203
Usual activity	0	0.050	0.063	0.162	0.184
Pain and discomfort	0	0.063	0.084	0.276	0.335
Anxiety and depression	0	0.078	0.104	0.285	0.289

SF-12

Patients were asked to report their views on health based upon their current status and the last four weeks in general. The short-form, 12 items, instrument was used to measure functional status in terms of physical and mental components. A set of 12 questions distributed among eight health domains targeting physical abilities and expectations, pain, vitality, social functioning, emotions, mental and general health (See Appendix 3.B). By answering these question a calculation of physical and mental summary scores can be completed.

SF-12 Scoring

Patient responses were entered into dedicated software (PRO CoRE 2.0 Smart Measurement® System), SF-12v2® Health Survey. Physical component summary score (PCS) and mental component summary score (MCS) are generated based on the responses. Higher scores indicate better health status.

5.2.3 Measurement of disease specific health status

SAQ

Participants were asked to complete a disease-specific questionnaire. The questionnaire consists of 19 questions, aiming to quantify physical limitation, angina status and quality of life. All the questions are designed to be directly related to angina in the form of chest pain, chest tightness and shortness of breath during the last four weeks (See Appendix 3.C). A UK version was licenced and used for this study (Garratt, Hutchinson and Russell, 2001). Outcomes Instruments, LLC, supplied the scoring instructions.

SAQ Scoring

Each domain was scored according to the official Outcomes Instruments, LLC scoring instructions. A principal equation was used for all domains, the main difference being the number of possible responses. Each domain is scored separately, on a scale of 0-100, where higher scores indicate better health status.

For domains with five possible answers, the following equation was used:

$$Domain\ summary\ score = 100\ x\ \frac{Mean\ response - 1}{4}$$

For domains with six possible answers, the following equation was used:

$$Domain\ summary\ score = 100\ x\ \frac{Mean\ response - 1}{5}$$

5.2.4 Change in physiology

Change in FFR was calculated as:

If no intervention, a value of 0% was given

If one vessel: $\frac{\Delta FFR}{Pre-PCI\ FFR} x100$

If two vessels: $\frac{\frac{\Delta FFR}{Pre-PCI\ FFR} + \frac{\Delta FFR}{Pre-PCI\ FFR}}{2} x100$

Change in FFR_{CUM} was calculated as:

$$\frac{\Delta FFR_{CUM}}{Pre-PCI\ FFR_{CUM}} x100$$

5.2.4 Statistical analysis

Data were reported as means, standard deviations and percentages unless stated otherwise. Histograms were used to display frequency of variables and bar charts to demonstrate differences. Unpaired t tests were used to compare the summary scores of the PCI and control groups, and paired t tests were used to compare the change in each domain summary score in individual patients after LHC±PCI. One-way ANOVA was used to assess statistical difference between control, single vessel and two vessel interventions. Pearson's correlation was used to investigate the relationship between disease severity and PROMs, and the relationship between the change in reported physical limitation and measured physical activity. GraphPad Prism (9.4.1) was used for statistical analysis.

5.3 Results

5.3.1 Patient characteristics

Forty patients who were planned to undergo elective LHC±PCI were recruited in this study and all completed baseline questionnaires at baseline. Six patients did not have three months follow up questionnaires for the following reasons; two underwent CABG, three were unable to meet for follow up assessment and one patient did not undergo LHC±PCI at the time of the analysis. All remaining 34 patients underwent LHC, of which 23 had PCI in one (n=13) or two (n=10) vessels. The patients without revascularisation (n=11) comprised the 'control' group, because they received all the assessments, and an invasive procedure, including pressure wire measurements in all relevant vessels, but without stent implantation. Patients' characteristics are shown in table 5.2.

Table 5.2 Baseline characteristics

Patient characteristics		34	Percentage	Mean (±SD)
Age				65 (±8)
	Male	28	82%	
	Female	6	18%	
Smoking status				
	Current smoker	3	9%	
	Ex-smoker	20	62%	
	Non-smoker	10	29%	
Risk factors				
	Hypertension	22	64%	
	Hyperlipidaemia	11	32%	
	Type 2 Diabetes	4	12%	
Procedural outcomes				
Underwent PCI*				
	Yes (PCI group)	23	68%	
	No (Control group)	11	32%	
Single vessel intervention		13	57%	
Double vessel intervention		10	43%	

PCI= percutaneous coronary intervention

5.3.2 PROMS for patients undergoing LHC±PCI

Three questionnaires were assessed separately for the full cohort. Starting with general health questionnaires, the mean EQ-5D UK index value was 0.77±0.18 [range 0.07 to 1.0] and the EQ-VAS was 72±14 [range 40 to 100] both at baseline. After three months, these values increased to 0.83±0.17 (+9%, p=0.10) and 75±20 (+3%, p=0.49) for EQ-5D UK index value and EQ-VAS, respectively (Figure 5.1). Similarly, this was done for the SF-12, in which the physical component increased minimally following the procedure (42.3±10 vs 44.3±12, 5%, p=0.03), but no difference was observed in the mental component (49.3±10 vs 50.3±9, +2%, p=0.51) (Figure 5.2). With regards to angina, SAQ scores for the full cohort were as follows; physical limitation domain (67±21 vs 78±19, +16%, p<0.001), QoL domain (41±25 vs 70±23, +70%, p<0.0001) and angina frequency domain (64±25 vs 89±15, +40%, p<0.0001) (Figure 5.3). The number of patients who reported to be angina free was two (6%) at baseline and 19 (56%) at follow up.

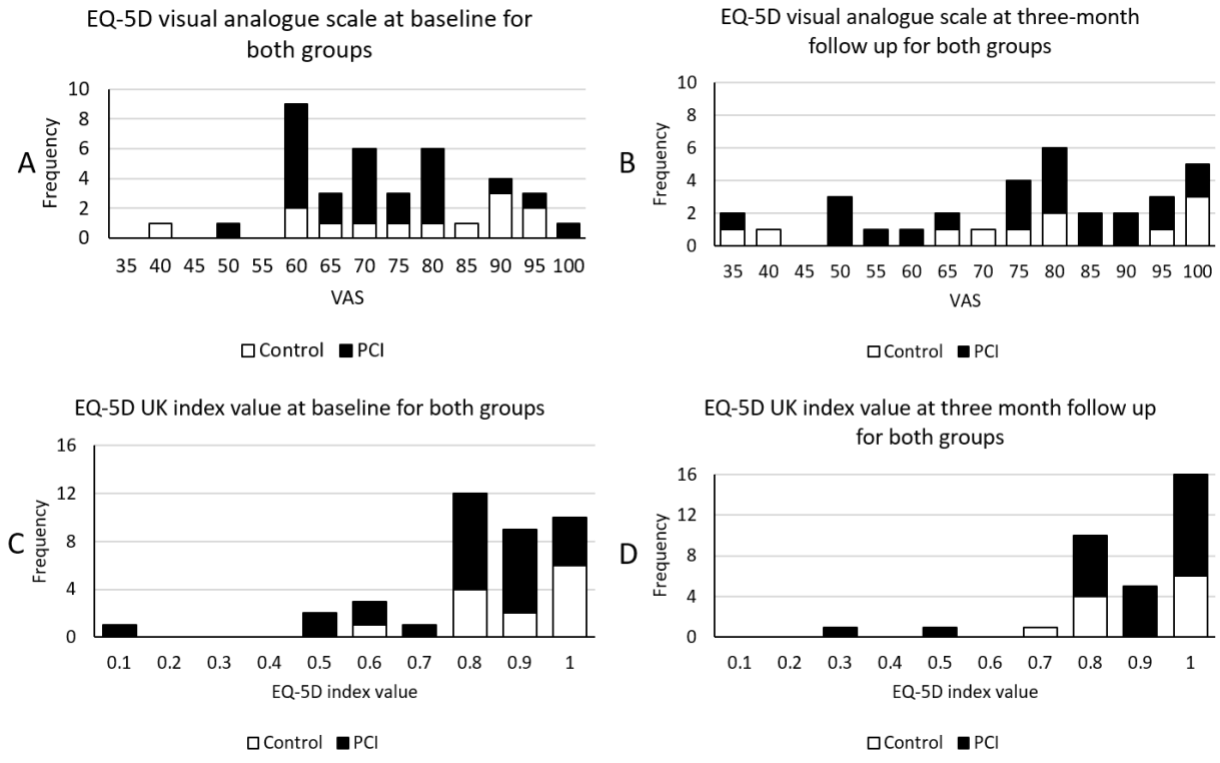


Figure 5.1 Full cohort frequency distribution demonstrating EQ-5D scores at baseline and at three-month follow up

PCI (Black) and Control (White) groups' summary scores using VAS tool are shown at baseline (A) and at follow up (B). Likewise but using EQ-5D UK index value at baseline (C) and at follow up (D)

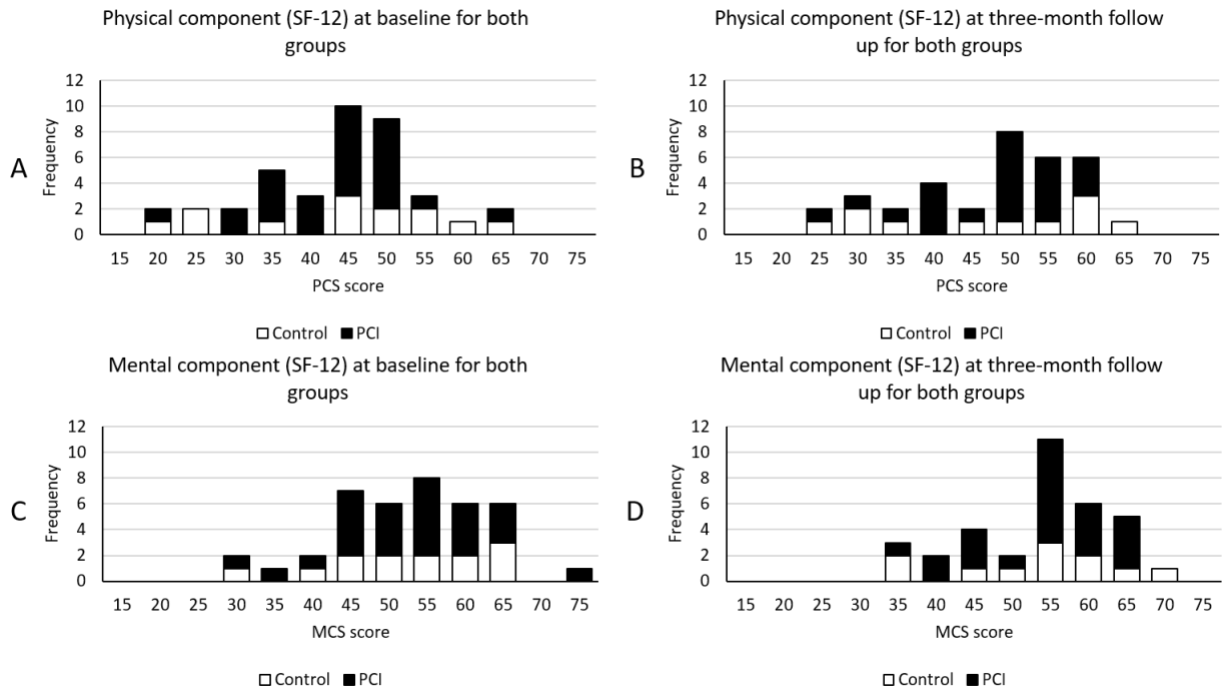


Figure 5.2 Full cohort frequency distribution demonstrating SF-12 summary scores at baseline and at three-month follow up

PCI (Black) and Control (White) groups' physical component summary score at baseline (A) and at follow up (B). Mental component is demonstrated in (C) at baseline and in (D) at follow up.

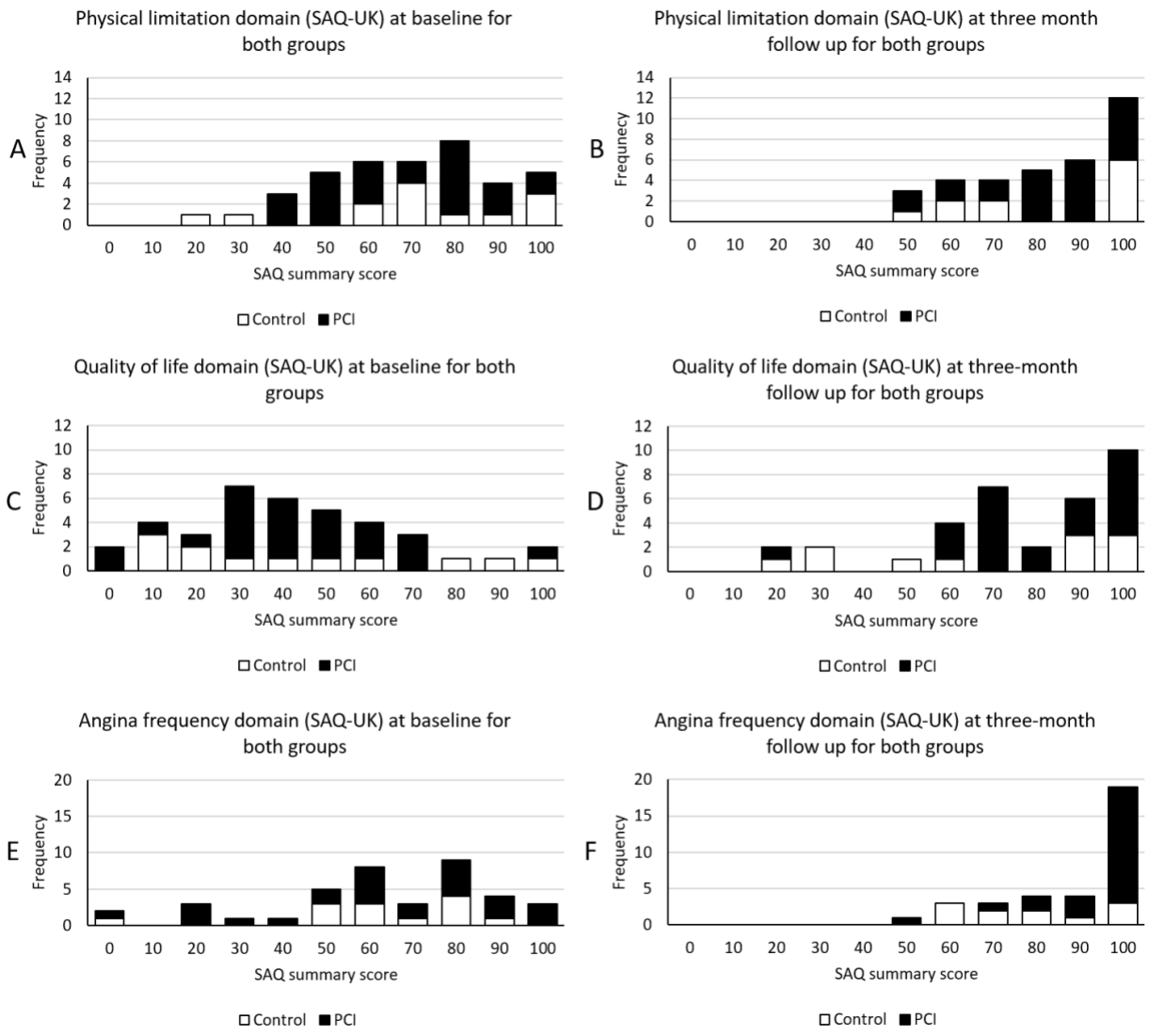


Figure 5.3 Full cohort frequency distribution demonstrating SAQ three domains summary scores at baseline and at three-month follow up

Frequency of physical limitation scores are shown in (A) at baseline and (B) at follow up. In the second row, quality of life scores are stacked at baseline (C) and at follow up (D), and finally, angina frequency is shown at baseline (E) and at follow up (F). Black bars represents PCI group and white bars represent control group.

5.3.3 Effects of revascularisation upon PROMS

General health PROMs

A) EQ-5D

There was no significant difference between the groups (n=34) in general health state using EQ-5D instrument at baseline and follow up. In addition, the change was non-significant for both groups. The results of EQ-5D at baseline and follow for both groups are presented in table 5.3. Histograms showing the differences between the time points and groups are illustrated in figure 5.4.

Table 5.3 Results of EQ-5D for PCI and control

EQ-5D	Control (n=11)		PCI (n=23)		p-value
	Mean	±SD (%)	Mean	±SD (%)	
Visual analogue scale					
Baseline	77	±17	72	±12	0.39
Follow up	76	±23	75	±18	0.99
Change	-1	(-1%)	+3	(+5%)	0.39
	p=0.91		p=0.28		
England Index value					
Baseline	0.83	±0.15	0.77	±0.14	0.24
Follow up	0.85	±0.15	0.84	±0.20	0.86
Change	+2	(4%)	+7	(13%)	0.42
	p=0.47		p=0.13		

EQ-5D= EuroQuality of life 5 domains

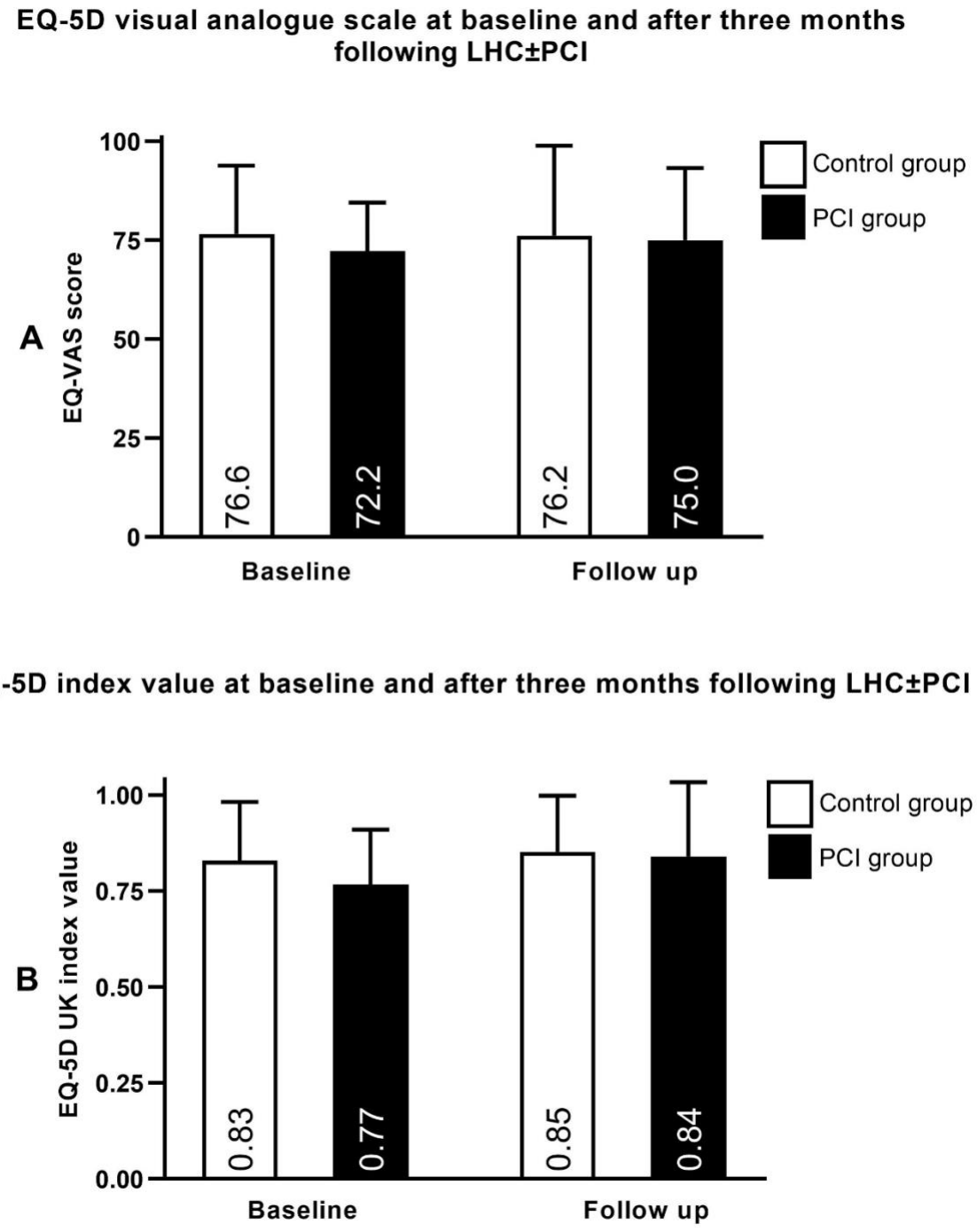


Figure 5.4 Euro Quality of Life (EQ-5D) instruments at baseline and follow up.

Histograms are used to demonstrate any differences between groups and changes at baseline and follow using (A) visual analogue scale and (B) EQ-5D UK index value. All comparisons are non-significant (p>0.05).

B) SF-12

There was no significant difference between the groups (n=34) using SF-12 physical and mental components at baseline and follow up. Moreover, only the PCI group has shown improvement in PCS at follow up ($p<0.01$). The results of SF-12 at baseline and follow for both groups are presented in table 5.4. Histograms showing the differences between the time points and groups are illustrated in figure 5.5.

Table 5.4 Results of SF-12 for PCI and control

SF-12	Control (n=11)		PCI (n=23)		p-value
	Mean	±SD (%)	Mean	±SD (%)	
Physical component					
Baseline	43	±13	41	±9	0.56
Follow up	43	±14	45	±9	0.66
Change	0	(0%)	+4	(+12%)	0.11
	p=0.98		p<0.01		
Mental Component					
Baseline	49	±10	50	±8	0.67
Follow up	50	±11	51	±9	0.66
Change	+1	(+4%)	+1	(+3%)	0.98
	p=0.78		p=0.51		

SF-12= Short-Form-12

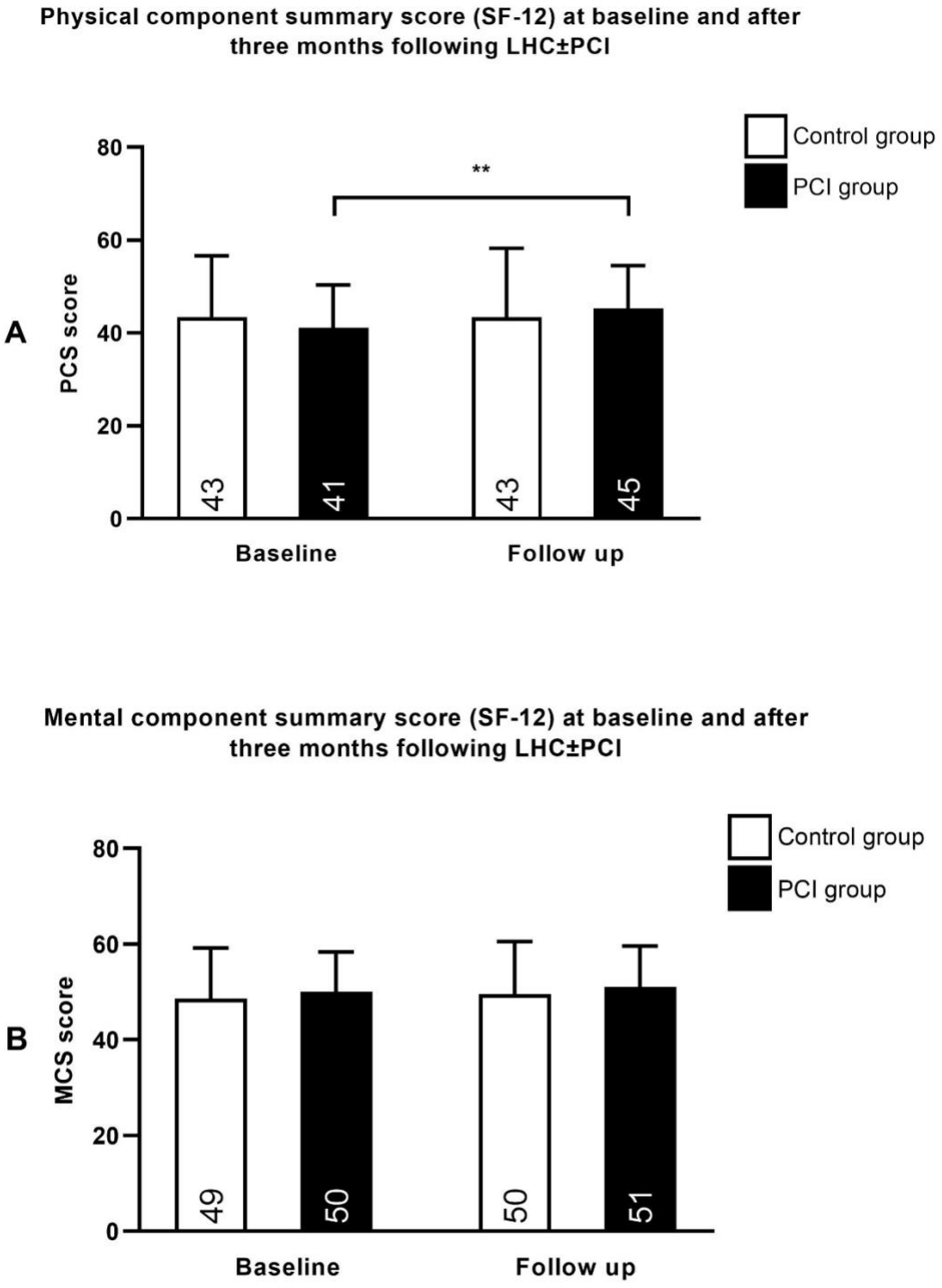


Figure 5.5 Short Form 12-item (SF-12) at baseline and follow up.

*Histograms are used to demonstrate differences between groups at baseline and follow and any associated changes following the procedure in the physical component (A) and mental component (B). All pairwise comparisons are non-significant except the labelled one (**p<0.01).*

Disease specific PROMs

SAQ-UK

No difference was observed between the groups in all domains at both time points except for angina frequency at follow up where PCI group reported better state compared to control (93 vs 80, p=0.01). Additionally, all groups reported improvement at follow up in all domains except the physical limitation domain for the control group (68 vs 78, p=0.26). The results of the Seattle Angina Questionnaire for both groups are presented in table 5.5. Histograms showing the differences between the time points and groups are illustrated in figure 5.6.

Table 5.5 Results of SAQ for PCI and control

SAQ domain	Control (n=11)		PCI (n=23)		p-value
	Mean	±SD	Mean	±SD	
Quality of life					
Baseline	44	±34	40	±24	0.71
Follow up	63	±31	74	±19	0.20
Change	+17	(+27%)	+35	(+47%)	0.09
	p<0.001		p=0.02		
Angina frequency					
Baseline	66	±14	62	±28	0.65
Follow up	80	±16	93	±12	0.01
Change	+13	(+19%)	+31	(+50%)	0.07
	p=0.02		p<0.01		
Physical limitation					
Baseline	68	±27	67	±18	0.89
Follow up	78	±22	80	±16	0.83
Change	+10	(+14%)	+12	(+18%)	0.72
	p=0.26		p<0.01		

SAQ=Seattle Angina Questionnaire

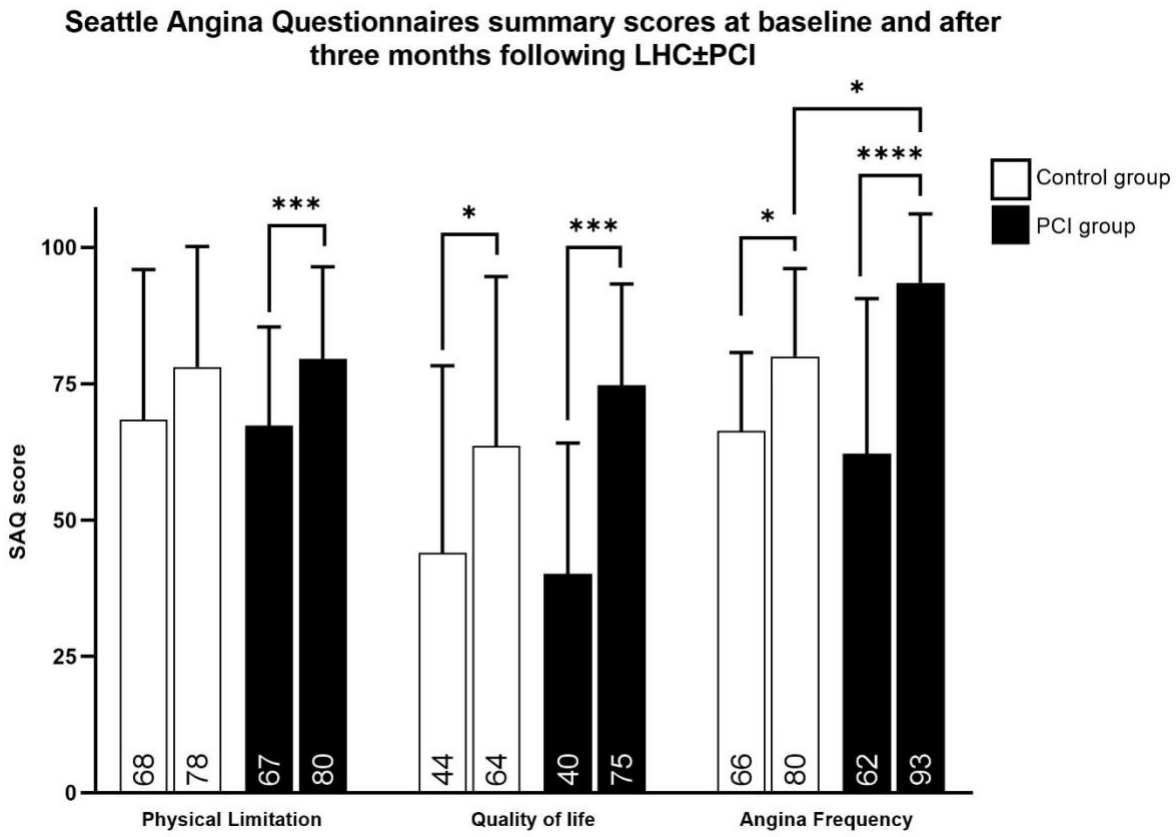


Figure 5.6 Comparison between PCI and control groups in three domains of Seattle Angina Questionnaire (SAQ).

PCI and Control groups are compared at baseline and at three-month follow up in physical limitation, quality of life and angina frequency. Comparisons included (group vs group) and (baseline vs follow up) for all domains. All pairwise comparisons are non-significant except the labelled ones
**p<0.5, **p<0.01, ***p<0.001, ****p<0.0001.*

5.3.4 Relationship between disease severity and PROMs in CCS patients

5.3.4.1 Number of treated vessels: sub group analysis

General health PROMS

A) EQ-5D

There was no significant difference between the control group (n=11), single-vessel PCI group (n=13) and two-vessel PCI group (n=10) in EQ-5D scores at baseline and at follow up. Only the two-vessel group showed improvement at follow up in EQ-VAS (72 vs 83, p=0.01). The results of the EQ-5D are presented in table 5.6. Histograms showing the differences between the time points and groups are illustrated in figure 5.7.

Table 5.6 Results of EQ-5D based on the number of treated vessels

EQ-5D	Control N=11		Single vessel PCI N=13		Two vessel PCI N=10		p-value
	Mean	±SD (%)	Mean	±SD	Mean	±SD	
Visual Analogue scale							
Baseline	77	±	70	±	72	±	0.70
Follow up	76	±	68	±	83	±	0.21
Change	-0.4	(0%)	-2	(-1%)	+11	(+15%)	0.69
	p=0.91		p=0.65			p=0.01	
England index value							
Baseline	0.82	±	0.75	±	0.79	±	0.42
Follow up	0.85	±	0.78	±	0.91	±	0.24
Change	+0.02	(2%)	0.03	(+3%)	+0.12	(+15%)	0.45
	p=0.47		p=0.64		p=0.05		

EQ-5D= EuroQuality of life 5 domain

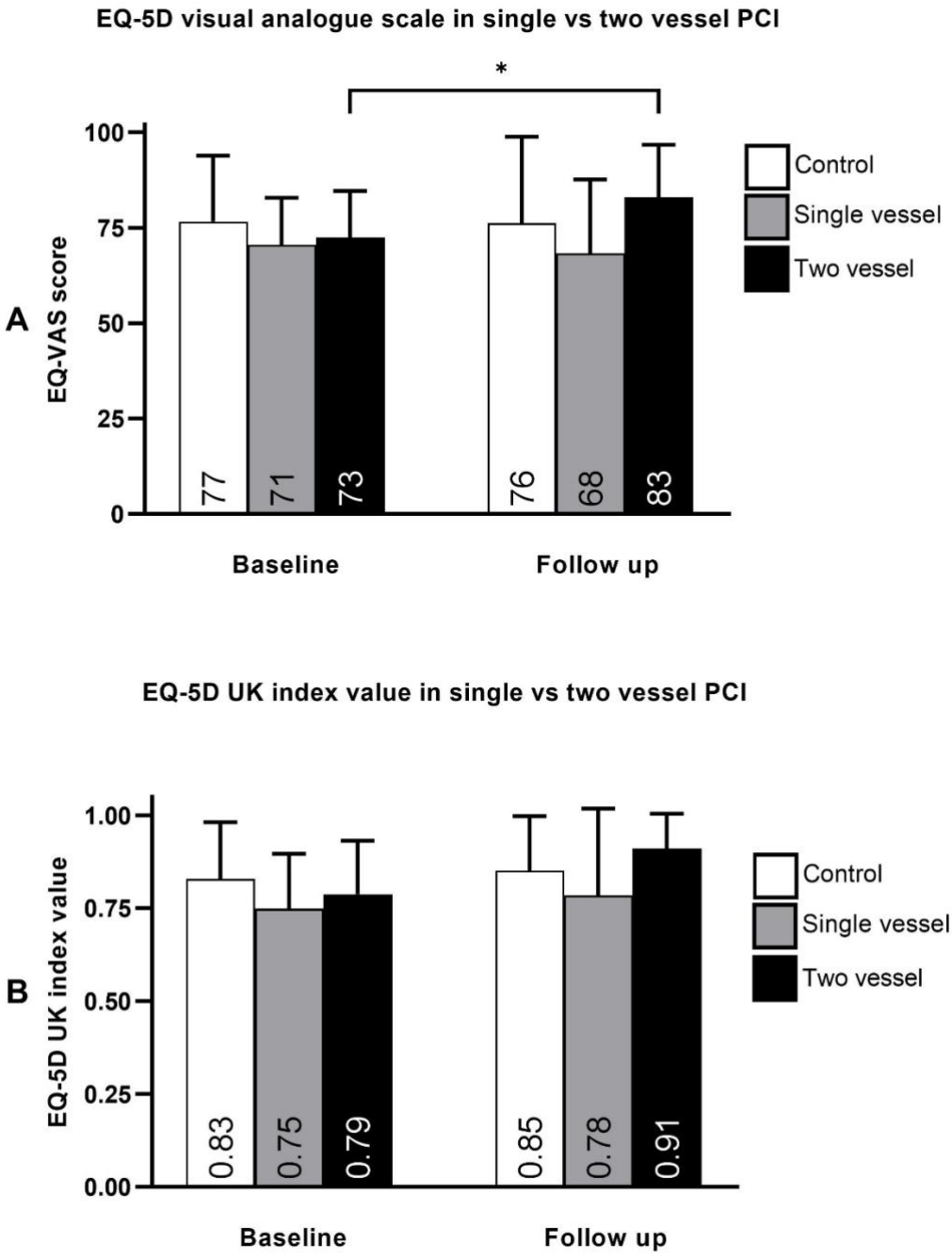


Figure 5.7 Euro Quality of Life (EQ-5D) instruments at baseline and follow up stratified by number of treated vessels.

*Histograms are used to demonstrate any differences between groups and changes at baseline and follow using (A) visual analogue scale and (B) EQ-5D UK index value. All comparisons are non-significant (p>0.05) except the labelled one (*p<0.05).*

B) SF-12

There was no significant difference between the groups in SF-12 scores at baseline and at follow up. Only the two-vessel group showed improvement at follow up in PCS score (43 vs 48, p=0.01). The results of the all components of SF-12 are presented in table 5.7. Histograms showing the differences between the time points and groups are illustrated in figure 5.8.

Table 5.7 Results of SF-12 based on the number of treated vessels

SF-12	Control N=11		Single vessel PCI N=13		Two vessel PCI N=10		p-value
	Mean	±SD (%)	Mean	±SD (%)	Mean	±SD (%)	
Physical component							
Baseline	43	±	40	±	43	±	0.71
Follow up	43	±	43	±	48	±	0.61
Change	0	(0%)	+3.7	(+9%)	+4.4	(+10%)	0.28
	p=0.91		p=0.65			p=0.01	
Mental component							
Baseline	50	±	49	±	51	±	0.86
Follow up	50	±	49	±	53	±	0.54
Change	-0.5	(-1%)	0.2	(0%)	2	(+4%)	0.87
	p=0.93		p=0.91		p=0.50		

SF-12= Short-Form-12

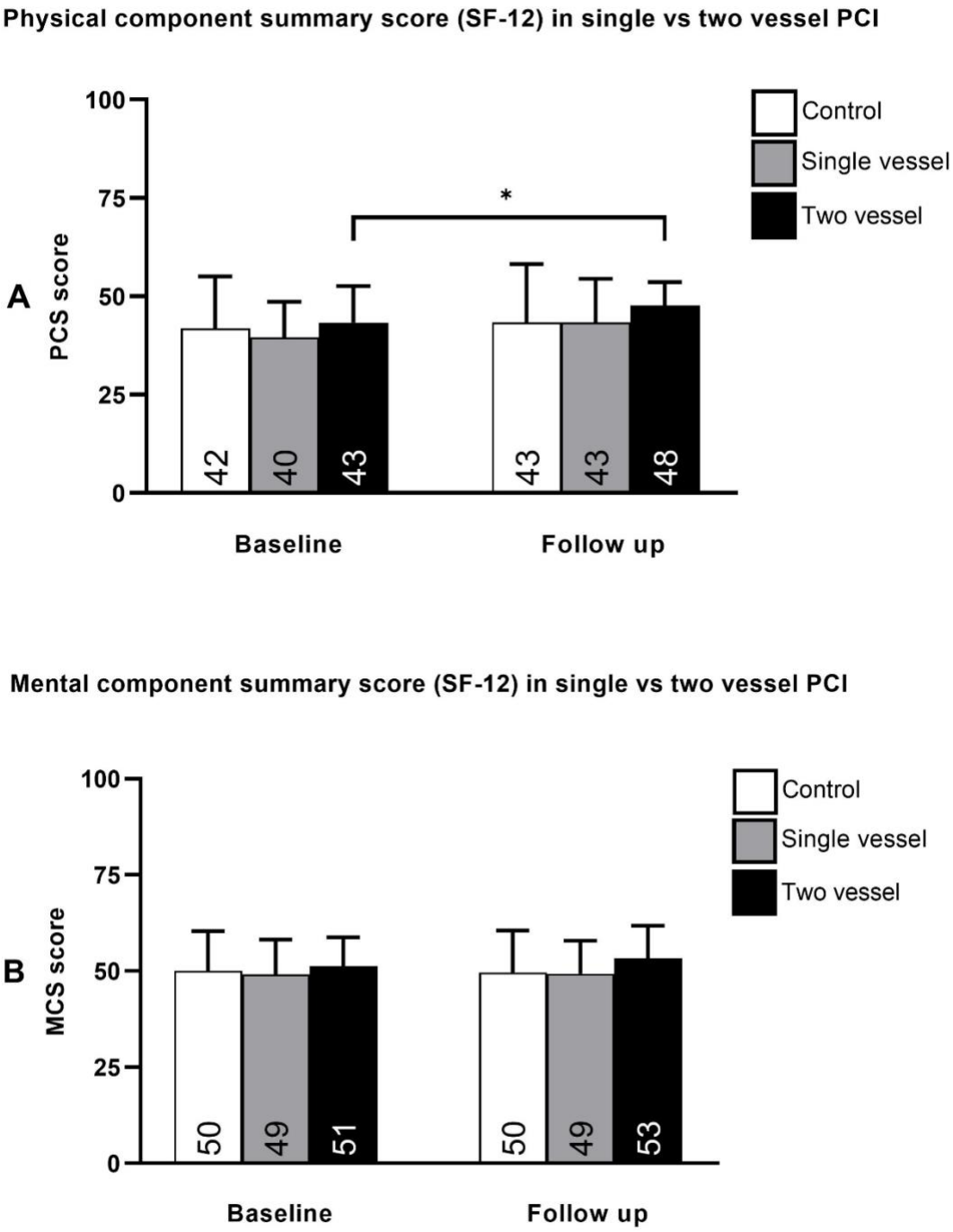


Figure 5.8 Short Form 12-item (SF-12) at baseline and follow up stratified by number of treated vessels.

*Histograms are used to demonstrate differences between groups at baseline and follow and any associated changes following the procedure in the physical component (A) and mental component (B). All pairwise comparisons are non-significant except the labelled one (*p<0.05).*

Disease specific PROMs

SAQ-UK

There was no significant difference between the groups in SAQ domains at baseline and at follow up. The only difference that was reported was in angina frequency domain at follow up between control group and two-vessel PCI group (79 vs 97, p<0.01). All groups reported improvement in quality of life and angina frequency, but only single vessel group reported improvement at follow up (64 vs 80, p<0.001). The results of SAQ summary scores are presented in table 5.8. Histograms showing the differences between the time points and groups are illustrated in figure 5.9.

Table 5.8 Results of SAQ based on the number of treated vessels

SAQ	Control N=11		Single vessel PCI N=13		Two vessel PCI N=10		p-value
	Mean	±SD (%)	Mean	±SD	Mean	±SD	
Quality of life							
Baseline	40	±	43	±	48	±	0.86
Follow up	63	±	70	±	81	±	0.88
Change	+18	(+37%)	+36	(+84%)	+32	(+66%)	0.52
	p=0.02		p<0.01		p=0.01		
Angina frequency							
Baseline	66	±	61	±	65	±	0.88
Follow up	79	±	91	±	97	±	0.24
Change	+13	(+20%)	+30	(+47%)	+32	(+49%)	0.17
	p=0.0.4		p<0.01		p<0.01		
Physical limitation							
Baseline	68	±	64	±	71	±	0.72
Follow up	78	±	80	±	79	±	0.97
Change	+10	(+14%)	+16	(+25%)	+8	(+11%)	0.56
	p=0.27		p<0.001		p=0.16		

SAQ= Seattle Angina Questionnaire

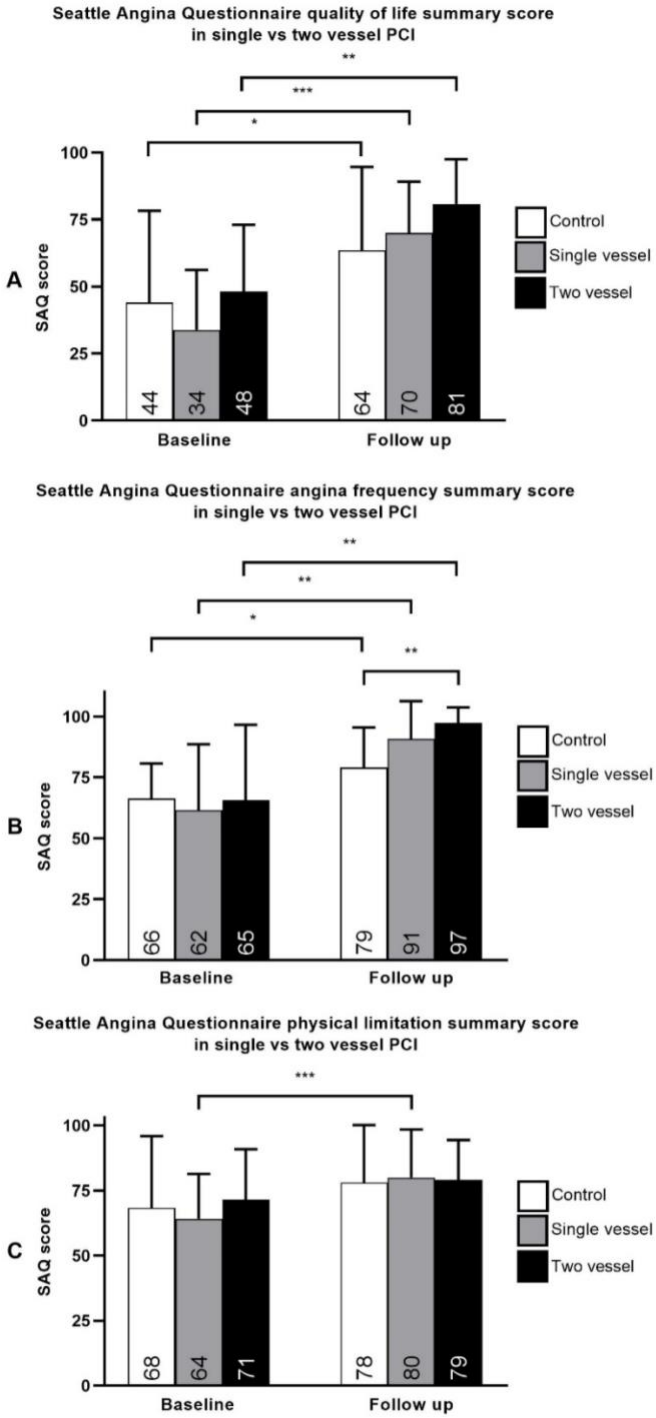


Figure 5.9 Three domains of Seattle Angina Questionnaire (SAQ-UK) at baseline and follow up stratified by the number of treated vessels.

*All groups are compared at baseline and at three-month follow up in quality of life domain (A), angina frequency domain (B) and physical limitation domain (C). All pairwise comparisons are non-significant except the labelled ones (*p<0.5, **p<0.01, ***p<0.001).*

5.3.4.2 PROMs vs FFR_{CUM}

Thirty patients (20 PCI, and 10 control) were included in this analysis. The change in each domain was compared to the change in FFR_{CUM}. A mild but significant correlation was found between the change in FFR_{CUM} and EQ-VAS (r=0.36, p=0.04). However, all other domains had weak to mild correlation with FFR_{CUM}. Pearson's correlations are shown in table 5.9, figure 5.10 (generic PROMs) and figure 5.11 (SAQ).

Table 5.9 Correlation analyses showing the relationship between FFR_{CUM} and PROMs domains.

		Change% in PROMS		
Change in FFR_{CUM}	Generic	Change in EQ-5D VAS 0.36 (p=0.04)*		Change in EQ-5D Index value 0.07 (p=0.70)
		Change in SF-12 PCS score 0.27 (p=0.15)		Change in SF-12 MCS score 0.05 (p=0.77)
	Disease specific	Change in SAQ Quality of life 0.14 (p=0.47)	Change in SAQ Angina frequency 0.26 (p=0.16)	Change in SAQ Physical limitation 0.24 (p=0.19)

FFR_{CUM}= Cumulative FFR, VAS= visual analogue scale, PCS= physical component summary, MCS= mental component summary, SAQ= Seattle angina questionnaire.
** Pearson's correlation (p<0.05)*

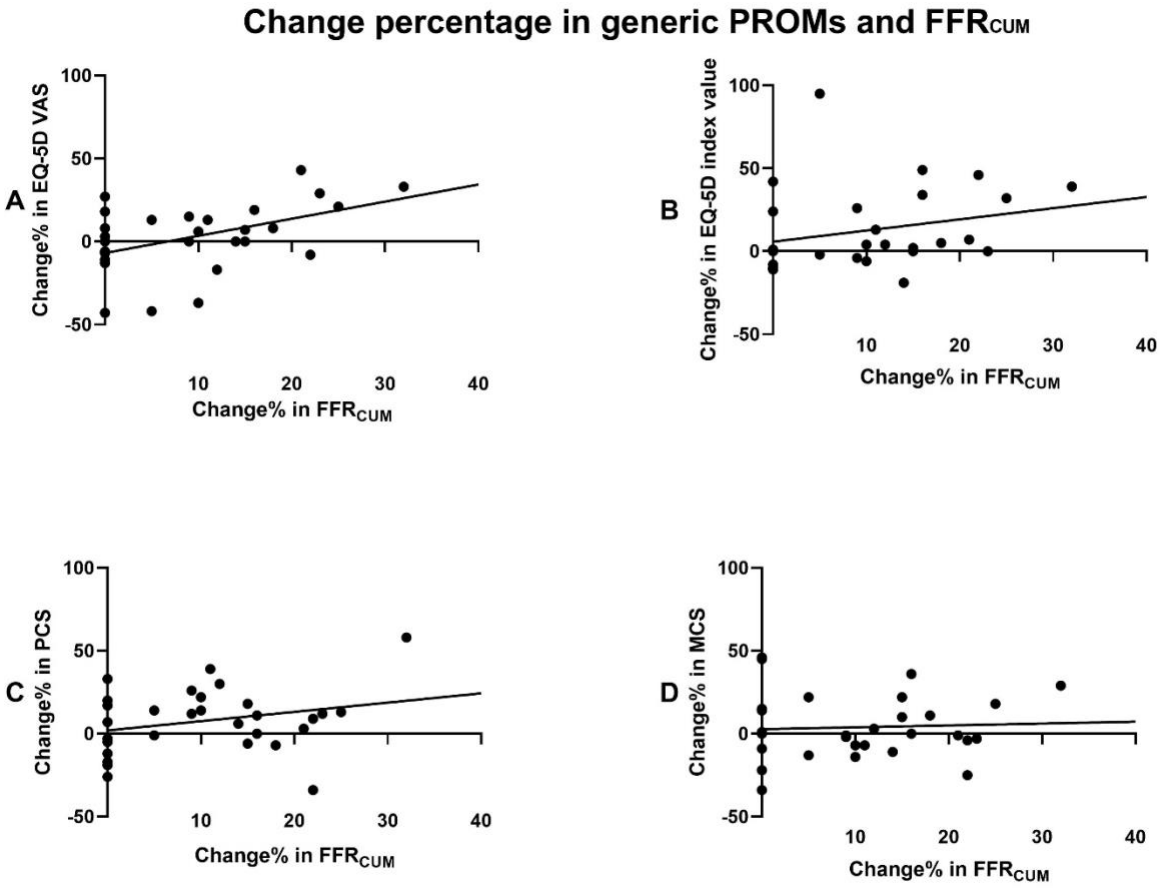


Figure 5.10 The relationship between FFR_{CUM} and generic PROMs

(A) Correlation between the change in FFR_{CUM} and EQ-VAS ($r=0.36$, $p<0.05$), (B) Correlation between the change in FFR_{CUM} and EQ-5D index value ($r=0.07$, $p=0.70$), (C) Correlation between the change in FFR_{CUM} and SF-12 physical component ($r=0.27$, $p=0.15$) and (D) Correlation between the change in FFR_{CUM} and SF-12 mental component ($r=0.05$, $p=0.77$).

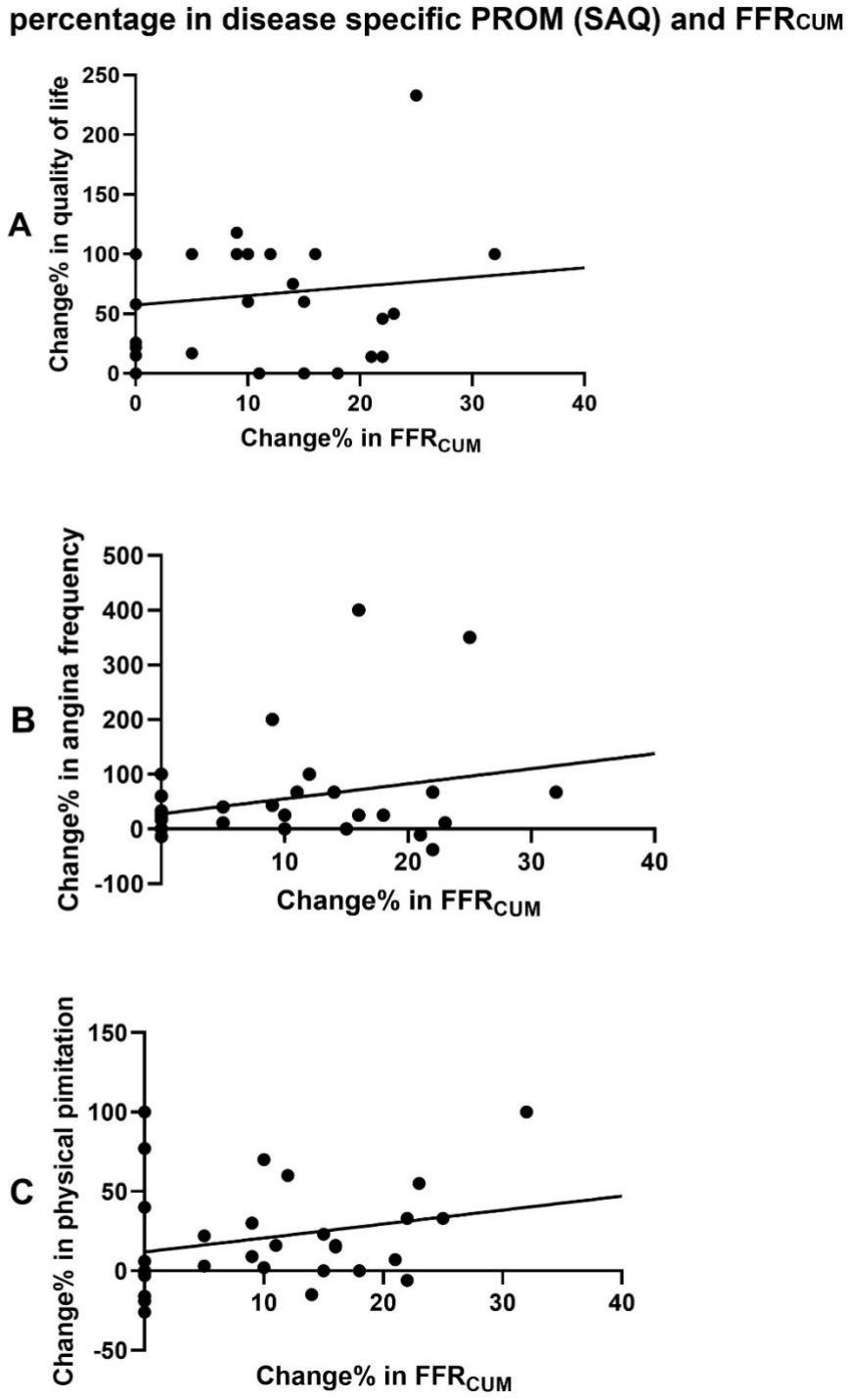


Figure 5.11 The relationship between FFR_{CUM} and SAQ

(A) Correlation between the change in FFR_{CUM} and quality of life (r=0.14, p=0.47), (B) Correlation between the change in FFR_{CUM} and angina frequency (r=0.26, p=0.16), (C) Correlation between the change in FFR_{CUM} and physical limitation (r=0.24, p=0.19).

3.3.4.3. PROMS vs FFR

Twenty-eight patients (18 PCI, and 10 control) with complete questionnaire and FFR data were included in this analysis. The changes in FFR and PROMs scores at three months were analysed. Both generic questionnaire failed to show relationship with the change in FFR (table 5.5). However, CAD specific questionnaire was capable to show a significant relationship between the number of angina episode at the third month compared to baseline and the averaged change in FFR after PCI. The correlation was only moderate but statistically significant (r=0.46, p=0.02). Other domains in SAQ failed to demonstrate a clear relationship. Pearson's correlations are shown in table 5.10, and correlation plots are demonstrated in figure 5.12 (generic) and 5.13 (SAQ).

Table 5.10 Correlation analyses showing the relationship between FFR and PROMs domains.

		Change% in PROMS		
Change in FFR	Generic	Change in EQ-5D VAS 0.16 (p=0.43)	Change in EQ-5D Index value 0.11 (p=0.57)	
		Change in SF-12 PCS score 0.20 (p=0.31)	Change in SF-12 MCS score -0.08 (p=0.68)	
	Disease specific	Change in SAQ Quality of life 0.19 (p=0.39)	Change in SAQ Angina frequency 0.46 (p=0.02)*	Change in SAQ Physical limitation 0.26 (p=0.21)

FFR= Fractional flow reserve, VAS= visual analogue scale, PCS= physical component summary, MCS= mental component summary, SAQ= Seattle angina questionnaire.
** Pearson's correlation (p<0.05)*

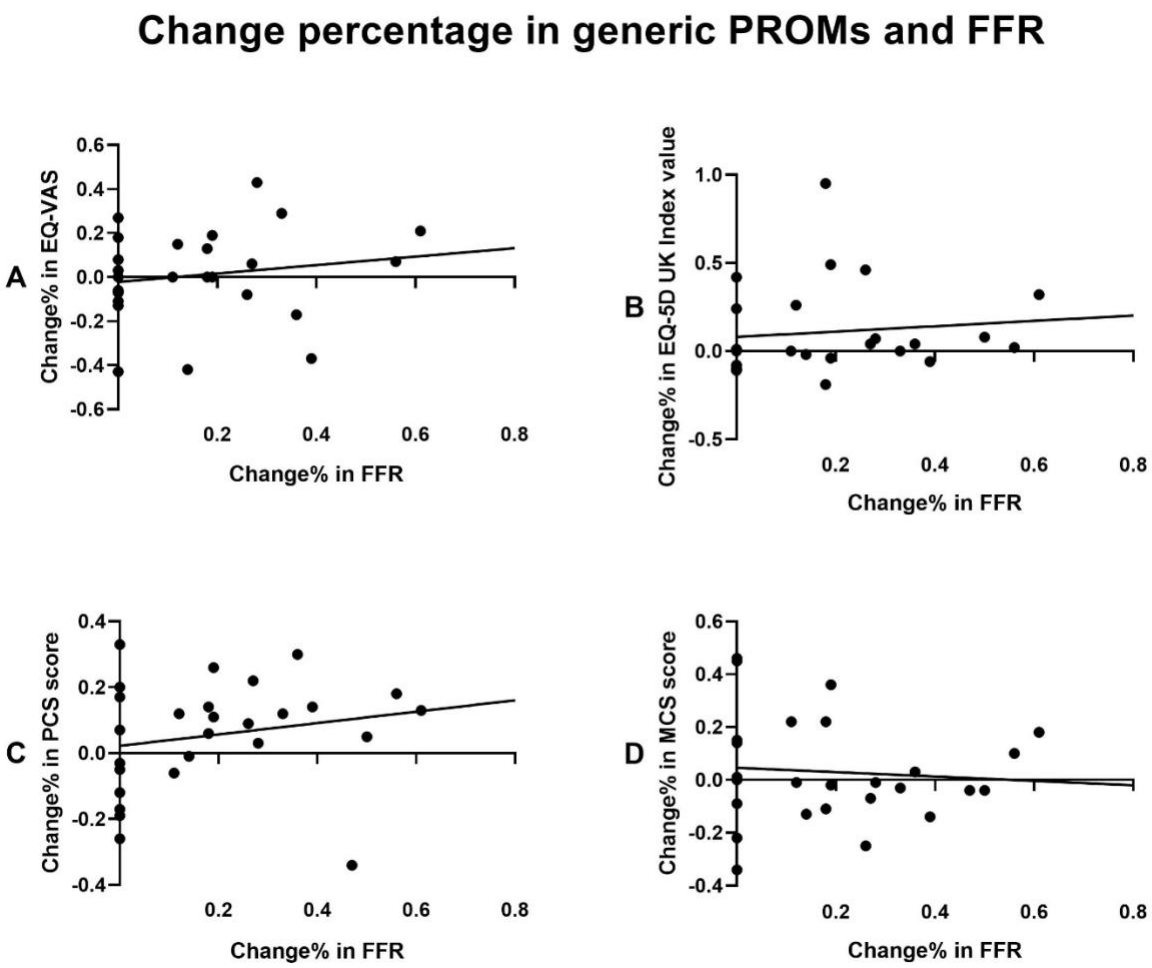


Figure 5.12 Correlation plots demonstrating the relationship between FFR and generic PROMs

(A) Correlation between the change in FFR and EQ-VAS (r=0.16, p=0.43), (B) Correlation between the change in FFR and EQ-5D index value (r=0.11, p=0.57), (C) Correlation between the change in FFR and SF-12 physical component (r=0.20, p=0.31) and (D) Correlation between the change in FFR and SF-12 mental component (r=-0.08, p=0.68).

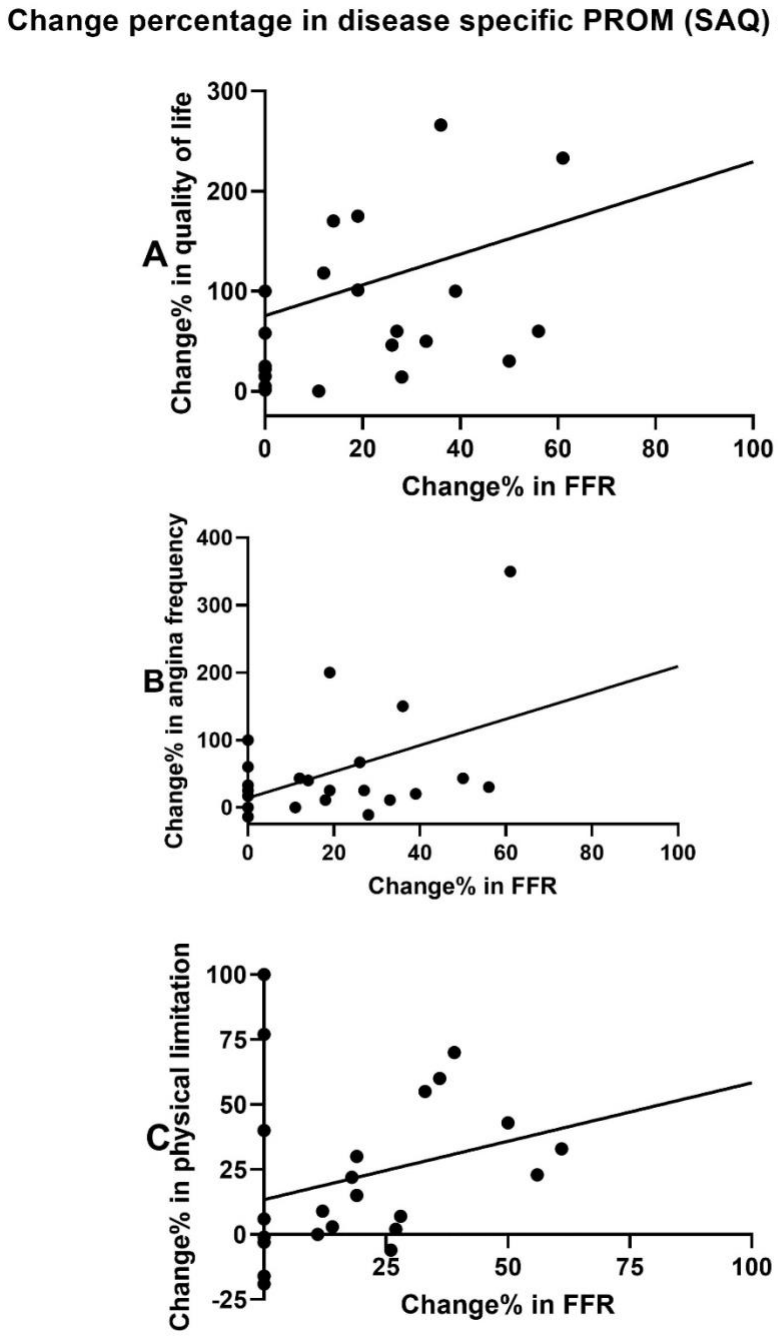


Figure 5.13 The relationship between FFR and generic PROMs

(A) Correlation between the change in FFR and quality of life (r=0.19, p=0.39), (B) Correlation between the change in FFR and angina frequency (r=0.46, p<0.05), (C) Correlation between the change in FFR and physical limitation (r=0.26, p=0.21).

5.3.5 Change in measured vs reported physical activity

Physical activity data of 28 patients (18 PCI, and 10 control) and physical activity domains from SAQ and SF-12 were included in the analysis. The change in third month's step count following LHC±PCI in comparison to averaged monitored period (three months) pre procedure was 10±29% and the change in MVPA was 37±49%. The change between baseline and follow up in SAQ physical limitation domain was 30±75% and SF-12 physical component summary score was 13±15%.

Steps and PROMs

First, the SAQ physical limitation domain, baseline score was mildly correlated with averaged daily step count pre-procedure (r=0.32, p=0.07), follow up SAQ physical limitation scores were compared with third months daily step count, the correlation was significant (r=0.37, p=0.04). The change in SAQ and step count did not show significant correlation (r=0.14, p=0.44). Second, the SF-12 PCS score, baseline score was poorly correlated with daily step count pre-procedure (r=0.22, p=0.22). However, daily steps and PCS both taken at third month following LHC±PC were significantly correlated (r=0.38, p=0.03). The change in PCS score did not reflect the change in daily step count (r=-0.17, p=0.31). Correlation plots are demonstrated in figure 5.14.

MVPA and PROMs

Similarly, SAQ physical limitation domain at baseline and minutes of MVPA pre-procedure were only very slightly correlated (r=0.34, p=0.06). This was the same after three months (r=0.33, p=0.08). The change in SAQ physical limitation and MVPA were poorly correlated (r=0.11, p=0.56). For PCS (SF-12), weak correlation was seen at baseline (r=0.20, p=0.25), and at follow up (r=0.27, p=0.16). However, the change in PCS score and daily minutes of MVPA were moderately correlated (r=0.41, p=0.02). Correlation plots are demonstrated in figure 5.15.

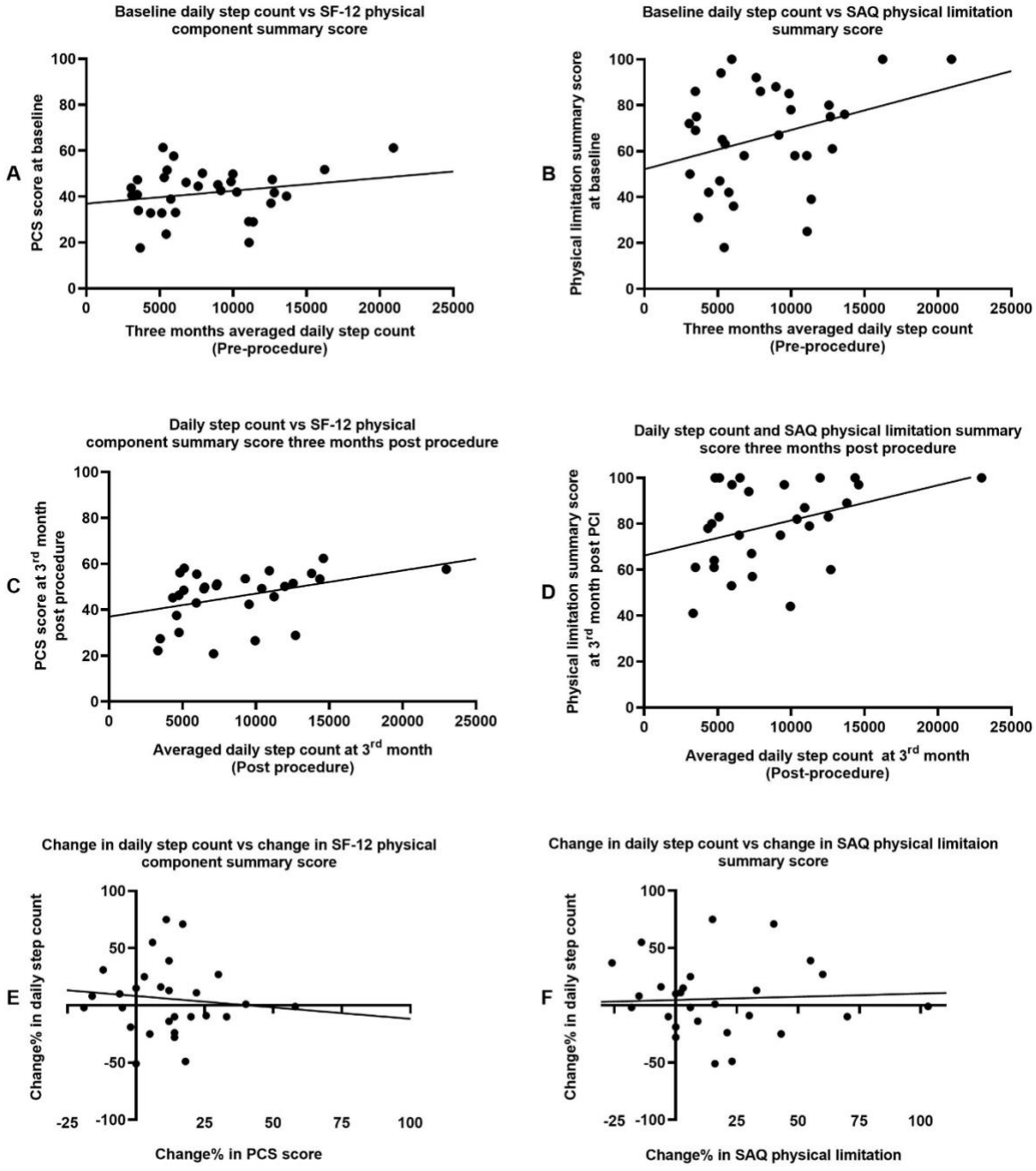


Figure 5.14 The relationship between daily step count and reported physical state

Correlation plots showing the relationship between daily step count and PCS score at (A) baseline (r=0.22, p=0.22), (C) follow up (r=0.38, p<0.05) and (E) the change in the two metrics (r=-0.17, p=0.31). The relationship between daily step count and SAQ physical limitation domain (r=0.32, p=0.06) is presented in (B) for the baseline, (D) for the follow up (r=0.37, p<0.05) and (F) for the change between the two metrics (r=0.14, p=0.44).

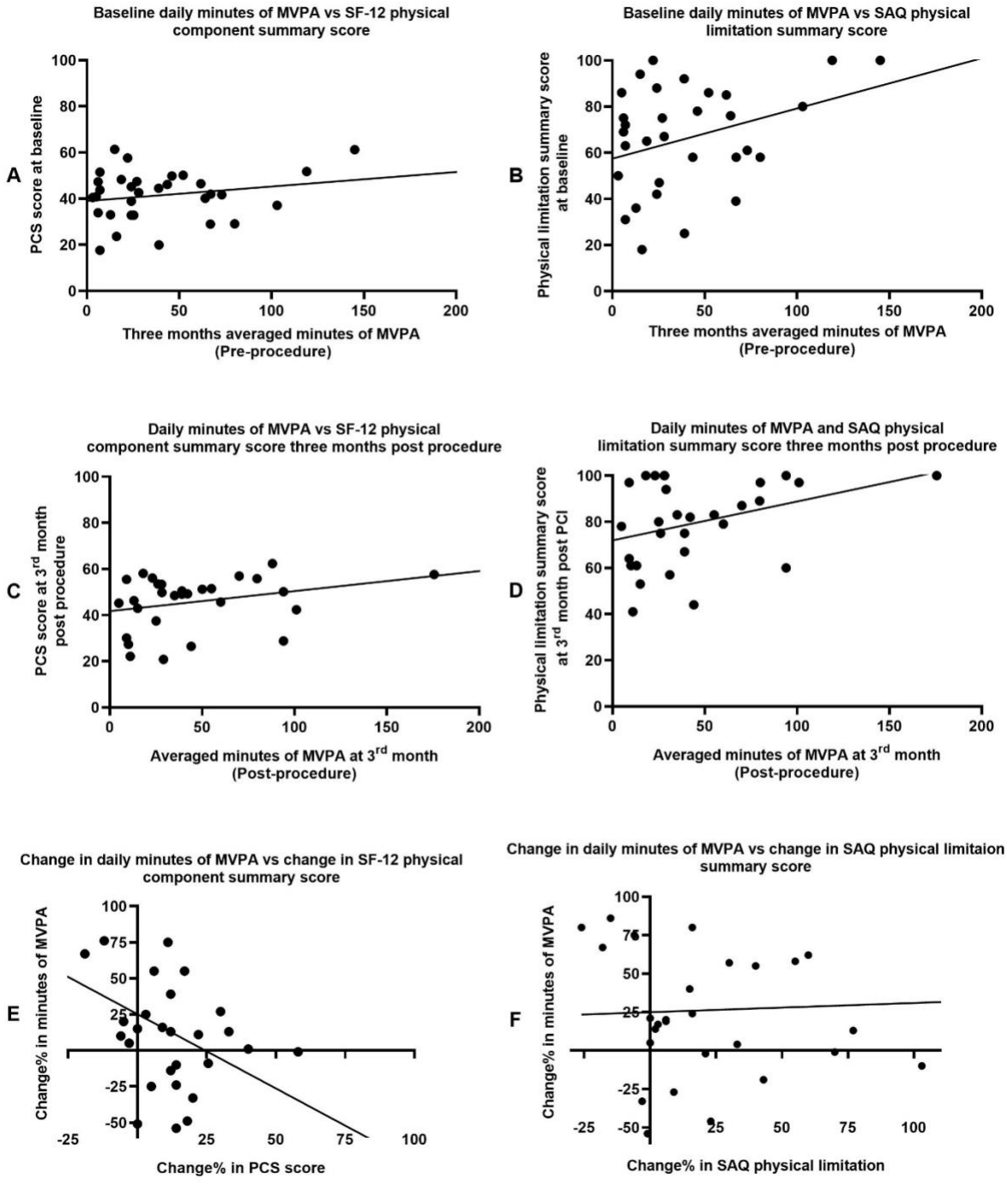


Figure 5.15 The relationship between daily minutes of MVPA and reported physical state

Correlation plots showing the relationship between MVPA and PCS score at (A) baseline (r=0.20, p=0.25), (C) follow up (r=0.27, p=0.16) and (E) the change in the two metrics (r=0.41, p<0.05). The relationship between MVPA and SAQ physical limitation domain (r=0.34, p=0.06) is presented in (B) for the baseline, (D) for the follow up (r=0.33, p=0.08) and (F) for the change between the two metrics (r=0.11, p=0.56).

5.4 Discussion

Summary

In this chapter, I have demonstrated the effect of intervention upon PROMs in patients with CCS. The full cohort did not show a significant improvement in quality of life following LHC±PCI when a general health questionnaire (EQ-5D) was administered. When another generic questionnaire (SF-12) was used, with the ability to generate specific scores for mental and physical health, significant improvement at three months was noted the PCI group only. Furthermore, when a disease specific questionnaire, concerned with angina (SAQ), quality of life, physical health and angina frequency domains were used, these parameters were found to be significantly improved after three months in the PCI group and for all except the physical limitation in the control group. Both patients who underwent PCI, and those who did not, had similar scores at baseline and at follow up in all generic questionnaires. When SAQ scores were analysed, differences between the groups became more apparent. Generally, both groups had similar scores at baseline and follow up, except for angina frequency, in which the PCI group demonstrated fewer episodes compared to the control group (93 vs 80, p=0.01). When patients were stratified by the number of treated vessels no relationship was noted except that angina frequency scores in the two-vessel PCI group were significantly greater than in the control group, indicating fewer angina episodes. The change in FFR_{CUM} was a predictor of the change in EQ-VAS. The change in wire-based FFR was a predictor of the change in angina frequency, suggesting that greater pressure increase (ΔFFR) is associated with fewer angina episodes. A summary of the chapter's finding is shown in table 5.11 and figure 5.16.

Table 5.11 Chapter five summary of the findings

Summary of the PROMs findings	
PCI vs non-PCI (Control)	
EQ-5D VAS	- No significant difference was observed between PCI and control groups - No significant change after procedure in both groups - The change in FFR_{CUM} was a predictor of the change in EQ-VAS
EQ-5D Index	- No significant difference was observed between PCI and control groups - No significant change after procedure in both groups
SF-12 MCS	- No significant difference was observed between PCI and control groups - No significant change after procedure in both groups
SF-12 PCS	- No significant difference was observed between PCI and control groups - The PCI group reported significant improvement at follow up
SAQ – Quality of life	- No significant difference was observed between PCI and control groups - Both groups reported significant improvement at follow up
SAQ – Angina Frequency	- The PCI group reported significantly better angina state than control group - Both groups reported significant improvement at follow up - Larger proportion of patients were angina free in the PCI group at follow up - The change in mFFR was associated with change in angina frequency
SAQ – Physical limitation	- No significant difference was observed between PCI and control groups - Only the PCI group had reported better state at follow up
Stratified by the number of treated vessels	
Control	- Improvement was only reported in SAQ (QoL and angina frequency domain) - SAQ - Angina frequency score was significantly lower than two-vessel PCI at follow up
Single-vessel	- The only group to show improvement in all SAQ domains at follow up - No improvement in EQ-5D and SF-12
Two-vessel	- The only group to report improvement in both generic PROMs (EQ-VAS and SF-12 PCS) - Did not report improvement in SAQ physical limitation

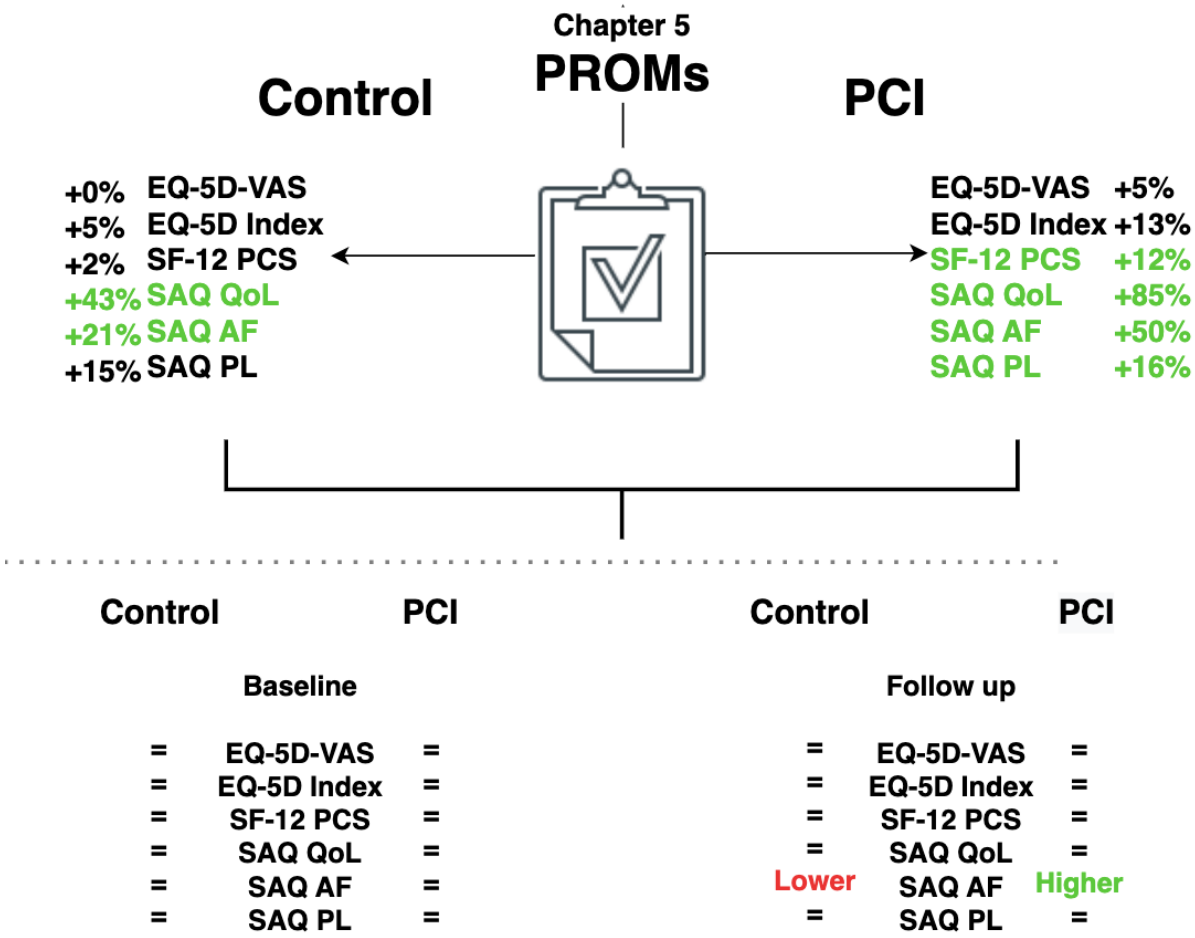


Figure 5.16 Schematic summary of the findings from chapter five

5.4.1 PROMs in the whole cohort of CCS patients

Quality of life, symptoms and physical limitations are supposedly all affected by angina, and in this study 94% of the participants reported fewer angina episodes compared to when they were recruited, as demonstrated by the improvement in angina frequency summary score which assesses the number of episodes and use of nitroglycerin (GTN) spray or tablets. When generic PROMs were used, a single value reported as a crude mean of what the patient believed to be his or her overall health on that day (EQ-VAS) was not significantly improved by the procedure. When

more detailed analysis of each domain (mobility, usual activity, self-care, pain, anxiety) was performed, a similar finding emerged. Another generic questionnaire (SF-12) to examine the difference in physical and mental state revealed similar results, whilst the physical score did improve after the procedure. There are differences between the two questionnaires, even though they are both labelled as generic. The main difference is that SF12 does not provide one value that describes overall health as EQ-VAS does. Instead, SF-12 provides detailed physical and mental summary scores as the main outcomes of the questionnaire. Although one question asks about the general health in the form of 'In general, would you say your health is' and it offers five responds ranging from poor to excellent, it is not reported as a benchmark of the questionnaire. Both questionnaires have been utilised for CCS patients in large trials such as RITA-II and MASS-II, which used the longer version (SF-36), and FAME-II, ISCHEMA and ORBITA, which used EQ-5D-5L as a secondary endpoint. All of these trials report the differences between the trial arms (intervention vs OMT) only, and not the results at baseline vs 3-months or 1-year for the entire cohort.

When I compared three domains related to angina with SAQ, a significant improvement was found again in physical limitation, quality of life and angina frequency, for all included patients. Interestingly, when patients answered the quality of life questions in the light of chest pain, chest tightness and shortness of breath, their summary score was significantly increased at follow-up. This was not seen in the EQ-5D Index value or VAS, as discussed above. SF-12 and SAQ both revealed reduced limitations in physical activity after the procedure. SAQ provides nine separate questions with six possible answers for the physical limitation domain alone, with questions ranging from low intensity activities (e.g. walking) to strenuous activities (e.g. jogging), thus, allowing the participants to clearly describe what activities are limited. See Appendix 3.C for an overview of the questions. It is interesting that although both SAQ and SF-12 revealed significant improvements in reported physical activity, when this was objectively assessed in the previous chapter, no statistical difference was seen in both daily step count and minutes of MVPA (see section 4.3.1). Furthermore, the highest summary score that was reported at follow up among all domains was the angina frequency (89/100) with an increase by 25 points. Please note that the

highest the score in the SAQ the better the state. More than half of the cohort (56%) were angina free (scored 100 points) three months after LHC± compared to (6%) when recruited.

5.4.2 Difference in PROMS between PCI and control groups

There was no difference between the groups at baseline in all questionnaire summary scores and follow up in EQ-5D, SF-12, SAQ (physical limitation and quality of life). This is remarkable, considering the 'control' group had, by definition, FFR-negative disease, and the PCI group FFR positive. However, it is in agreement with randomised trials, such as ISCHEMIA, which also showed similar scores at baseline, and numerically higher scores at three months in both SAQ summary scores and EQ-VAS (Spertus *et al.*, 2020). However, the difference between the two groups increased with time in ISCHEMIA and was diminished after three years. This was not assessed in my work. The PCI group reported less angina as reported by the summary score compared to the control group at follow up. Seventy percent of the PCI group became angina-free (100 points) compared with 27% of the control group (p=0.02). Similar findings were observed in ORBITA and COURAGE using the SAQ-UK questionnaire (Weintraub *et al.*, 2008; Al-Lamee *et al.*, 2018). Moreover, a secondary analysis of ORBITA revealed 'angina freedom' more in the PCI compared to the placebo group (49% vs 31%). This was also found in COURAGE (53% vs 42%). A small, non-significant, increase in quality of life following the procedure was observed for both groups using EQ-5D. This non-significant increment was also observed in ORBITA trial where the index value increased by 0.03 (3.8%) for both groups (Al-Lamee *et al.*, 2018). However, other major trials have shown more benefit from PCI as assessed by EQ-5D index value (FAME 2) and VAS (ISCHEMIA) (Fearon *et al.*, 2018; Spertus *et al.*, 2020). One patient in the PCI group had an extremely reduced EQ-5D index value at follow up compared to baseline (0.92 vs 0.22), and this may have resulted in diminishing the effect in the whole group despite the increase (+0.07). When SF-12 was used to assess the change at follow-up, the control group did not show change in the MCS (1, 2%) and PCS (-0.05, 0.1%). The PCI group similarly did not show change in MCS (+1, 2%), yet the physical score significantly improved (+4, 10%) The improved physical state was also observed in SAQ for the PCI group (+12, 18%, vs +10, 14% for the control group). The RITA-2 trial reported a similar finding, with an improvement in PCS in both groups, which was greater in the PCI arm (Pocock *et al.*, 2000).

The reported improvement in physical ability could be related to the findings from chapter four, in which both groups failed to show significant improvement despite the numerical increase in steps and time spent in high intensity activities; yet patients believed that they were less limited by their angina than before. It may be that, even if daily measured physical activity does not change in response to coronary intervention, if patients can do the same activities without triggering an angina episode, then one of the purposes of elective PCI is achieved. Furthermore, angina frequency in the PCI group was improved (+31 point, +50%), tending to support this proposition.

5.4.3 Disease severity

Disease severity in CCS varies between the patients, and this might have been responsible for some of the variability in symptoms. In this chapter, I investigated the relationship between number of treated vessels and their relationship to PROMs. I also studied forms of association between the change in objective measures of flow reduction (i.e. FFR) and PROMs. Control, single vessel and two-vessel groups were similar at baseline in all domains of EQ-5D, SF-12 and SAQ. This was also observed at follow up, except for angina frequency, for which greater improvement in the two vessel group was seen compared to the control group (97,+49% vs 79,+20%; p=0.003). The absence of a meaningful difference between control and single-vessel PCI is similar to the findings of ORBITA. ORBITA-2 may provide more insights. This trial is investigating the placebo-controlled effect of PCI in single and multi-vessel disease up to three months (Nowbar *et al.*, 2022). In my study, generic questionnaires also showed that only the two-vessel group showed significant improvement at follow-up. The values for two vessel, single vessel and controls, respectively, were, in EQ-VAS (+10,+15% vs -2,-3% vs 0,+0.5%) and PCS score (+4.4, 10% vs +3.7, 9% vs -0.05, 0%). However, in the SAQ, all groups showed improvement in quality of life (+33, +67% vs +36, 105% vs +20, +37%), angina frequency domain (+32, 49% vs +29, +47% vs +13, 20%) for the same groups, respectively. It appears that when questions are asked in regards to angina, patients who underwent PCI scored higher at follow up compared to the control group (figure 5.9). Physical limitation was improved in all groups but was only significant in the single vessel group (+8, +11% vs +16, +25% vs +10, +14%), for the same three groups, respectively. When physical activity was stratified according to the number of treated vessels in chapter four, the findings suggested a non-

significant improvement in all groups for step count and MPVA, except for the two vessel PCI group, which showed significant improvement in MPVA. What has been reported using PROMs suggests otherwise; the single vessel PCI group being the only group to report significant improvement. However, according to the analysis conducted in this chapter to assess the relationship between measured physical activity and reported (SAQ) physical limitation, the relationship appeared to be weak, which may explain the contradictory outcomes. The disagreement between what was measured and what was reported in physical activity may merit further investigation with a larger sample size. Perhaps qualitative research in which open-ended questions are asked in regards to physical activity with the use of modern fitness tracker may help us understand more about these controversies in measured and reported physical activity.

5.4.4 Coronary physiology and PROMS

The change in FFR was related to the change in angina frequency at the third month compared to baseline (r=0.46, p=0.02). Moreover, it is suggested from this finding that the higher the flow restored (ΔFFR), the better angina state up to three months (r=0.46, p=0.02). However, prior studies have shown that there is no evidence to support the interaction between SAQ angina frequency and FFR (Al-Lamee *et al.*, 2018). The sub-analysis conducted in this chapter remains preliminary, however, and it highlights the importance of post-stent FFR in order to understand the effect of PCI and specifically physiological measurements in angina symptoms. In the case of FFR_{CUM}, the change in overall health as measured by EQ-VAS, which is the simplest form of defining health, was predicted by the change of FFR_{CUM}. A mild but significant relationship was observed only in the EQ-VAS, while all other domains generic or disease specific failed to show any association.

5.4.4 Limitations

In this work, only 34 patients were included; a modest sample size. Furthermore, the 'control' group was not randomised, but a group which had less severe disease, as judged by FFR. The nature of questionnaire research is that it relies upon the patient to provide an accurate assessment of their own status, and this may be prone to bias. Another problem was the inconsistent period between the baseline questionnaire (which was completed at recruitment) and the three months follow up. This was due to variable waiting lists and the influence of COVID-19. Another potential limitation is that the control group may have been a different phenotype than the PCI group. For example, they may have had a greater proportion of patients with microvascular, as opposed to epicardial, disease.

5.5 Conclusion

In this study, I have shown 'real life' patients' responses to LHC±PCI using multiple PROMs. Any benefit in quality of life after PCI appears to be small, and not very different to patients who undergo a procedure which does not involve improvement in (hyperaemic) coronary blood flow. Improvement may not be seen after stenting when measured using a general health questionnaire. However, CCS patients tend to report a better quality of life if questions are asked in regards to angina. Nevertheless, reported physical state is generally better after PCI, as shown by different PROMs, although this is not corroborated with fitness tracker data. All participants reported fewer angina episodes whether receiving a stent or not; however, a larger percentage of those who did receive stents were angina free at three months; particularly those who had PCI in two vessels. The change in angina frequency may be predicted by the change in FFR, yet this is a preliminary work and further investigations are needed. Similarly, the change in FFR_{CUM} predicted the change in EQ-VAS.

Chapter six: Final discussion and conclusion

6.1 Key findings

In this thesis, I evaluated the change in response to PCI in CCS patients and compared the measurable differences between patients who received PCI and those who did not (figure 6.1).

In chapter two, I started with the physiological response to PCI, at the coronary level. I demonstrated the feasibility of deriving physiological metrics including coronary absolute flow, MVR, HSR and CFR using ICA and invasive intra-coronary pressure data only. I then evaluated the relationship between FFR and these derived metrics in order to provide a broader understanding of FFR, because the latter has been criticised as being a surrogate of flow reduction. I showed that even with a small increase in FFR (ΔFFR=0.18, 28%), the flow restoration was substantial (50 ml/min, 80%). Moreover, the change was not only limited to coronary absolute flow; both HSR and, most interestingly, MVR, showed a significant drop after intervention. The physiology of flow limiting lesions was compared to non-flow limiting lesions based upon the binary cut-off value of FFR≤0.80. Surprisingly, it was demonstrated that coronary absolute flow was the only metric that did not significantly differ between the groups.

In chapter three, I took a step back and evaluated the global flow reduction by developing a novel method as an index of assessing the myocardium at risk (FFR_{CUM}), with a possible useful value when calculated after intervention. The method, which incorporates both physiology (FFR) and anatomy (coronary vasculature size and distribution), was successfully calculated in all suitable cases; the only exception being patients who underwent CABG or had missing data. FFR_{CUM} revealed a significant difference between the patients who need PCI (0.72±0.1) and those who do not (0.84±0.07). When calculated after intervention, the mean change was 17%, bringing the FFR_{CUM} post PCI to a similar level to those who did not need PCI, even if it was not complete revascularisation. Initial validation of the method with previous similar methods showed good correlation when used to assess myocardium at risk (MJI) and acceptable concordance with other methods that investigated risk stratification post intervention using a sum of FFR values.

In chapter four, I produced a comprehensive perspective of the level of change in response to PCI. An objective measurement and analysis of the patient's daily life was conducted, with the aim of

quantifying any meaningful improvement following intervention, at up to three months. Using wearable devices, I was able to monitor physical activity for prolonged periods, including baseline and post-procedure monitoring. My analysis suggested similar levels of activities at baseline and after three months among patients who underwent PCI and those who did not. Additionally, PCI did not result in a meaningful improvement up to three months (+9% for step count, and +20% for minutes of MVPA). This numerical increase was also observed in the control group (+7% for step count, and +10% for minutes of MVPA). However, further sub-analyses based on number of treated vessel showed some levels of improvement on the third month in patients who received PCI in two vessels. Apparently, the changes in PA were independent of physiological changes (FFR and FFR_{CUM}). Later, but in the same chapter, I investigated the change in submaximal exercise in controlled environment (6MWT), testing whether the similar outcomes of free-living activity can be achieved. The findings were the opposite, although the walked distance did not differ between the groups at baseline or at follow up, and both groups were able to walk a significant extra distance. However, these findings raised more questions than answered it, the question of physical activity improvement after PCI was more complex using a mere analysis of physical activity, even when stratified by disease severity.

In chapter five, I completed the full picture of patient assessment by studying what patients believed and reported in terms of quality of life, physical limitation and angina symptoms. Supposedly, by using different PROMs, a better understanding than our usual assessment of how revascularisation changes patients' lives in a general way, and in relation to angina, can be achieved. When patients reported their health in general terms, neither group showed a significant increase in quality of life, but the PCI group reported a better physical state. The findings are consistent with the findings from chapter four, in which significant differences were absent, but a numerical increase was recorded for the PCI group. In SAQs, a significant improvement was reported in quality of life and angina frequency for both groups, and in physical activity for the PCI group only. The PCI group showed greater improvement (higher scores) in all domains than the control group. Both groups reported similar scores at baseline and follow up ($p>0.05$) except for the number of angina attacks per month, in which the PCI group showed greater scores than the control (+13.5 points, $p=0.01$). This finding was consistent with freedom from angina, although

this did not achieve statistical significance. More patients in the PCI group reported no angina episodes at three months compared with the control group (70% vs 27%, respectively). This shed some light on the importance of the questions we ask patients, because QoL was reported by the patients at similar levels when a generic questionnaire was used (EQ-5D), but the difference was greater when these questions were specifically around angina.

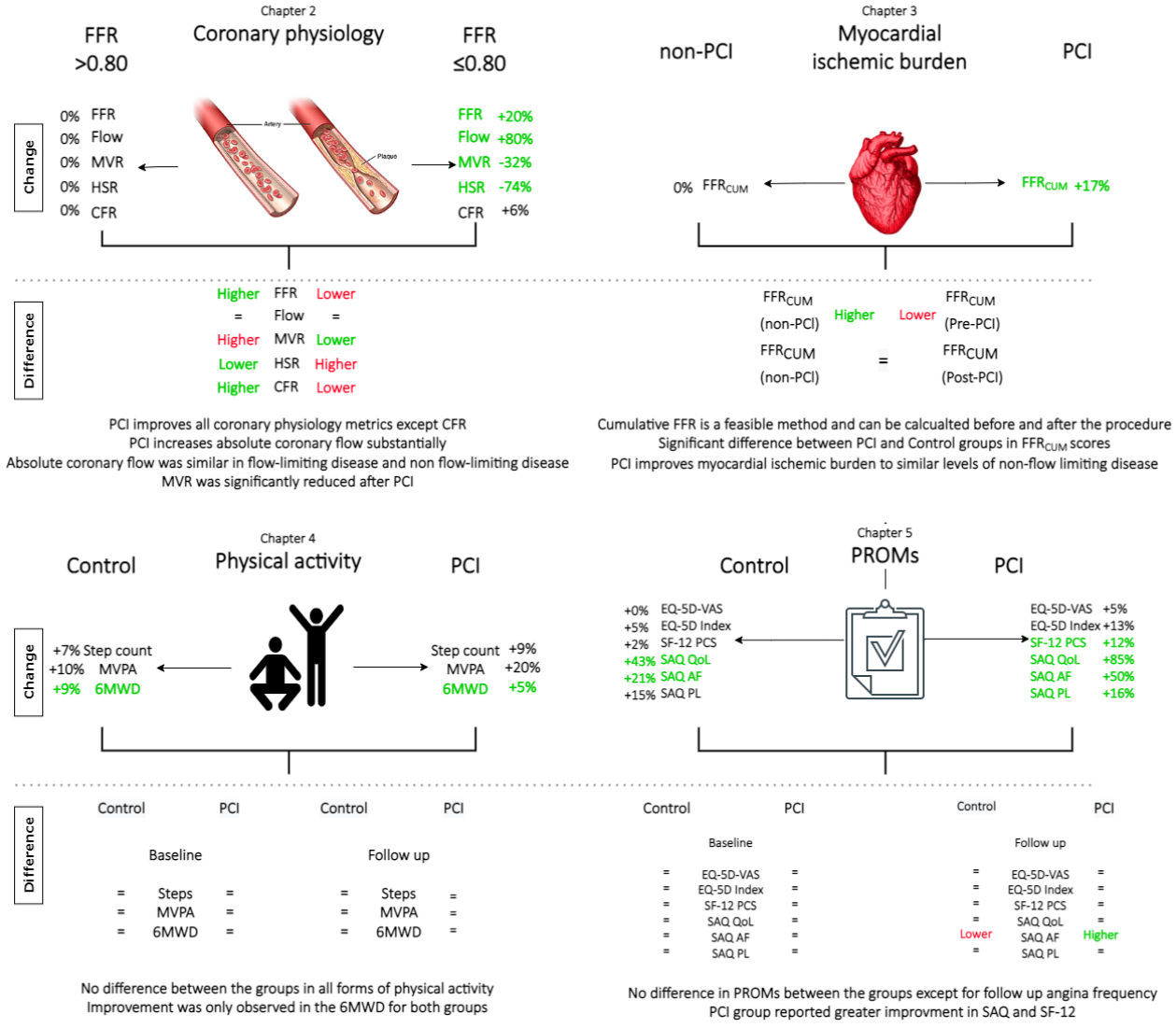


Figure 6.1 Infographic summary of the thesis findings

6.2 Study Implications

6.2.1 Is FFR the right measure to start with?

We know from this, and previous, studies that PCI improves coronary physiology, as assessed by FFR. Moreover, FFR guided revascularisation is associated with desirable outcomes in both short and long term (Tonino *et al.*, 2010; Van Nunen *et al.*, 2015). Nevertheless, we also know from ORBITA that revascularisation in single vessel disease, in a highly intensive study setting, may not provide the advantage in symptoms or exercise time that we might expect (Al-Lamee *et al.*, 2018). My study demonstrated significant improvement in FFR and computed absolute coronary flow after intervention, but that did not result in a measurable difference in physical activity or overall QoL. This raises further questions of how much we should depend on FFR in planning management in CCS. Furthermore, the RIPCORD-II trial, which randomised (unblinded) patients into PCI based on systemic FFR strategy (all major arteries) or angiographic guidance alone, and reported no difference in QoL, angina symptoms and MACE at one year (Stables *et al.*, 2022). This finding is interesting, because one would expect that treating flow-limiting disease, using a method of identifying flow limiting disease would result in superior outcomes to coronary angiogram to guide intervention, as the latter was reported to underestimate disease severity. The trial did not report on the complexity of the disease in each arm yet, in which the benefit of physiology maybe more observable. FFR is identified as a pressure surrogate of coronary flow reduction, but remains ambiguous in assessing absolute flow reduction. Fascinatingly, absolute coronary flow was the only physiological metric in my study that did not significantly differ between FFR positive and FFR negative vessels. This may be a clue to a parameter we should use next to investigate symptomatic and QoL improvement. What these findings suggest is that blood flow can be improved with a stent in (hyperaemic) flow-limiting disease, but the absolute flow initially was not significantly different between FFR +ve and -ve method of classification. This raises the question of whether the magnitude of absolute flow reduction, irrespective of FFR, could be the main indication for intervention. Consistent with this concept is the fact that patients who received an intervention (FFR +ve) and those who did not (FFR -ve) were not statistically different at baseline in terms of physical activity measures and PROMs. However, when FFR based methods (FFR and mean FFR_{CUM}), were used to compare the difference between PCI and non-PCI groups, they both showed

significant differences, unlike absolute flow, in favour of the control group, although this was not shown in PROMs or physical activity.

Current optimal practice is built upon the landmark trials of FFR, which were a 'game-changer'. However, soon may be the time to incorporate absolute flow measurements into clinical decision-making. Doppler ultrasound and thermodilution are too time consuming, challenging and inaccurate to be in routine use, although useful in research to understand the physiology of coronary stenosis. But the actual contribution of these metrics, whether to assess microvascular or epicardial disease, towards patients' symptoms and experience is unknown. In chapter two, I showed that generating not only absolute flow but other metrics is feasible with very high success rate (96%). Although modelling physiology may have some limitations, the recently developed model (virtuQ) was able to generate all required data in 'real-life' patients with no more than pressure-wire data and well captured coronary angiograms. In particular, in order to understand how coronary physiology in general responds to intervention, post-stent assessment of absolute flow could be useful in future research. Post-stent FFR, and other metrics, remain understudied, with no consensus opinion on targeted values.

6.2.2 Are we assessing exercise tolerance and functional capacity improvement after revascularisation correctly?

The use of exercise testing is well validated to discriminate ischemia and to assess the outcomes of PCI. However, its feasibility might be argued in contemporary CCS patients, who rarely perform this high intensity form of exercise in daily basis, especially if the age factor is taken into consideration. In this work, I used another form of assessing the effect of PCI upon physical activity, namely normal exercise measured freely throughout the day, independent of encouragement or targets. The analysis demonstrated an absence of a significant increase in physical activity after intervention. In fact, even those who did not have intervention exhibited a (similarly non-significant) numerical increase. Patients who had PCI reported an improved physical state, and improved symptoms, related to angina, at follow up. These are complementary findings with daily physical activity data and should be interpreted together. If patients are not reporting a meaningful increase in activity, yet they are reporting that they are less limited physically, and are

having less angina episodes, then it might be argued that a significant increase in physical activity is not necessary to prove benefit from PCI. Behaviours and lifestyle may not be changed in a course of months, but how much angina limits these behaviours might be changed and possibly measured. Interestingly, there was significant improvement in both groups when a submaximal exercise test (6MWT) was used. An improvement following PCI was generally expected until ORBITA reported otherwise. Although 6MWT and treadmill exercise tests are performed differently, perhaps, the controlled environment may play a role in this finding. Both types of test require vital signs assessment before and after the test, with clinical supervision, and participants arrive at the follow up site with the intention and instruction of performing as much as they can. Thus, the blind randomisation effect in ORBITA may be responsible for the absence of significant increase in exercise time, whereas, in my study, patients knew their procedure outcome. This may also explain the difference between daily activity and 6MWT differences. Therefore, the differences between controlled and free environment assessments should be established and considered when the effect of PCI is to be evaluated. Nevertheless, patients reported improvement in angina symptoms (both groups) and physical limitation (PCI group), and therefore, an improvement in 6MWT in both should not be surprising. The daily physical activity failed to show significant increase but the 6MWT did, despite the moderate to strong relationship between the two when correlation was assessed. This final finding highlights the importance of being cautious when interpreting improvement in physical limitation after intervention, because there are multiple factors that might be involved.

6.2.3 Is the number of treated vessels explanatory of the changes?

Revascularisation strategies differ between patients based upon multiple factors, but the decision to perform PCI in a specific lesion is mainly taken if the lesion is perceived to be flow-limiting and suitable for stenting. My study was not limited to a certain population of CCS patients, so patients with either single or multi-vessel disease were recruited and were assessed and evaluated alike. In this work, only single and double vessel PCI were performed, reflecting FFR positivity. To understand the effect in each group I also studied patients who did not receive a stent (who also had a procedure, but no FFR positive vessels) to evaluate with a wider perspective. In ORBITA, patients with single vessel disease were included, and no benefit of PCI was seen after six weeks

in exercise testing or quality of life. My findings were consistent with ORBITA for single vessel disease, with no improvement at three months in light activities (daily steps) and moderate to vigorous activities. The only significant improvement in daily physical activity in my entire analysis was in the group of patients who had revascularisation in more than one vessel. This group was also the only group to report an improvement in general health and physical state. However, with SAQ, all groups tended to improve after three months in QoL and angina frequency. Moreover, the two vessel PCI group scored highly in the angina frequency domain (97 points; 100 being free from angina), and was the only one to show improvement in daily step count. Also, the only significant difference in PROMS between the three groups was the angina frequency between control and two vessel PCI at follow up. Patients who received more than one stent seem to show greater improvement in physical activity and symptoms than the others, but this conclusion should be treated with caution because the number of patients for each group is modest.

6.2.4 Development of a single index value to represent global coronary flow reduction

Producing a single value to stratify patients is not a new concept. It was first introduced through anatomical scoring using the Duke Jeopardy Score (Califf *et al.*, 1985), and the BARI-MJI score (Alderman and Stadius, 1992). Both provide a number that accounts for the myocardium at risk. Subsequently, emphasis shifted to the need for a functional measure, with the introduction of FFR and the superiority it provided to the classic angiogram. Functional SYNTAX score, $_{GLOBAL}$FFR and $_{3V}$FFR all aimed to provide a single value based upon FFR that aimed to stratify patients based upon some sort of global assessment (Nam *et al.*, 2011; Lee *et al.*, 2018; Fournier *et al.*, 2020). My method, FFR_{cum}, addresses some limitations of the previous methods, and it proved to be comprehensive and feasible, with the advantage of using computated (virtual) assessment to substitute for wire-based FFR. I showed that my segmentation and processing of vFFR is not different from mFFR; therefore, with practice, FFR_{CUM} can be calculated by a well trained operator. Moreover, FFR_{CUM} is not a simple sum, because coronary arteries vary in their size and branches. It has an elegant and usable simplicity, as a relative ratio that sums up to 1.0, similar to FFR. This novel method complements existing computational physiology. Any system that can provide reliable vFFR (e.g. CAAS, Pie Medical) is suitable to be used for this method. However, this initial work needs to be supported by a larger study. Also, validation work needs to be done to address

the original hypothesis behind its development. Further details about how this could be done is described in the next section.

6.3 Challenges and future work

6.3.1 Coronary physiology: what is next?

In the current state of coronary artery assessment, FFR is the gold standard method to discriminate ischemic lesions, and can determine whether the lesion is causing hyperaemic flow limitation. Additionally, FFR is supported by strong evidence that it can result in improved MACE in the long term compared with angiographic assessment. Absolute flow quantification in routine practice may prove to have even greater value, but is presently neglected, due to the difficulty of using flow assessment methods (see section 1.3.5). However, computational methods are advancing rapidly and being recognised. For example, FFR_{CT} is part of the 2021 ACC/AHA guidelines (Gulati *et al.*, 2021). Using virtuQ for computation of coronary physiology, and particularly coronary absolute flow, should be investigated further. Perhaps, with a larger sample of 'real-world' data, we would be able to advance further with our flow model. My study had a limited number of vessels with pre and post data (n=17) and, although this may be sufficient for hypothesis generating work, further analysis with a larger data set would be a necessary.

6.3.2 FFR_{CUM}

The method that was described in chapter three (FFR_{cum}) is a strong starting point to produce an index with potential clinical use. This index is intended to provide an overview of the global myocardial flow reduction, and thereby offer a glimpse of the myocardial ischemic burden at the management planning stage. However we are currently dependent upon a local assessment of a few major vessels to resolve the flow impairment of one component of a sophisticated coronary system. FFR_{cum} may provide a thorough assessment with minimal cost (by using vFFR) and time. However, it would also need to be validated by non-invasive myocardial perfusion analysis as was done for FFR (Pijls *et al.*, 1996). Validating the prognostic value of FFR_{CUM} could be addressed by calculating the residual FFR_{cum} at the end of the procedure for almost every patient, with or without an intervention, and performing clinical follow up to validate its feasibility for risk stratification. There is also the potential to incorporate coronary absolute flow in the calculation,

to produce an absolute global flow reduction index, which may be a realistic start of utilising the coronary absolute flow in treatment management.

6.3.3 Global model incorporating myocardial ischemic burden

A systemic mathematical model with a dedicated compartment for the coronary circulation is currently being developed at the University of Sheffield. The model is believed to be able to accurately simulate the systemic state of the personalised pathophysiological effects of CAD, and to place the global ischemic burden in context. The data collection for this project will continue beyond my work. Invasive time-series pressure data of left ventricle, aorta and coronary vessels (hyperemic and non-hyperemic) are being collected. Additionally, left ventriculogram and research grade cardiac MRI scans that include LV, perfusion, and 4D flow analysis are being collected. The relevant data will be incorporated into the model alongside the derived coronary physiology metrics (absolute flow, MVR and HSR) that were generated using CFD in chapter two.

6.3.4 General limitations of the study

Each chapter has addressed the limitations concerning its scope of VIRTU-5, but some general limitations might need to be addressed. It is worth highlighting that the recruitment for this study was very selective. Candidates were carefully selected following a large screening for example, documented coronary disease was needed, and patients should be able to mobile freely. These factors may have resulted in some unintentional bias causing less patients to be on the elder side (>80 years old). However, this could be explained by the nature of the study, which aims to provide detailed assessment of the coronary circulation, which in turns requires the presence of coronary artery disease and hence using pressure wire assessment. Also, the monitoring of everyday life, and how would that might be changed following the intervention requires some sort of unlimited mobility, at least at this point where I tried to robustly assess physical activity for prolonged periods. Studying changes in everyday life in this sample of patients proved to be feasible and informative, perhaps, a comparison against exercise capacity would have been of value. As the latter was extensively used in previous studies, it would be interesting to investigate the difference between the two forms of activity, and can inform the community about the effectiveness of the current practice of assessing the changes following PCI. This was not realistic to be performed in

this study for different reasons, the first was the funding which was limited, the second was the time limitation and the third was the researcher's availability. Moreover, this study was funded by KSAU-HS as part of a student consumable budget, and by the SHC for the MRI scans, therefore, further assessment and involvement of research staff might not be applicable or realistic. Data wise, I collected and analysed the data, and it could be argued that I was not blinded to the clinical assessment (FFR measurement) and outcomes (intervention or not). Yet, data collection and analysis were vital components of the learning process of this PhD, especially for the coronary data which require exposure to coronary angiography, downloading pressure and activity data, processing and segmentation using VIRTUheart™ system. Finally, it is important to highlight the uncontrollable delays resulted from the pandemic and lasted for the entire course of data collection.

6.4 Final conclusion

In this thesis, I conducted a comprehensive assessment of the changes following coronary revascularisation in CCS patients at multiple levels, from coronary artery, through myocardium, to everyday life activity and patient perception. I showed that increase in absolute coronary flow to the myocardium could be achieved with PCI if intervention was based upon the hyperemic cut-off point of FFR≤0.80. In addition, improvements in other coronary physiology metrics can be observed. Similarly, global flow reduction can be improved with PCI, as assessed by the new method (FFR_{CUM}). This novel method may more usefully relate to symptomatic improvement than current parameters, but this has yet to be investigated. However, the measured response to PCI is slightly 'obscured' if assessed according to the patient's reported experience. Objectively measured daily physical activity exhibited (non-significant) trends towards improvement in patients with and without PCI; and both groups achieved similar levels of activity at three months. Health state and quality of life were not different prior to or after the procedure between these two groups. However, reports of better quality of life, symptoms and physical limitations were noted if the questions were asked in regards to 'angina', particularly if PCI were undertaken. These are conclusions drawn based upon a modest number of patients, and larger studies would be required to confirm these findings. They support the findings of ORBITA in questioning long-held assumptions.

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Appendices

1. Data collection sheets

The University Of Sheffield.

Department of Infection, Immunity and cardiovascular Disease

Catheter laboratory data recording sheet
Virtu-5 study

Patient study ID: _____

Operator: _____

Initial HR:			Initial BP:		
Access site:					
Disease location:	1		2	3	
Visual severity :	%		%	%	
FFR result : Rest/hyperaemia					
PCI? :	Yes [ ]	No [ ]	Yes [ ] No [ ]	Yes [ ]	No [ ]
Post-PCI angiogram?	[ ]		[ ]	[ ]	

60 second ventricular pressure snapshot acquired [ ]	Data anonymized and uploaded to G drive [ ]
Ventriculogram acquired [ ]	Invasive coronary pressure uploaded to G drive [ ]

Notes:
LV:
AO:

RFR:	**LAD**	**LCx**	**RCA**	**Other**:
Pre-PCI				
Post-PCI				

Completed by: _____
Date: _____

The University Of Sheffield.

Department of Infection, Immunity and cardiovascular Disease

6-Minute Walk Test Checklist and Recording Sheet
Virtu-5 Study

Equipment Checklist:		**Test operator:**
❖ 6MWT checklist and recording sheet	☐	
❖ Borg scale sheet	☐	_____
❖ Stop watch or timer	☐	
❖ 2 chairs	☐	**Test Date:**
❖ Automated BP machine and pulse oximeter	☐	
❖ Trundle wheel for measuring 6MWD	☐	_____
❖ Clipboard	☐	
❖ Portable oxygen and suitable facemask	☐	**Subject study number:**
❖ Rescue nitrate therapy	☐	
❖ 2 small cones	☐	
❖ SOP document	☐	_____

Clinical Parameters prior to test start:

Heart Rate	bpm	**Blood Pressure**	mmHg
Worsening chest pain in the last month?	Yes / No	**Resting SpO2**	% on air
Medications taken this morning and dose			

Stop the test in the event of any of the following:

- ❖ Chest pain suspicious of angina
- ❖ Evolving light-headedness
- ❖ Intolerable dyspnoea
- ❖ Excessive sweating
- ❖ Pale or ashen appearance that occurs during rest
- ❖ Any clinical concern regarding subject safety

Subject Instruction:

The objective of this test is to walk as far as possible for 6 minutes. You will walk back and forth along this course *(demonstrate one lap)* ***for 6 minutes. You will walk around the cones (****indicate towards cones)* ***clockwise so that the cones are always to your right. I will now show you how to do this*** *(perform one lap of circuit).*
You may slow down if necessary. If you stop, I want you to continue to walk again as soon as you feel able to.You will be informed of the time and encouraged each minute. Please do not talk during the test unless you have a problem or I ask you a question. You must let me know if you have any chest pain or dizziness. Remember, the objective is to walk as far as possible, not as fast, don't jog or run.
When 6 minutes is over I will ask you to stop where you are. I will bring a chair over to you so that you can sit.
The test will be performed twice, after the first 6 minutes there will be a 15 minute break, after which we will start the second test exactly like the first.
Do you have any questions?
Once subject is ready and has no further questions:
When you are ready, please start walking.

At minute one: ***You are doing well. You have five minutes to go.***
At minute two***: Keep up the good work. You have four minutes to go.***
At minute three***: You are doing well. You are halfway done.***
At minute four***: Keep up the good work. You only have two minutes left***
At minute five***: You are doing well. You have only one minute to go.***
At six minutes: ***Stop, please stay where you are.***

Test results

	1st Attempt		2nd Attempt	
	Before test	After test	Before test	After test
Heart Rate	bpm	bpm	bpm	bpm
Blood Pressure	mmHg	mmHg	mmHg	mmHg
SpO2	%	%	%	%
Borg Scale				
Laps completed				
Distance Walked	m	m	m	m
Reason test terminated + time walked				

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Patient Identification Number for this trial: ☐

CONSENT FORM
Towards a complete virtual (computed) model of myocardial ischaemia
(VIRTU 5)
Professor Julian Gunn

Please initial boxes

I confirm that I have read and understand the information sheet Version 2 dated for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

I understand that sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust or University where it is relevant to me taking part in this research. I give permission for these individuals to have access to my Records. ☐

I agree to answer the questionnaires (1). ☐

I agree to have the MRI scan[s] (2). ☐

I agree to have the activity monitoring (3). ☐

I agree to perform the 6 minute walk test[s] (4) ☐

I agree to take in the whole of the above study ☐

Name of Patient	Date	Signature

Name & Job Title of Person Taking Consent	Date	Signature

When completed 1 for participant; 1 for researcher site file; 1 (original) for medical notes

2. Ethical approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Julian Gunn
Professor of Interventional Cardiology
University of Sheffield
The University of Sheffield
Western Bank
Sheffield
S10 2TN

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

23 March 2020

Dear Professor Gunn

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**VIRTU-5: towards a complete model of myocardial ischaemia**
IRAS project ID:	**272069**
REC reference:	**20/NS/0033**
Sponsor	**Sheffield Teaching Hospitals NHS Foundation Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper		21 January 2020
IRAS Application Form	272069/1413 118/37/927	21 January 2020
Letter from funder [Sheffield Hospital Charity (SHC) Grant Acceptance Form]		07 November 2019
Letters of invitation to participant	1.3	05 March 2020
Other [Seattle licence (Outcomes Instruments LLC)]		11 September 2019
Other [SF12 licence (Optum)]		25 October 2019
Other [EQ-5D licence (registration)]		11 September 2019
Other [Phone Slip]	1.0	15 February 2020
Other [Appendix 1 - Guidance Doc for Undertaking a Local Risk Assessment for Lone Working]	2 *date received	03 March 2020
Other [Appendix 3 - Lone Worker Off Site Checklist]	*date received	03 March 2020
Other [Lone Worker Policy]	2.1	13 January 2012
Other [Appendix 2 - Lone Working in Building Checklist]	*date received	03 March 2020
Other [Response to assessment queries (email)]		10 March 2020
Participant consent form [Consent Form]	2	18 February 2020
Participant information sheet (PIS)	4	08 March 2020
Research protocol or project proposal	1.0	08 December 2019
Summary CV for Chief Investigator (CI) [Prof Julian Gunn]		08 August 2019
Summary CV for student [Gareth Wiliams]		16 February 2020
Summary CV for student [Abdulaziz Al-Baraikan]		24 September 2019
Summary CV for supervisor (student research) [Dr David Hose]		18 February 2020
Summary CV for supervisor (student research) [Dr Paul Morris]		10 February 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language	1.1	14 December 2019
Validated questionnaire [EQ-5D-5L Health Questionnaire © 2009]	1.2	
Validated questionnaire [SF-12 Health Survey © 1994, 2002]	2	
Validated questionnaire [Seattle Angina Questionnaire © 1992-2004]	SAQ-UK	

IRAS project ID	272069

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
This is a single site study sponsored by the participating NHS organisation therefore there is only one site type.	This is a single site study sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	This is a single site study sponsored by the participating NHS organisation therefore no agreements are expected.	External study funding has been secured.	A Principal Investigator should be appointed at study sites.	The sponsor has stated that local staff in participating organisations in England who have a contractual relationship with the organisation will undertake the expected activities. Therefore no honorary research contracts or letters of access are expected for this study.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated they intend to apply for inclusion on the NIHR CRN Portfolio.

3. Questionnaires and licences

A. EuroQuality of life – 5 Dimensions (Licence)

Dear Mr. Abdulaziz Albaraikan ,

Thank you for your registration.
The study / project titled "Towards a complete virtual (computed) model of myocardial ischaemia (VIRTU5)" you registered fulfils the conditions for you to use the requested version(s) free of charge.

Below you find our Terms of Use. We will provide you with the requested versions free of charge once we have received your agreement with our Terms of Use. You can indicate your agreement by pressing the green "Agree" button below. If you do not agree, please press "Disagree".

If you have any questions please contact us by sending an email to userinformationservice@euroqol.org.

Thank you in advance.

Kind regards,

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3. In order to request use of the EQ-5D Paper version and/or the EQ-5D Digital module version in a new study/project a new registration should be made on the website of EuroQol.
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   - A maximum of 5,000 unique respondents when used in a Study or Registry;
   - A maximum of 100,000 unique respondents when used in a ROM/PROMs Project;
   - 5 years from the date of acceptance of the Terms of Use when used in a ROM/PROMs project or Registry.
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9. The provided Paper version and/or EQ-5D Digital module version may **only be used in accordance with the written instructions** of EuroQol as set out in the corresponding user guide (https://euroqol.org/publications/user-guides/). For the proper use of the EQ-5D Digital module version a separate guide will be issued, together with the EQ-5D Digital module version.
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3. The User of the EQ-5D Digital module version is responsible for the correct representation of EQ-5D in the Study. The EQ-5D should be represented as shown in the demo pages that can be found on the EuroQol website (https://euroqol.org/eq-5d-instruments/sample-demo/).
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1. In case of questions regarding data analysis, User is requested to send an e-mail to **userinformationservice@euroqol.org.** Please refer to the ID number and Study title.
2. Frequently asked questions relating to the EQ-5D are answered on EuroQol's website (https://euroqol.org/support/faqs/).

Article 6. Governing law

These Terms of Use shall be governed by, and construed in accordance with, the laws of the Netherlands.

Agree

Best regards,

Bernhard Slaap
Executive Director
EuroQol Research Foundation

EQ-5D

T +31 88 4400196 | E slaap@euroqol.org | www.euroqol.org | Marten Meesweg 107 | 3068 AV Rotterdam The Netherlands

EuroQuality of life – 5 Dimensions (Questionnaire)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

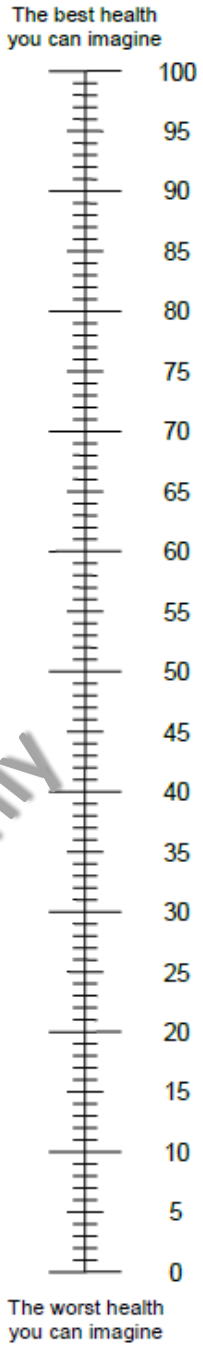
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



B. Short Form-12 (Licence)

NON-COMMERCIAL LICENSE AGREEMENT
Office of Grants and Scholarly Research (OGSR)

License Number: QM051067

Licensee Name: University of Sheffield

Licensee Address: Firth Court, Western Bank, , Sheffield S10 2TN UK

Approved Purpose: Towards a complete virtual (computed) model of myocardial ischemia VIRTU 5

Study Type: Non-commercial academic research and/or thesis: Grant Funded

Therapeutic Area: Heart and Circulation

A. Effective Date: This Non-Commercial License Agreement (the "Agreement") from the Office of Grants and Scholarly Research (OGSR) is made by and between OptumInsight Life Sciences, Inc. (f/k/a QualityMetric Incorporated) ("Optum"), 1301 Atwood Ave, Suite 311N, Johnston, RI 02919 and Licensee. This Agreement is entered into as of the date of last signature below and is effective for the Study Term set forth on Appendix B.

B. Appendices: Capitalized terms used in this Agreement shall have the meanings assigned to them in Appendix A, Appendix B and Appendix D. Licensee agrees the study information completed on Appendix D – Project details form (Questionnaire) is for non-commercial use. The appendices attached hereto are incorporated into and made a part of this Agreement for all purposes.

C. Grant of License: Subject to the terms of this Agreement: (a) Optum grants to Licensee a non-exclusive, non-transferable, non-sublicensable worldwide license to use, solely for the Approved Purpose and during the Study Term, the Licensed Surveys, Software, SMS Scoring Solution, and all intellectual property rights related thereto ("Survey Materials"), in the authorized Data Collection Method, Modes of Administration, and Approved Languages indicated on Appendix B; and to administer the Licensed Surveys only up to the total number of Administrations (and to make up to such number of exact reproductions of the Licensed Surveys necessary to support such Administrations) in any combination of the specific Licensed Surveys and Approved Languages, Data Collection Method, and Modes of Administration; (b) Licensee agrees to purchase the Services described in Appendix B (if applicable); and (c) Licensee agrees to pay Optum the fees on Appendix B ("Fees") in accordance with the invoice to be provided.

EXECUTED by the duly authorized representatives as set forth below.

OptumInsight Life Sciences, Inc.	**University of Sheffield**
Signature: DocuSigned by: 693E21C86222484	Signature:
Name: Martha bayliss	Name: Abdulaziz Albaraikan
Title: VP Patient Insights and Principal Consultant	Title: Ph.D student
Date: 10/25/2019	Date: 17/10/2019

Short Form-12 (Questionnaire)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
○	○	○	○	○

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b. Climbing several flights of stairs	○	○	○

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	○	○	○	○	○
b. Were limited in the kind of work or other activities	○	○	○	○	○

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	○	○	○	○	○
b. Did work or other activities less carefully than usual	○	○	○	○	○

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	○	○	○	○	○
b. Did you have a lot of energy?	○	○	○	○	○
c. Have you felt downhearted and depressed?	○	○	○	○	○

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the	Most of the	Some of the	A little of the	None of the

C. Seattle Angina Questionnaire (Licence)

OUTCOMES
Instruments, LLC

LICENSE AGREEMENT

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B. Licensee is engaged in that certain study more particularly described on Schedule B attached hereto and incorporated herein by this reference (the "Subject Study").

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4. Licensor's Representations and Covenants. Licensor represents and warrants to Licensee that Licensor has the full power and authority to execute and deliver this Agreement and to perform its obligations hereunder without need to obtain the consent of any third party.

5. Site Visits. Licensor shall have the right to inspect and observe from time to time through such agents or representatives as Licensor may designate, on Licensee's site, the activities conducted by or for Licensee with respect to the Licensed Properties to determine whether Licensee is using the Licensed Properties in a proper fashion as provided hereunder. To the extent Licensor is granted access to a patient's "protected health information" ("PHI"), as such term is defined in the Health Insurance Portability and Accountability Act of 1996 and the regulations promulgated thereunder, the parties agree to negotiate and execute a Business Associates Agreement containing customary covenants regarding the confidentiality and limited use of such PHI.
6. Reports. Licensee shall keep and maintain comprehensive and accurate records pertaining to its use of the Licensed Properties, and the status and progress of the Subject Study. Such reports shall be available for examination by Licensor and its agents or representatives at any time upon reasonable advance notice.
7. Licensee's Conduct. Licensee agrees that it shall use the Licensed Properties only as permitted hereunder and further agrees to refrain from modifying, altering or amending the Licensed Properties or taking any action which could adversely affect the validity, goodwill and reputation thereof. Upon the termination or expiration of this Agreement, Licensee shall immediately discontinue all use of the Licensed Properties.
8. Litigation. As between Licensor and Licensee, only the Licensor shall have the right to commence or prosecute any claims or litigation to protect or enforce its rights in and to the Licensed Properties. Licensee agrees that it will immediately provide notice to Licensor upon learning of any litigation, whether actual or threatened, against Licensee in connection with Licensee's use of the Licensed Properties. Licensee further agrees that it will cooperate fully with Licensor by providing any information requested by Licensor in any litigation arising in connection with Licensee's use of the Licensed Properties.
9. Disclaimers; Limitations of Liability. LICENSEE ACKNOWLEDGES THAT THE LICENSED PROPERTIES ARE LICENSED "AS IS", WITH ALL FAULTS. LICENSOR HAS MADE NO REPRESENTATION OR WARRANTY THAT THE LICENSED PROPERTIES ARE SUITABLE FOR LICENSEE'S USE IN CONNECTION WITH THE SUBJECT STUDY. LICENSEE SHALL RELY ON ITS OWN JUDGMENT IN EVALUATING ITS USE OF THE LICENSED PROPERTIES AND ANY OUTCOMES ATTRIBUTABLE THERETO, WITHOUT RELYING ON ANY MATERIAL OR INFORMATION PROVIDED BY LICENSOR. LICENSOR DISCLAIMS ANY REPRESENTATIONS OR WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY REPRESENTATIONS OR WARRANTIES AS TO THE LICENSED PROPERTIES' MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IN NO EVENT SHALL LICENSOR BE LIABLE FOR SPECIAL, CONSEQUENTIAL, EXEMPLARY OR PUNITIVE DAMAGES. LICENSOR'S LIABILITY HEREUNDER SHALL BE LIMITED TO LICENSEE'S DIRECT DAMAGES RESULTING FROM LICENSOR'S BREACH OF ANY OF ITS OBLIGATIONS HEREUNDER WHICH CONTINUES UNREMEDIED FOR THIRTY DAYS AFTER WRITTEN NOTICE BUT SHALL IN NO EVENT EXCEED THE AMOUNT OF THE FEES ACTUALLY PAID BY LICENSEE TO LICENSOR HEREUNDER.
10. Indemnification of Licensor. Licensee hereby agrees to hold Licensor harmless of and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensor may incur or be obligated to pay, or for which it may become liable or be compelled to pay in any action, claim or proceeding for or by reason of any acts, whether of omission or commission, that may be claimed to be or are actually committed or suffered by Licensee arising out of Licensee's use of the Licensed Properties. The provisions of this paragraph and Licensee's obligations hereunder shall survive the expiration or termination of this Agreement.
11. Indemnification of Licensee. Subject to Section 9 hereof, Licensor hereby agrees to hold Licensee harmless of and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensee may incur or be obligated to pay, or for which it may become liable or compelled to pay in

any action, claim or proceeding for or by reason of any breach of any representation, warranty or agreement on the part of Licensor under this Agreement.

12. Nondisclosure. During the term of this Agreement, the parties may have access to trade secrets, proprietary information, or other sensitive materials belonging to the other which are not generally known to the public ("Confidential Information"). During the term of this Agreement and for a period of five (5) years after termination or expiration hereof, the receiving party ("Recipient") agrees to maintain in trust and confidence all Confidential Information of the other party (the "Disclosing Party"). The Recipient agrees to safeguard the Confidential Information using the same standard of care it uses to protect its own Confidential Information. The Recipient will not disclose any Confidential Information to any third party, or make any use thereof other than as expressly permitted hereby, without the prior written consent of the Disclosing Party. As used herein, Confidential Information does not include any information which the Recipient can demonstrate (i) was known to the Recipient or to the general public at the time of disclosure; (ii) was independently developed by the Recipient without the use of any of the Confidential Information; or (iii) was disclosed by a third party without violating any restriction or duty to the Disclosing Party.
13. Publications. Notwithstanding the general restrictions set forth in Section 12 above, the parties agree that publication of the results of research activities serves their mutual interests in improving the quality of health care. Accordingly, Licensee shall be free to publish the results of its research and development activities carried out with respect to the Licensed Properties and the Subject Study. Licensee agrees to refer to Licensor and the Licensed Properties in the bibliography section of the publication.
14. Term. Subject to the provisions of Section 15 hereof, this Agreement shall remain in effect from 01/01/2020 to 01/01/2023. Subsequent renewal of this Agreement shall be optionally available through application through the web site.
15. Licensor's Right to Terminate. Licensor shall have the right to immediately terminate this Agreement by giving written notice to Licensee in the event Licensee: (i) fails to perform any of its duties and obligations set forth herein, and the continuation thereof for thirty (30) days after notice; (ii) files a petition in bankruptcy or is adjudicated a bankrupt or insolvent, or makes an assignment for the benefit of creditors; (iii) makes any use of the Licensed Properties not otherwise expressly permitted herein or (iv) the Subject Study is cancelled, abandoned, withdrawn or suspended. In such event, Licensee shall immediately cease and terminate its use of any of the rights granted hereby and shall, upon the request of Licensor, return to Licensor all records, copies, documents, media and files making use of the Licensed Properties, or furnish evidence, satisfactory to Licensor, of the destruction thereof.
16. Equitable Remedies. The parties further acknowledge that the breach, whether threatened or actual, of any of the terms hereof by Licensee shall result in immediate, irreparable injury to Licensor and its goodwill and that accordingly, Licensor shall be entitled to apply for a preliminary and/or permanent injunction to restrain the threatened or actual violation of the terms hereof by the Licensee or to compel specific performance of the terms and conditions of this License Agreement. Nothing set forth herein shall be construed as prohibiting the Licensor from pursuing any other remedies available for such breach or threatened breach, including the recovery of damages and costs incurred, together with attorneys' fees.
17. Miscellaneous.

a. This Agreement together with the exhibits hereto constitutes the entire understanding between the parties with respect to this Agreement. No change or modification of any of the provisions of this Agreement shall be effective unless memorialized by an instrument in writing signed by the parties hereto. All notices required or permitted to be given hereunder shall be given in writing, to the parties at their addresses set forth herein, or to such other address with respect to which notice has been given in accordance herewith. Whenever possible, each

provision of this License Agreement shall be interpreted in such a manner as to be effective and valid under applicable law. If any covenant or other provision of this Agreement, or portion thereof, under circumstances not now contemplated by the parties, is invalid, illegal or incapable of being enforced, by reason of any rule of law, administrative order, judicial decision or public policy, all other conditions and provisions of this Agreement shall, nevertheless, remain in full force and effect, and no covenant or provision shall be deemed dependent upon any other covenant or provision unless so expressed herein. The parties desire and consent that the court or other body making such determination shall, to the extent necessary to avoid any unenforceability, so reform such covenant, term, condition or other provision or portion of this Agreement to the minimum extent necessary so as to render the same enforceable in accordance with the intent herein expressed.

b. This Agreement shall inure to the benefit of Licensor, its successors and assigns. Licensee shall not have the right to assign this Agreement, or delegate its duties, by operation of law or otherwise, without first obtaining the written consent of Licensor.
c. This Agreement shall be governed by and construed in accordance with the laws of the State of Missouri.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be duly executed as of the day and year first above mentioned.

Outcomes Instruments, LLC	**The University of Sheffield**
John Spertus	
By: John Spertus	By: Abdulaziz Albaraikan
Title: President	Title: Ph.D student
"Licensor"	"Licensee"

SCHEDULE A: LICENSED PROPERTIES

SAQ – English (UK)

This version of the SAQ has been designed for English-speaking patients in the UK.
This zip file includes two PDF files: the SAQ itself and scoring instructions.

SCHEDULE B: DESCRIPTION OF STUDY

Project Name

Towards a complete virtual (computed) model of myocardial ischaemia VIRTU 5

Project ID

7627

Project Type

Other

Project Dates

Start: 01/01/2020

End: 01/01/2023

Duration: 1096 days

Enrollment

Sites: 1

Seattle Angina Questionnaire (Questionnaire)

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during a normal week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or anginal attacks <u>over the past 4 weeks</u>:**

Place an x in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not Limited at all	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering or bathing	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a hundred yards at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects such as furniture, or lifting children	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

SAQ – UK (English)

2. Compared with 4 weeks ago, how often do you have **chest pain**, **chest tightness**, or **anginal attacks** when doing your **most strenuous** activities?

I have **chest pain**, **chest tightness**, or **anginal attacks**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain**, **chest tightness**, or **anginal attacks**?

I have had **chest pain**, **chest tightness**, or **anginal attacks**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take GTN (nitroglycerin tablets or spray) for your **chest pain**, **chest tightness**, or **anginal attacks**?

I have taken GTN...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for **chest pain**, **chest tightness** or **anginal attacks** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	Not bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the past 4 weeks, how much has your **chest pain**, **chest tightness**, or **anginal attacks** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your **chest pain**, **chest tightness**, or **anginal attacks** the way it is at the moment, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I think or worry about it **all the time**	I **often** think or worry about it	I **occasionally** think or worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐