ANGLIA RUSKIN UNIVERSITY

FACULTY OF HEALTH, EDUCATION, MEDICINE AND SOCIAL CARE

THE EFFECT OF HYDROSTATIC PRESSURE ON INVASIVE MEASURES OF CORONARY PHYSIOLOGY

FIRAS AL-JANABI

A thesis in partial fulfilment of the requirements of Anglia Ruskin University for the degree of MD by Research

This research was carried out in collaboration with the Essex Cardiothoracic Centre, Basildon and Thurrock University Hospital NHS Foundation Trust

Submitted: August 2020

Acknowledgements

I would like to thank Dr Thomas Keeble and Dr John Davies of the Essex Cardiothoracic Centre, for their unfaltering support during my research period. They offered all the help I needed and would always go the extra mile. Approachable, knowledgeable, hardworking and dedicated, I am forever grateful for their supervision and time. Thank you both so much.

Many thanks to Dr Christopher Cook from Imperial College London, for his training and knowledge in the use of coronary doppler, as well as for the mutual support between two new fathers!

To Dr Rudolph Schutte, Leica Claydon, Jufen Zhang and Selim Cellek of Anglia Ruskin University, for their knowledge and assistance during my time there, thank you.

To the nurses, radiographers, physiologists and consultants at the Essex Cardiothoracic Centre who gave their time and effort to this study, I am hugely thankful. Without all of you, this would not have been possible. The willingness to dive into this study with enthusiasm and interest was truly flattering. An amazing place to work with fantastic people.

Thank you to Medtronic PLC for their interest, commitment and financial support during the study period.

To my mother and father, for their love, support, kindness and encouragement during difficult times. It makes one strive to do as much as you for their own children. Thank you.

To my wife and two daughters. Thank you for your patience and understanding. They have taught me more than I could imagine and everything is truly for them.

ANGLIA RUSKIN UNIVERSITY

ABSTRACT

FACULTY OF HEALTH, EDUCATION, MEDICINE AND SOCIAL CARE

DOCTOR OF MEDICINE BY RESEARCH

THE EFFECT OF HYDROSTATIC PRESSURE ON INVASIVE MEASURES OF CORONARY PHYSIOLOGY

FIRAS AL-JANABI

August 2020

Introduction: Coronary arteries are at differing vertical heights in a supine patient relative to the aortic root. Pressure within an artery varies based on distance from the aorta due to hydrostatic effect. This could impact pressure-based indices of stenosis severity, as the vertical distance between distal and proximal pressure sensors creates a baseline pressure difference. This is neglected in clinical practice, as distal and proximal sensors are considered at the same vertical level.

Methods: Pd/Pa, instantaneous wave free ratio (iFR), fractional flow reserve FFR and doppler flow velocity were recorded in 23 coronary stenoses in the standard supine patient position, and in the prone position. Measurements between positions were compared using a Student's t test for matched pairs.

Results: There were significant differences in mean Pd/Pa (0.05), iFR (0.06) and FFR (0.06) when comparing prone and supine positioning ($p<0.05$). When inferior to the aorta, mean Pd/Pa, iFR and FFR were 0.96±0.05, 0.93±0.11 and 0.84±0.10 respectively. When superior, mean Pd/Pa, iFR and FFR were 0.91±0.07, 0.87±0.11 and 0.78±0 respectively. Resting and hyperaemic doppler flow measurements did not change significantly when comparing prone and supine patient position. 26% of all FFR and 36% of all iFR values were re-classified across a treatment threshold when hydrostatic effect was corrected.

Conclusion. Patient position alters physiological stenosis severity as quantified by invasive coronary pressure measurements. Coronary stenoses positioned inferiorly to the aorta, produce significantly higher Pd/Pa, iFR and FFR values when compared to a superior position. Conversely, patient position did not influence coronary doppler flow velocity. This is the first study to quantify the effect of hydrostatic pressure on invasive measures of coronary stenosis. The data supports hydrostatic effect as a potential confounding factor leading to inaccurate lesion assessment.

Keywords: Hydrostatic pressure, prone, supine, FFR, iFR, doppler

Publications arising from this research:

1. Coronary artery height differences and their effect on fractional flow reserve.
   Al-Janabi F, Karamasis G, Cook CM, Kabir AM, Jagathesan RO, Robinson NM, Sayer JW, Aggarwal RK, Clesham GJ, Kelly PR, Gamma RA, Tang KH, Keeble TR, Davies JR.
   Cardiol J. 2019 Mar 26. doi: 10.5603/CJ.a2019.0031

Presentations at scientific meetings

1. The Effect of Hydrostatic Pressure on FFR. F. Al-Janabi, G. Karamasis, C. Cook, G.J. Clesham, R.K. Aggarwal, R. Gamma, P. Kelly, K. Tang, J. Davies, T. Keeble

   European Association for Percutaneous Cardiovascular Interventions 2018 Poster Presentation (PCR Abstract book, 2020) Euro18A-POS201

2. Comparing prone and supine measurements of pressure and doppler based indices across the same coronary stenosis: a first in man case series. F. Al-Janabi

   European Associated for Percutaneous Cardiovascular Interventions 2019 - Shortlisted for oral presentation in PCR's got talent / Young investigator

Contents

ABSTRACT ii
List of Figures ix
List of Tables xii
Abbreviations xiv
Thesis Structure 1
Chapter I - Introduction 9
1.1 - Acute Coronary Syndrome 10
1.1.1 - ST Elevation Myocardial Infarction 10
1.1.2 - Non-ST Elevation Myocardial Infarction and Unstable Angina 12
1.2 - Chronic Coronary Syndrome 15
1.3 - Assessing the Coronary Circulation 17
1.3.1 - Diagnostic Coronary Angiography 17
1.3.2 - Basic Concept 18
1.3.3 - Contrast Injection 19
1.3.4 - Fluoroscopy 21
1.4 - Percutaneous Coronary Intervention 22
1.4.4 - Balloon Angioplasty and Bare Metal Stents 22
1.4.2 - Drug Eluting Stents 23
1.4.3 - Drug Eluting Stents vs. Bare Metal Stents 24
1.5 - Risks of Percutaneous Coronary Intervention 25
1.6 - Identifying Significant Lesions in Stable Coronary Artery Disease 25
1.7 - Non-Invasive Ischaemia Assessment 26
1.7.1 - CT FFR 27
1.8 - Invasive Ischaemia Assessment 27
1.8.1 - History of Invasive Coronary Physiology 28
1.8.2 - The Theory of Fractional Flow Reserve 30
1.8.3 - Pressure and Flow 30
1.9 - Clinical Evidence Supporting FFR 35
1.9.1 - DEFER Study 35
1.9.2 - FAME Study 36
1.9.3 - FAME II Study 36

1.9.4 - Registry Data 38
1.9.5 - FFR in Current Clinical Guidelines 39
1.9.6 - FFR Use in Acute Coronary Syndrome 40
1.10 - Resting Indices 40
1.11 - Pitfalls of Pressure Derived Indices 42
1.12 - Hydrostatic Pressure 44
1.12.1 - Magnitude of Effect 46
1.12.2 - Hydrostatic Effect in Clinical Literature 47
1.13 - Research Hypotheses and Pre-Work 48
1.13.1 - CT Coronary Angiogram Pre-work 50
1.14 - CT Coronary Angiography (CTCA) 51
1.14.1 - Limitations of CT Coronary Angiography 52
1.15 - Feasibility of in Vivo Research 53
1.15.1 - Current Relevant Literature 53
1.15.2 - Calculating Hydrostatic Effect from Vertical Measurements 54
1.15.3 - The Clinical Effect on FFR 55
1.15.4 - The Effect on Resting Indices 56
1.15.5 - Clinical Relevance and Mathematical Model 57
1.15.6 – Research Questions, Aims and Objectives 57
Chapter II - Methods, Results and Interpretation from CT Coronary Angiography 58
2.1 - Inclusion and Exclusion Criteria 58
2.2 - CT Coronary Angiogram 59
2.3 - FFR Mathematical Model 60
2.4 - Statistical Analysis 61
2.5 - Results 61
2.5.1 - Patient Demographics 61
2.5.2 - Vertical Height Measurements 62
2.5.3 - Effect on FFR 64
2.5.4 - FFR and cFFR Discordance 66
2.6 - Discussion and Interpretation 67
2.6.1 - Height Variations 68
2.6.2 - Al-Janabi vs.Härle Data 70
2.6.3 - FFR Magnitude of Effect 72

2.6.4 - Potential Impact on Clinical Practice 72
2.6.5 - PDA vs. PLV Wire Placement - A Clinical Case Example 74
2.7 - Limitations 76
2.7.1 - Patient Demographic 76
2.7.2 - Coronary Visualisation 78
2.7.3 - Measurement Point 78
2.7.4 - Mathematical Model 79
2.8 - Conclusions 79
Chapter III - Methods and Results from Invasive Physiology 80
3.1 - Method Overview 80
3.2 - Primary and Secondary Endpoints 80
3.3 - Ethical Approval and Study Population 81
3.3.1 - Ethical Approval 81
3.3.2 - Clinical Study Registration 81
3.3.3 - Study Population 81
3.4 - Sample Size Calculation and Statistical Analysis 85
3.5 - Study Challenges 86
3.5.1 - Vascular access 86
3.5.2 - Turning Manoeuvre 88
3.5.3 - Procedural Considerations 89
3.6 - Study Protocol 91
3.6.1 - Prone Component 91
3.6.2 - Physiology Wire 92
3.6.3 - Combomap System 93
3.6.4 - Physiology Measurements 93
3.6.5 - Supine Component 95
3.6.6 - Post Procedure and Recovery 96
3.7 - Midpoint Protocol Changes 96
3.7.1 - Clinical Measurement Point 96
3.7.2 - Left Lateral View and Vertical Height Measurement 97
3.8 - Data Analysis 98
3.9 - Statistical Analysis 98
3.10 - Outcome Measures 99

3.11 - Results Overview 100
3.12 - The First Patient 100
3.13 - Patient Demographics 100
3.14 - Lesion Characteristics 103
3.15 - Guide to Wire Measurement 106
3.16 - Pressure Based Indices 108
3.16.1 - Delta Change 108
3.16.2 - Pd/Pa 110
3.16.3 - Instantaneous Wave Free Ratio (iFR) 118
3.16.4 - Fractional Flow Reserve 127
3.16.5 - FFR Clinical Measurement Point 136
3.17 - Summary of Pressure Based Measurements 140
3.18 - Stenosis Re-classification 141
3.19 - Doppler Measurements 142
3.20 - Summary of Doppler Based Measurements 149
3.21 - Guide to Wire Correlation Data 149
3.21.1 - Pd/Pa 149
3.21.2 - iFR 150
3.21.3 - FFR 151
3.22 - Estimated Hydrostatic Effect versus in Vivo Effect 152
3.33 - Summary of All Results 153
Chapter IV - Discussion and Interpretation 155
4.1 - Overview 155
4.2 - Patient Population / Demographic 156
4.3 - Angiographic Data 157
4.3.1 - Stenosis Percentage 157
4.3.2 - Position of Stenosis 158
4.3.3 - Guide to Wire Measurement Correlation 158
4.4 - Pressure Results 160
4.4.1 - Pressure Based Values > 1.0 160
4.4.2 - Pd/Pa 161
4.4.3 - iFR 161
4.4.4 - FFR and Hyperaemia 162

4.5 - Supporting Evidence in the Clinical Literature 163
4.6 - Doppler Measurements 166
4.6.1 - Dysfunctional Microcirculation 169
4.7 - Potential Clinical Implications 170
4.7.1 - Pressure Based Measurements : A 'Level' Playing Field 170
4.7.2 - Clinical Measurement Point 173
4.7.3 - Statistical Significance versus Clinical Significance 173
4.7.4 - Wire Placement - PLV versus PDA 174
4.7.5 - Diffuse Disease and Serial Stenosis 175
4.7.6 - Other Physiological Indices 175
4.7.8 - Accounting for Hydrostatic Pressure Effect 175
4.8 - Anatomical FFR and Hydrostatic Pressure 178
4.8.1 - CT FFR 179
4.8.2 - Angio-FFR 179
4.8.3 - Hydrostatic Effect in Non-invasive FFR 180
4.9 - Arguments Against Hydrostatic Effect 181
4.10 - Study Limitations 182
4.11 - Future Research 183
4.11.1 - Ideal Study Protocol 183
4.11.2 - STEMI 184
4.11.3 - Chronic Total Occlusion 187
4.11.4 - Vessel Mapping 187
4.12 - Novel Pressure Wires Immune to Hydrostatic Effect 189
4.13 - Final Thoughts 190
References 192
Appendix A - General Introduction to Coronary Artery Disease 217
Appendix B - Risks of Percutaneous Coronary Intervention 223
Appendix C - Standard Angiography and Laboratory Set-up 227
Appendix D - Turning Checklist and Description 230
Appendix E - Image Acquisition During Angiography 233
Appendix F - Published CT Coronary Paper (Original Manuscript) 234

List of Figures

Figure 1 - STEMI ECG 11

Figure 2 - Cardiac Biomarkers 14

Figure 3 - First Invasive Coronary Catheter 18

Figure 4 - Coronary Anatomy 19

Figure 5 - Right Coronary Angiogram 21

Figure 6 - Pd/Pa 29

Figure 7 - Ohm's law. 31

Figure 8 - Ohm's law, applied to the cardiovascular system 31

Figure 9 - Pressure and Flow 32

Figure 10 - FFR Myo 33

Figure 11 -FFR Cor 34

Figure 12 - The Wave Free Period 41

Figure 13 - Close Fluid Model of the Coronary Circulation 45

Figure 14 - Superior vs. Inferior Coronary Arteries 49

Figure 15 - Cardiac CT Showing Coronary Anatomy. 51

Figure 16 - Estimated Hydrostatic Effect 54

Figure 17 - Height Measurement Using Coronary CT 60

Figure 18 - Coronary Height Data 64

Figure 19 - Coronary Branch Points 69

Figure 20 - Case Study 75

Figure 21- 2018 NICE Guidelines for Stable Angina 77

Figure 22 - Patient Flowchart 84

Figure 23 - Power Calculation - 85

Figure 24 - Prone Positioning 87

Figure 25 - Prone Positioning 2 88

Figure 26 - Prone Angiographic Projection 90

Figure 27- ComboWire 92

Figure 28 - Combomap System 93

Figure 29 - Invasive Pressure Normalisation 94

Figure 30 - Hyperaemic Pressure and Flow Measurements 95

Figure 31 - Guide to Wire Measurement 97

Figure 32 - Estimated Hydrostatic Effect 108

Figure 33 - Pd/Pa of Superior vs. Inferior artery position 111

Figure 34 - LAD Pd/Pa Delta Change 114

Figure 35 - Cx Pd/Pa Delta Change 116

Figure 36 - RCA Pd/Pa Delta change 118

Figure 37 - Superior vs. Inferior iFR. 120

Figure 38 - LAD iFR Delta Change 123

Figure 39 - Cx iFR Delta Change 125

Figure 40 - RCA iFR Delta Change 127

Figure 41 -FFR Delta Change 129

Figure 42- LAD FFR Delta Change 131

Figure 43- Cx FFR Delta Change 133

Figure 44 - RCA FFR Delta Change 135

Figure 45 - LAD Clinical Measurement Point 138

Figure 46 -Doppler Flow Data 145

Figure 47 -Resting and Hyperaemic Doppler flow per artery 148

Figure 48 - Height Versus Delta Change in Pd/Pa 150

Figure 49 - Height Versus Delta Chaneg in iFR 151

Figure 50 -Height Versus Delta Change in FFR 152

Figure 51 - Coronary Flow Versus Stenotic Gradient and Resistance 168

Figure 52- Hydrostatic Pressure Effect Per Artery. 171

Figure 53 - Suggested STEMI Pathway 186

Figure 54 - Graduated Hydrostatic Correction 189

Figure 55 - Hydrostatic Effect Immune Wire 190

List of Tables

Table 1 - summary of DEFER, FAME and FAME II 38

Table 2 - the effect of a change in Pd of -0.05 on Pd/Pa with various systemic/Pa 56

Table 3 - CT Data Patient Demographics. 62

Table 4 - CT Height Data. 63

Table 5 - CT Heights to Ostium and Effect On Pressure 66

Table 6 - cFFR Values Crossing Ischaemic Threshold. 67

Table 7 - Al-Janabi vs. Härle CT data. 71

Table 8 - Superior vs. Inferior Stenosis Position 73

Table 9 - Pressure and Flow Case Study Data. 76

Table 10 - Inclusion and exclusion criteria 83

Table 11 - Patient Demographics - In Vivo Data. 102

Table 12 - Stenosis Data for All Cases 105

Table 13 - Treated Lesions. Stent lengths are in mm. 105

Table 14 - Guide to Wire Data. 107

Table 15 - Anticipated Direction of Change. 109

Table 16 - Prone vs. Supine Pd/Pa. 111

Table 17 - LAD Pd/Pa 113

Table 18 - Cx Pd/Pa 115

Table 19 - RCA Pd/Pa 117

Table 20 - Prone vs. Supine iFR. 119

Table 21 - LAD iFR 122

Table 22 - Cx iFR 124

Table 23 - RCA iFR 127

Table 24 - Prone vs. Supine FFR. 128

Table 25 - LAD FFR. 131

Table 26 - Cx FFR 133

Table 27 - RCA FFR. 135

Table 28 - LAD Clinical Measurement Point. 137

Table 29 - Cx Clinical Measurement Point 139

Table 30 - RCA Clinical Measurement Point 140

Table 31 - Stenosis Re-classification 142

Table 32- Prone vs. Supine Resting Doppler Flow. 143

Table 33 - Prone vs. Supine Hyperaemic Doppler Flow. 144

Table 34 - Per Artery Resting and Hyperaemic Doppler Flow. 147

Table 35 - Predicted vs. Actual Hydrostatic Effect in Vivo 153

Table 36 - Pa Pressure During Prone and Supine Pd/Pa, iFR and FFR. 162

Table 37 - Delta Change Between Patient Position - Al-Janabi vs. Härle Data. 164

Table 38 - Al-Janabi vs. Kawaguchi Data. 165

Table 39 - Vessel Specific FFR 177

Abbreviations

ACS - Acute Coronary Syndrome(s)

ARDS - Acute Respiratory Distress Syndrome

AV - Atrioventricular

BMS - Bare Metal Stent

cFFR - Corrected Fractional Flow Reserve

CT - Computed Tomography

CTCA - CT Coronary Angiography

Cx - Circumflex Artery

DES - Drug Eluting Stent

EF - Ejection Fraction

FFR - Fractional Flow Reserve

iFR - Instantaneous Wave Free Ratio

IMR - Index of Microvascular Resistance

IRA - Infarct Related Artery

LAD - Left Anterior Descending Artery

LDL - Low Density Lipoprotein

LV - Left Ventricle / Left Ventricular

LVEDP - Left Ventricular End Diastolic Volume

MACE - Major Adverse Cardiac Events

MRI - Magnetic Resonance Imaging

NHS - National Health Service

NICE - National Institute for Health and Care Excellence

NSTEMI - Non-ST Elevation Myocardial Infarction

OM - Obtuse Marginal (Branch of the Circumflex)

OMT - Optimal Medical Therapy

OMT - Optimal Medical Therapy

PCI - Percutaneous Coronary Intervention

PCI - Percutaneous Coronary Intervention

POBA - Plain Old Balloon Angioplasty

PPCI - Primary Percutaneous Coronary Intervention

QCA -Quantitative Coronary Analysis

RCA - Right Coronary Artery

STEMI - ST Elevation Myocardial Infarction

TAVI - Transcatheter Aortic Valve Implantation

UA - Unstable Angina

UK - United Kingdom

Thesis Structure

Chapter I – Introduction

Having only two years to contribute new scientific knowledge in a subject area studied for decades, by incredibly gifted scientists and clinicians, appears initially a rather daunting task. As often occurs similarly in the entrepreneurial world, when faced with a potentially new or novel idea, someone has almost certainly thought of it first. Which leaves a scientific researcher with two choices. Firstly, delve into exceedingly niche areas which are yet to be explored, risking the possibility that they hold little potential for new discovery. Or go back to basic principles and aim to find something relevant, simple and unexplored. The latter options seem rather more appealing, however, the possibility of finding such a research topic within the basic concepts of a scientific method studied for decades, seems rather small. By chance, and rather by accident, I feel the second scenario applies to my research work and I will briefly try to explain why in this preface.

Coronary artery disease is the most common cause of death in the UK after cancer (Avoidable mortality in England and Wales - Office for National Statistics, 2018). Working in a heart attack centre, and observing the positive outcomes for some patients, and the negative for others, one finds themselves asking; why did Mrs X do better than Mr Y? The initial idea for my research came from Dr John Davies, an interventional cardiologist at the Essex Cardiothoracic Centre, who has spent his consultant and training years treating emergency heart attacks. It is clear that the most important step in managing acute coronary syndrome (ACS), is reducing the size of the heart attack (or infarct size) (Stone et al., 2016). His initial idea was simple; could we increase blood flow to areas of heart muscle, simply by changing the position of the patient (e.g. lying them on their front during a heart attack)? This in turn would reduce the infarct size, and potentially improve the prognosis of the patient. The initial idea was met with scepticism by colleagues, and also initially by myself for a simple reason. There was a potential physiological explanation for the theory, but there was no relevant scientific literature in the area, no previous studies, and not even a mention of such a concept in academic literature. It may have been possible that a relatively simple idea, had just not been explored. As I started my research journey, this was the question I initially set

out to answer; does physiology and blood flow within a coronary artery change when comparing supine (standard) measurements, with prone (experimental) measurements.

It became clear early into my research that this was an evidence free zone. Another realisation from a medical and ethical standpoint was that to understand what when a patient changes position during a heart attack, we needed to understand the science in stable (and relatively normal) coronary arteries first. In stable patients, we expect physiological mechanisms to be preserved (autoregulation intact), whereas during an acute heart attack, these mechanisms may be disrupted (autoregulation not intact). We set out to understand what 'normal' was before attempting to do the same for 'abnormal'. Elective patients who were referred for pressure wire assessment of a coronary artery lesion became the obvious starting point for a study cohort. Standard measurements occur when the patient is supine, but repeating the measurements when prone, in the same artery, for the same lesion, would provide a direct comparison, with position change being the only variable. Comparing measurements in coronary arteries with a focus on the difference in patient position change, had never been done and hence became the true starting point for my thesis, and research. One case report of a prone diagnostic coronary angiogram existed at the time of study conception (Kwon, Cha and Rhee, 2012), but no reported cases of prone invasive coronary physiological measurements did, and certainly no literature was available comparing prone measurements to supine.

The next milestone was to understand which measurements I needed to obtain within the coronary artery. Blood flow was the key endpoint which we hypothesised may reduce infarct size during a heart attack. Several methods existed to measure this. The most widely used and validated, are pressure-based systems (FFR - fractional flow reserve), which use coronary artery pressure across a stenosis, as a surrogate measurement for flow, and contribute to decisions made regarding treatment. The principle revolves around a ratio of distal vessel pressure versus proximal pressure (aortic / origin of artery). Another less commonly used method (but arguably more accurate), due to the difficulty in acquiring measurements and time constraints, are velocity or flow-based measurements.

The use of pressure-based measurements is widespread and forms a cornerstone of interventional cardiology. However, from basic physical principles, it is known that blood pressure at varying vertical heights from a fixed point (usually the heart, or aorta) will change. Coronary arteries in

their natural state lie in different vertical planes, yet we assume they are vertically level and use a standardised cut-off point across all arteries to indicate a significant stenosis, rather than vessel specific ones. Some coronary arteries take a superior path, and others an inferior one. Their path inherently alters the pressure within them compared to the aorta. This realisation was a major milestone, in that rather by chance, it appeared such a widely used and trusted coronary measurement system, based on pressure, would be altered by changing the patient's position even when all other variables remain constant. Changing position (supine to prone) may give a different measurement result for the same artery, due to a change in vertical height between a fixed proximal (aorta) and a changing distal pressure sensor (physiology wire)

There may be potential clinical implications of this, as measurements in some arteries may be over or underestimated due to their position in a vertical plane and hydrostatic pressure effect. The change in pressure due to vertical height variations in a closed fluid loop is explained by Pascal's Law and is well documented in principles of fluid dynamics. The effect of hydrostatic pressure on physiological measurements is documented in medical textbooks, but disregarded clinically as a minor variable.

Realising that the change in position alone may alter pressure-based measurements, independent of the stenosis itself, it was clear I also had to measure flow (doppler velocity, and not pressure based) which should not be affected by position. Coronary arteries regulate flow to the heart muscle over a wide blood pressure range. This phenomenon is known as autoregulation (Ramanathan and Skinner, 2005). Therefore, despite pressure alterations when changing position, coronary arteries react to keep flow to the muscle constant. My hypothesis is therefore in two parts. Firstly, I expect pressure derived indices to change between prone and supine measurements in the same artery, across the same stenosis, as they are reliant on pressure readings. The pressure change is due to the vertical shift in an artery, when a patient moves from supine to prone. Secondly, in stable and preserved coronary physiology, with functional autoregulation, I expect flow (velocity readings) not to be altered by position change and hydrostatic effect. The study aimed at answering these questions was called GRAVITY, and was designed, written and implemented by myself. The magnitude of effect between position change was not known at study conception, with limited clinical literature. Height measurements from CT coronary angiography, obtained before invasive

research, helped gauge the size of effect, and whether its clinical impact would be relevant, and measurable in an achievable sample size.

If proven true, hydrostatic effect would affect the diagnostic tool that we use in aiding our treatment decisions, and not necessarily reflect a true change in physiology when changing position. Due to vertical variations between the coronary arteries, pressure-based indices could be confounded. This phenomenon exists in daily practice yet is widely ignored. This has the potential for misguiding treatment of coronary lesions in our patients.

The treatment of coronary artery disease is separated into acute presentations (i.e acute coronary syndrome) and stable coronary artery disease. The treatment of stable coronary artery disease is a contentious issue, re-ignited by recent evidence (ORBITA and ISCHEMIA trials).

The identification of stable coronary lesions which are ischaemic is a complex area. This has led to the development of invasive and non-invasive coronary physiology as a diagnostic aid in stenosis assessment. Both are covered in brief.

The basic concepts of pressure based coronary physiology and angiography are introduced, highlighting the underlying physical principles. A wealth of data exists for the use of pressure-based indices, and the most well-known landmark papers are described. Newer resting indices have gained clinical popularity over the past few years and form a part of the clinical methodology in the GRAVITY study. Pressure based indices have limitations and pitfalls, which are addressed. The most significant one in relation to this thesis is hydrostatic pressure.

Hydrostatic pressure theory is described, comparing the coronary circulation to a closed fluid loop system. This is a theoretical model of fluid dynamics in physical science which mirrors the coronary circulation. There is a significant lack of published literature on the subject.

The last section introduces CT coronary angiography in daily clinical practice and the specific relevance to this research. It will be preliminarily used to measure coronary height differences which produce hydrostatic effect *in vivo*. This was critical in vitro data, as the potential magnitude of effect in real patients was poorly understood. In turn, it was utilised to understand sample size

calculation, and whether hydrostatic theory could be effectively measured and demonstrated *in vivo*.

Chapter II - Methods, Results and Interpretation from CT Coronary Angiography

Data from this chapter has since been published in a peer reviewed journal (Al-Janabi et al., 2019) - see appendix G for the full paper. 100 selected CT coronary angiograms were analysed to assess the height differences between the ostium of the relative vessel, and the most distal point (where the physiology wire would be placed in a patient).

In summary, the results showed significant variation from the ostial vessel to the distal vessel in all main coronary arteries (LAD, Cx, RCA-PLV and RCA -PDA). The vertical distance data was then used to calculate an estimated hydrostatic pressure effect using a pre-defined equation. The effect of this was translated into a computer model of 100 pressure wire recordings ranging from 0.75 to 0.85. Up to 47% of these recordings were found to cross a physiological threshold of significance if corrected for hydrostatic pressure.

The data from these CT scans provided an estimation of the magnitude of effect, meaning sample size could be estimated from a power calculation. Interestingly, during the study period, similar data was published by a German group in substantially different cohort of patients (Härle et al., 2017a). Their data is compared with ours.

A pre-study case example illustrates the potential hydrostatic effect in a real-life scenario, adding further indication that a difference would exist in vivo. The stenosis shown is at a branch point, where one branch travels superiorly and another inferiorly. Each branch produces different pressure-based results, which was a re-assuring finding so early on in the study's conception.

Chapter III - Methods and Results from Invasive Physiology

The physical process of conducting this study was a significant obstacle in itself. Prone angiography is certainly not routine, and prone angiography with invasive coronary physiology had never been done before. This was new territory for everybody involved in the catheter laboratory.

This chapter outlines some of the hurdles the team had to overcome to acquire the necessary data efficiently, safely and correctly. Several trial runs were conducted in a simulated patient scenario between team members. The act of turning the patient itself is described, along with the other challenges of prone angiography (the reversal of imaging views, altered positional anatomy of the coronary arteries and comfort of the patient). There was a substantial amount of forward planning required in the case of procedural complications or events (such as cardiac arrest)

The study protocol is shown, focusing on inclusion and exclusion criteria, sample size calculation, and the physical steps taken to acquire all data. Sample traces and a description of the required equipment is also shown.

When positioned supine (standard position), the circumflex and RCA-PLV are inferior, whereas the LAD and RCA-PDA are superior. This is reversed when prone. Due to hydrostatic pressure, inferior artery position should produce higher pressure-based indices across the same stenosis when compared to superior position. It was the logical choice to therefore compare superior and inferior artery position.

The mean delta change across all values for Pd/Pa was 0.05, for iFR 0.06 and FFR 0.06. These are all statistically significant ($p < 0.05$).

In a subset of patients, FFR measurement were taken in a more 'clinical' position, i.e. less distal than outlined in the study protocol. The clinician placed the wire where they would normally during a routine case. There was a mean delta change of 0.06 in a subset of LAD stenoses which was statistically significant ($p<0.05$). The aim of this was to show that even when the wire was less distal and under lesser hydrostatic effect, the magnitude of effect was still significant.

There was no change in doppler flow velocity at rest or during hyperaemia across all territories. The findings correlate with the initial hypothesis that the change in pressure-based indices do not

necessarily reflect a true change in coronary physiology, but rather the tool that is used in the assessment of a coronary stenosis. There is an inherent flaw in current pressure-based technology which makes it susceptible to hydrostatic pressure effect in the coronary circulation. This may over or underestimate stenosis severity. Doppler flow, which is a surrogate for coronary flow did not change, meaning this is not a true physiological change between prone and supine positioning.

Correlation graphs shown at the end of the chapter show a trend but no significant correlation between guide to wire distance and delta change in FFR, Pd/Pa and iFR. From combined data, it appears that predicted changes in hydrostatic pressure from CT data, correlate closely with actual changes seen in vivo overall.

Chapter IV - Discussion

Chapter IV highlights differences in demographic and angiographic data. The rationale behind significant changes in pressure-based indices and non-significant doppler flow measurements are discussed. Potential explanations are offered for the lack of correlation between guide to wire distance and delta change in Pd/Pa, iFR and FFR.

The clinical implications of the data are discussed. This includes the lack of a 'level playing field'. There will be a resting gradient before the introduction of any stenosis, due to hydrostatic pressure alone. This confounds measurements using pressure-based indices.

If the already existent pressure gradient is corrected, up to 36% of pressure-based indices will re-classify across a significance threshold. The changes may appear small (0.05-0.06), but clinically appear to be important. Hydrostatic pressure effect may also be important in other clinical situations, such as in diffuse coronary disease, and in the measurement of IMR.

Suggestions are made in how clinical practice could be changed to correct for hydrostatic effect. Adding or subtracting from measured FFR results could produce a more accurate result. The addition of a single correction factor per vessel is unlikely to be adequate on its own, and more data is required to 'map' hydrostatic effect at multiple points in each vessel. In vivo, this would require pressure wire measurements in normal coronary arteries, which is ethically unfavourable. Retrospective CT coronary angiograms may be useful in providing raw height data at multiple points in a single artery, which could then be converted to pressure change at proximal, mid and distal vessel. Limitations with the current study are discussed. Topics surrounding anatomical FFR (CT and Angio FFR) are discussed. These methods are not confounded by hydrostatic effect but have their own flaws.

Study limitations and counter arguments are highlighted. Very recent evidence has emerged during the study period, with studies similar to the current research adding to the data pool. Data between studies are compared.

Finally, future plans are suggested, leading back to the initial research question proposed three years ago. STEMI patients and CTO patients are possible next steps. Vessel mapping with further CT scanning could allow provide further information on hydrostatic correction per section of artery. The advent of newer pressure wires which are immune to hydrostatic pressure is an exciting possibility for the future. The basic principle behind these wires is described.

Chapter I - Introduction

Percutaneous coronary intervention (PCI) is the mainstay of treatment for acute coronary syndromes (ACS), specifically ST elevation myocardial infarction (STEMI). The treatment of

chronic coronary syndromes (CCS - ESC Guidelines on Chronic Coronary Syndromes (Previously titled Stable Coronary Artery Disease), 2020) is more complex and requires expert clinical decision making. Diagnostic aids such as fractional flow reserve (FFR) have been used for over two decades as diagnostic tools, to guide this decision-making process. The impact of hydrostatic effect on these measuring tools is unknown.

A general overview of coronary artery disease pathology, prevention, medical treatment and future implications is described in Appendix A. Below is a brief introduction to ACS, CCS, diagnosis and invasive treatment of coronary artery disease. Ischaemia testing, invasive and non-invasive, are critical in lesion selection for treatment. Invasive testing (Pd/Pa, iFR and FFR) and the potential confounding factor of hydrostatic pressure are the focus of this research.

1.1 - Acute Coronary Syndrome

Three presentations are classed as acute coronary syndromes (ACS). They are; ST elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA).

1.1.1 - ST Elevation Myocardial Infarction

In ST elevation myocardial infarction, occlusion of a coronary artery causes ST segment elevation and a classically recognisable ECG pattern (Figure 1). Biomarkers such as troponin are raised.

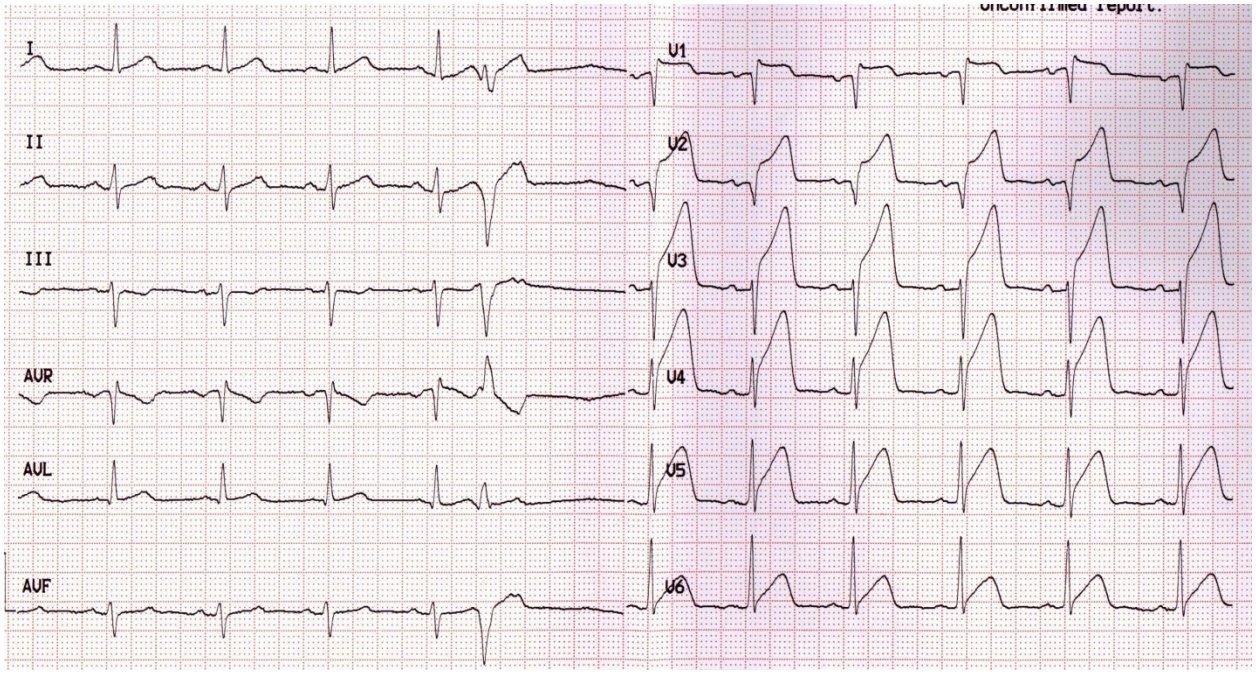


Figure 1 - STEMI ECG - an ECG of a patient attending the Essex Cardiothoracic Centre with an anterior STEMI (ST elevation myocardial infarction). Notice the raised ST segments in leads V1-V5 (consent obtained for image use).

The treatment for this presentation is immediate restoration of blood flow in the infarct related artery (IRA). The initial treatment for this was administration of a thrombolytic drug, but this has since been surpassed by primary percutaneous coronary intervention (PPCI) (Schömig et al., 2000; Le May et al., 2001; Busk et al., 2008). The main aim of treatment is reduction in infarct size, which has profound impacts on mortality and morbidity (Sobel et al., 1972; Stone et al., 2016).

The most serious presentation is with cardiac arrest, caused by ventricular arrhythmia as a consequence of myocardial ischaemia. These patients are at higher risk of mortality (Siudak et al., 2012; Demirel et al., 2015; Kvakkestad et al., 2018), should they reach hospital, of which a high proportion (approximately 75%) unfortunately do not (Perkins and Cooke, 2012). Survival to discharge is 5-8% from out of hospital cardiac arrests (Nichol et al., 2008; Perkins and Cooke, 2012)

The time to reperfusion holds prognostic value, with data showing reperfusion within two hours is important for left ventricular recovery and survival (Brodie et al., 1998). Before primary angioplasty, thrombolysis was shown to provide a clear survival advantage for patient suffering

with STEMI (Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group, 1994). There was an early hazard associated with thrombolysis use within the first 24 hours, which was vastly outweighed by the survival benefit thereafter.

Currently, the preferred method of reperfusion is Primary PCI (PPCI) and this has replaced thrombolysis in areas where tertiary cardiac centres are accessible within 30 minutes to an hour. Early trials showed improved outcomes when using PPCI compared to thrombolysis, leading to a reduction in mortality and re-infarction, as well as intracranial haemorrhage (Grines et al., 1993). Similar trials at the time demonstrated improved vessel patency at follow-up and higher left ventricular (LV) ejection fractions (EF) (Zijlstra et al., 1993).

Two randomised controlled trials comparing PCI and thrombolysis followed in 1997 with Gusto IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators, 1997) and 2003 with DANAMI-2 (Andersen et al., 2003). Gusto IIb demonstrated a significant difference favouring PCI in the composite endpoint of death, non-fatal myocardial infarction and non-fatal stroke in 1138 patients presenting within 12 hours for treatment. DANAMI-2 further supported the use of PCI in STEMI with a reduction in the composite endpoint of death, stroke and re-infarction. The composite endpoint was largely driven by much lower re-infarction rates in the PCI group, with no significant difference in mortality or stroke. The benefit was still seen after 8 years of with regards to the primary endpoint, however subsequent analysis showed mortality was also reduced in the PCI arm (Andersen et al., 2003).

A review of 23 trials comparing thrombolysis to angioplasty, totalling 7739 patients showed again superiority favouring angioplasty with lower mortality, re-infarction and stroke, independent of the thrombolytic agent used, which was maintained over long term follow-up (Keeley, Boura and Grines, 2003).

1.1.2 - Non-ST Elevation Myocardial Infarction and Unstable Angina

NSTEMI represent a group with vulnerable coronary plaques which have caused partial or total vessel occlusion. Blood has usually spontaneously been restored by the time of presentation (Kumar and Cannon, 2009). Re-occlusion could occur at any time, meaning prompt treatment within 48 hours is usually recommended. Biomarkers are raised, indicating myocyte damage or stress. An important differentiation which has clinical implications is the formation of clot in both STEMI and NSTEMI. In NSTEMI, clot is usually white, and formed predominantly of platelet rich aggregates. This is in contrast to STEMI, where clot is usually red, and formed predominantly of red blood cells (DeWood et al., 1980; Quadros et al., 2012).This alters clinical management, as medical therapy in NSTEMI is centred around platelet inhibition, which allows endogenous fibrinolysis to break down the thrombus (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators, 1998).

Lastly, unstable angina is only differentiated against NSTEMI by the lack of raised biomarkers. The most commonly used biomarker is troponin, although other biomarkers can be used with different properties, including time to peak concentration. Figure 2 demonstrates this.

Since the arrival or coronary stents, randomised control trials have compared optimal medical therapy, with coronary stenting (usually within 48 hours) and the effect on patient prognosis. A large trial of over two thousand patients published in 2001 demonstrated benefit in using early invasive coronary stenting for NSTEMI and UA over optimal medical therapy, with a reduction in mortality, myocardial infarction and re-hospitalisation for acute coronary syndrome (Cannon et al., 2001). The results were mirrored one year later, in a similarly sized trial, but the composite endpoint was significant mainly due to the reduction in on-going angina. Death and myocardial infarction rates were similar in both groups at 1 year follow-up (Fox et al., 2002). The same group of patients underwent follow-up at 5 years, and revealed significant benefits for the stent treatment group in relation to death and myocardial infarction (Fox et al., 2005). The benefit appears to be in the medium and long term, and maybe counter-acted in the first year by the increased risk of an invasive procedure.

The FRISC-II study followed patients for 15 years, who either underwent and invasive or non-invasive strategy for NSTEMI. At 15 years, patients who had invasive treatment postponed the

occurrence of death or myocardial infarction by 17 months, and re-admission by 17 months (Wallentin et al., 2016).

A meta-analysis of invasive versus non-invasive treatment in the stenting era was conducted by Hoenig et al. in 2006 (Hoenig et al., 2006) consisting of nearly eight thousand pooled participants. The results showed that during hospital admission, there was a trend towards hazard with an invasive strategy, but it was not statistically significant. There was a peri-procedural two-fold increase in risk of myocardial infarction and 1.7-fold increase in bleeding. When comparing long term outcomes (> 1 year) there was a significant reduction in death, non-fatal myocardial infarction and rehospitalisation in the invasive group (Hoenig et al., 2006).

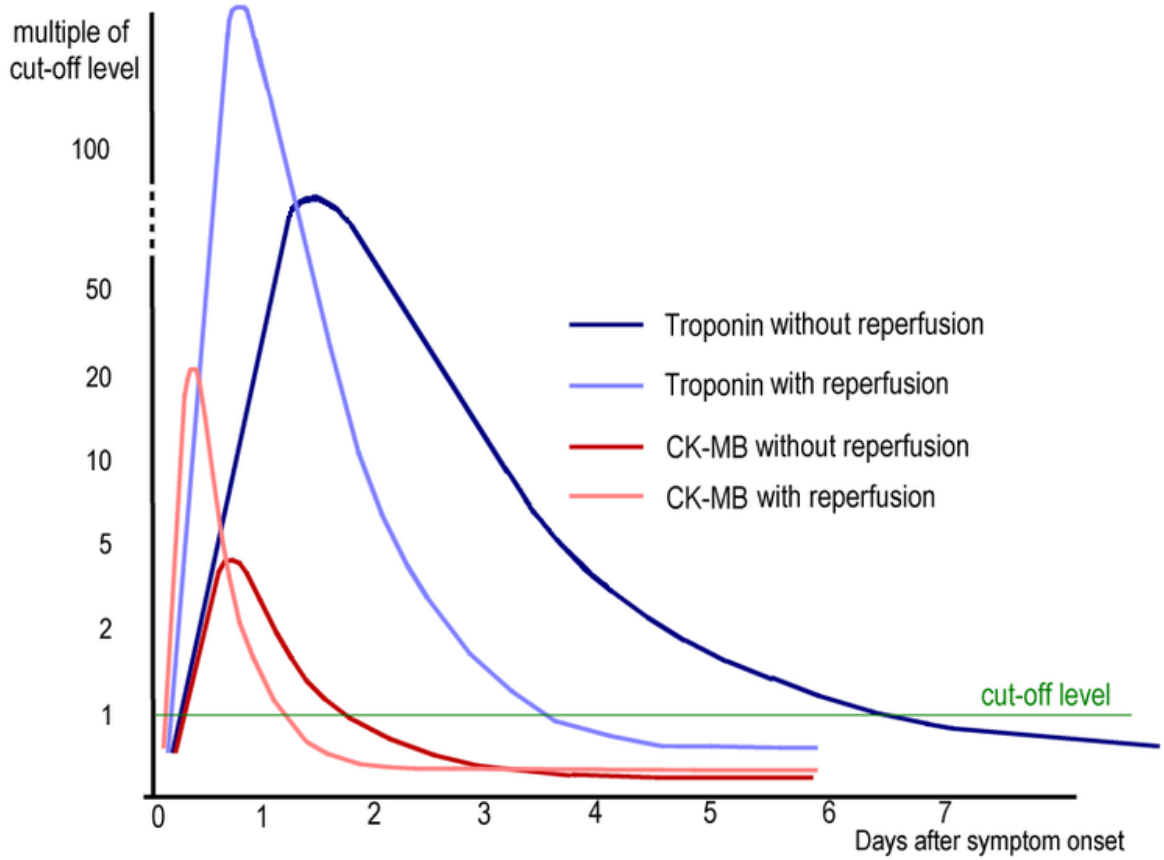


Figure 2 - Cardiac Biomarkers - Biomarker peaks and troughs shown against time. CK-MB (Creatine Kinase Muscle/Brain) peaks and falls earlier than troponin. (J. Heuser JHeuser (https://commons.wikimedia.org/wiki/File:AMI_bloodtests_engl.png), AMI blood testsengl, https://creativecommons.org/licenses/by-sa/3.0/legalcode).

1.2 - Chronic Coronary Syndrome

Stable angina by definition is the presence of cardiac chest pain on exertion or with emotional stress, which is relieved by rest or administration of nitroglycerin (Ohman, 2016).

The assessment and treatment of stable coronary artery disease has been a fierce topic of debate for decades. The role of coronary stenting as opposed to medical therapy in stable coronary artery disease remains controversial. This controversy has driven technological expansion, leading to huge interest in the assessment of stenosis severity, which is the basis of this study and thesis.

Coronary stenting has been compared with optimal medical therapy (OMT) in multiple randomised controlled trials. Results have been mixed, but no single trial has shown a reduction in mortality or rate of myocardial infarction, from the use of coronary stents (Al-Lamee, Davies and Malik, 2016).

The COURAGE trial, published in the New England Journal of Medicine in 2007, was one of the first landmark trials comparing OMT to PCI over a five-year follow-up period. There was no reduction in death or non-fatal myocardial infarction when comparing PCI to OMT. There was however a significant difference in the need for revascularisation, favouring the PCI group. There was also a numerical difference in the amount of patients who were angina free, again favouring PCI, although this did not reach statistical significance (Boden et al., 2007).

MASS II was a triple armed trial comparing OMT, coronary artery bypass grafting and PCI. PCI was found to be superior to medical therapy over a 10-year follow-up period, with regards to incidence of angina. Myocardial infarction rate favoured the use of PCI but was not statistically significant (Hueb et al., 2010).

BARI-2D was a trial in diabetic patients, randomised to OMT or PCI. PCI showed demonstrable benefit with regards to reduction in angina, and rate of revascularisation. There was no difference in death or myocardial infarction (BARI 2D Study Group et al., 2009).

From the three trials above, two showed a significant reduction in rates of angina, and two the need for repeat revascularisation. None showed a mortality difference, with one showing a reduction in myocardial infarction rate in diabetic patients. It is worth considering the limitations of these

randomised control trials, including the use of older PCI techniques, high rates of crossover from OMT to PCI groups, and the possibility of bias, due to the un-blinded nature of the trials. It has also been proposed that study power was not enough to meet the endpoint of mortality and softer endpoints such as symptom severity are subjective. More recent studies have attempted to use exercise time as a more reliable end-point for symptomatic relief after PCI, but showed no statistical improvement over OMT (Al-Lamee et al., 2018).

Meta-analyses have supported the use of PCI in the relief of anginal symptoms, with a significant reduction in angina with the use of PCI. Again, mortality and myocardial infarction rates did not differ between the two groups and the limitations outlined above were highlighted (Pursnani et al., 2012).It is also worth noting that other meta-analyses have shown no difference between PCI and OMT across all end-points, including mortality and rates of angina, myocardial infarction and need for revascularisation (Stergiopoulos et al., 2014).

Symptomatic relief is the main clinical indication for PCI in the context of stable angina. UK and European guidelines suggest PCI for anginal symptoms only after a trial of medical therapy (Stable angina: management | Guidance and guidelines | NICE, 2018; Montalescot et al., 2013). Medical therapy is often under prescribed however, with some studies showing up to 50% of patients are only taking one anti-anginal medication, with a third taking none (Borden et al., 2013). There is also the issue of medication compliance, which is difficult to accurately measure. ORBITA, a recent trial conducted in the UK with strict enforcement of medical therapy demonstrated no increase in exercise time with PCI compared to medical therapy (Al-Lamee et al., 2018). There was strict medical optimisation over a 6-week period, which is difficult to replicate in NHS patients. There was however a reduction in ischaemia assessed by stress echocardiography after PCI.

Very recently, the ISCHEMIA trial randomised patients to medical therapy or invasive treatment (stenting or surgery), based on demonstrable non-invasive ischaemia testing only (ISCHEMIA Trial Research Group et al., 2018). Provisional results were presented at the American Heart Association (AHA) conference, in November 2019. Interestingly, the invasive arm did not provide benefit with regards to reducing mortality, reducing the rates of myocardial infarction, improving anginal symptoms or quality of life. It has shown for the first time that medical therapy alone for

ischaemia may be a suitable alternative, without knowing coronary anatomy. Patients were permitted to have revascularisation for refractory symptoms, of which 23% did at 4 years.

ISCHEMIA has divided opinions. Ischaemia on an appropriate testing modality plus refractory angina probably favours invasive treatment, unless there is a significant contraindication. However, treatment decisions in patients with ischaemia or symptoms only, is less clear. There is still substantial debate on how to interpret the trial results (Murthy and Eagle, 2018).

1.3 - Assessing the Coronary Circulation

1.3.1 - Diagnostic Coronary Angiography

The focus of this thesis is the change in physiological measurements when comparing prone and supine patient positioning during angiography. To position the wire and conduct the procedure, a baseline coronary angiogram is needed.

Coronary catheterisation was first conducted in man by Werner Fossman in 1928, who passed a 65cm urinary catheter into his own cubital vein, until he felt it reach the right atrium (Meyer, 1990). With the catheter hanging from his arm, he walked to the hospital basement to take an X-ray and confirm its position (Figure 3). The first selective coronary angiogram, however was described by Dr. Mason Sones in 1958. Hand injected contrast media was passed into the right coronary artery of a middle aged man by accident whilst trying to image other cardiac structures (Ryan, 2002).

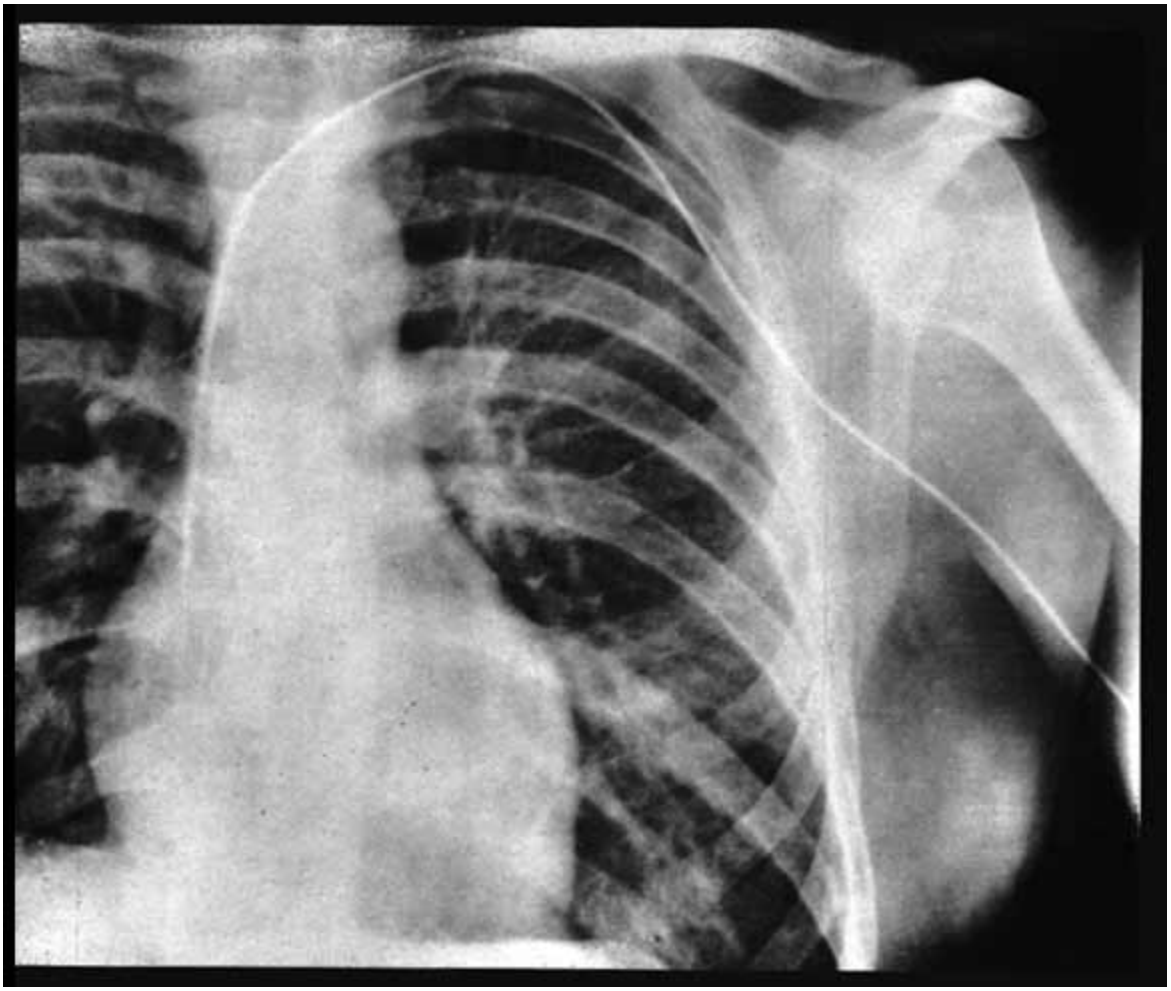


Figure 3 - Original X-ray of a urinary catheter in Werner Forssman's right atrium (Meyer, 1990)

1.3.2 - Basic Concept

The aim of a coronary angiogram is to identify luminal obstruction or narrowing of a coronary artery. This is done by injecting iodinated contrast media directly into an artery, under X-ray supervision to create an 'outline' of the vessel and identify stenosis. Access is usually gained via the right radial artery (85-90% at our institution but left can also be used). Initially femoral access was the method of choice but has been steadily replaced with radial access unless larger catheters are required.

Three main coronary arteries exist. The left anterior descending artery (LAD), circumflex artery (Cx) and right coronary artery (RCA). The LAD and Cx normally originate from the left coronary ostium, and the RCA from the right coronary ostium. Both of these ostia originate from the aorta as it leaves the left ventricle and lie above the aortic valve. Figure 4 demonstrates this. The anatomy and position of these arteries is important with relevance to this research, as they are in different vertical planes in a supine patient.

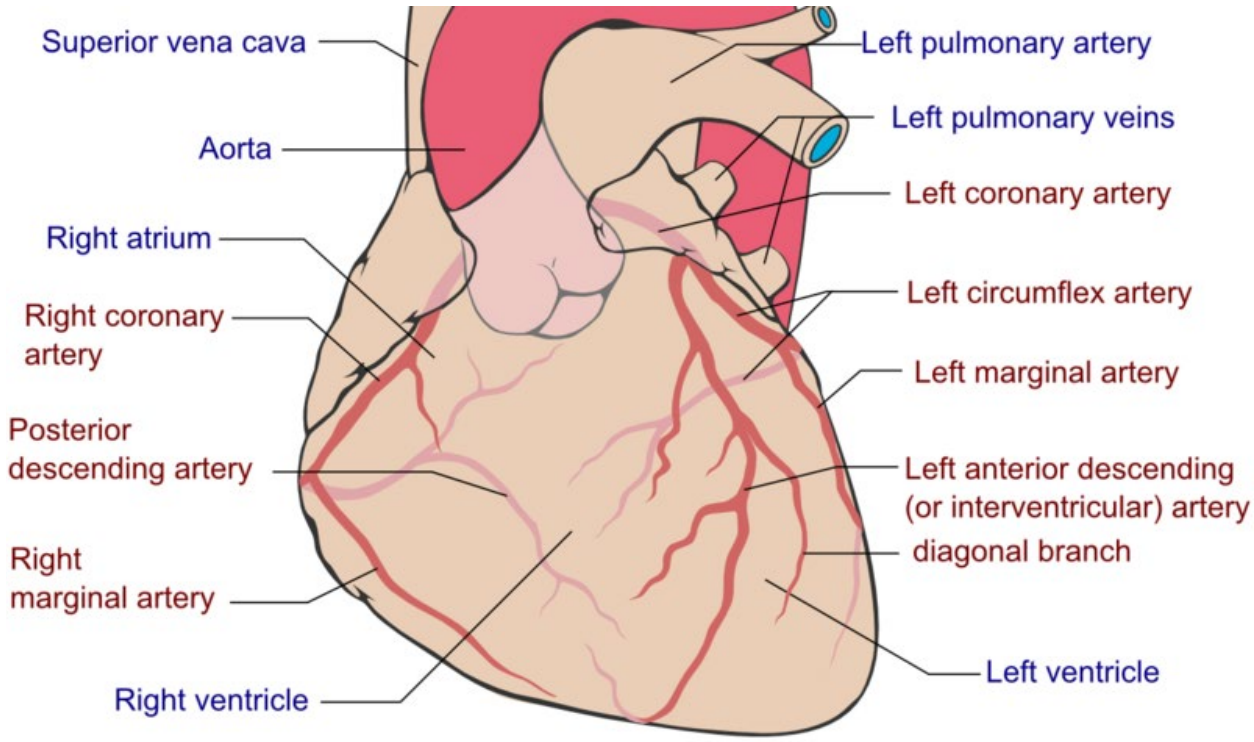


Figure 4 - coronary anatomy showing coronary arteries and major cardiac venous and arterial vessels
(Coronary.pdf: Patrick J. Lynch, medical illustrator derivative work [1]: (https://commons.wikimedia.org/wiki/File:Coronary_arteries.png) Coronary arteries, https://creativecommons.org/licenses/by-sa/3.0/legalcode)

1.3.3 - Contrast Injection

Iodinated contrast media is necessary for acquisition of X-ray pictures, as the contrast fluid is x-ray dense (Figure 5). The main concern regarding contrast use is the potential nephrotoxic effects, the most serious of which is contrast induced nephropathy (CIN). In turn, development of CIN has short and long term impacts on morbidity and mortality (Wi et al., 2011), (James et al., 2013). This was of importance with regards to the study protocol due to the extra measurements compared with standard care. The extra measurements inevitably meant higher contrast use for wire positioning and lesion visualisation. The incidence of CIN in elective patients is <3.5% (Rihal et al., 2002). For this reason, patients with significant baseline kidney dysfunction were excluded, as this is the most important risk factor for the development of CIN (Nash, Hafeez and Hou, 2002).

Many contrast agents exist, but all are iodine based. The pathophysiology of CIN is complex and not completely understood, but culminates in hypoxia in the renal medulla, and eventually cell death (Wong et al., 2012). The osmolality (measure of the number of dissolved particles in a fluid) of contrast media, appears to have an impact on the risk of developing CIN. Contrast agents are divided into high, low or iso-osmolar (highest to lowest osmolality respectively). Meta-analyses have shown a risk reduction in the development of CIN when using low osmolar versus high osmolar agents (Barrett and Carlisle, 1993), and iso-osmolar versus low osmolar agents (McCullough et al., 2006). In our study patients, all received Visipaque™ which is classed as iso-osmolar, and from current evidence, the safest agent available for use. There is clear evidence that volume of contrast media is correlated to the risk of developing CIN (Davidson et al., 2006).

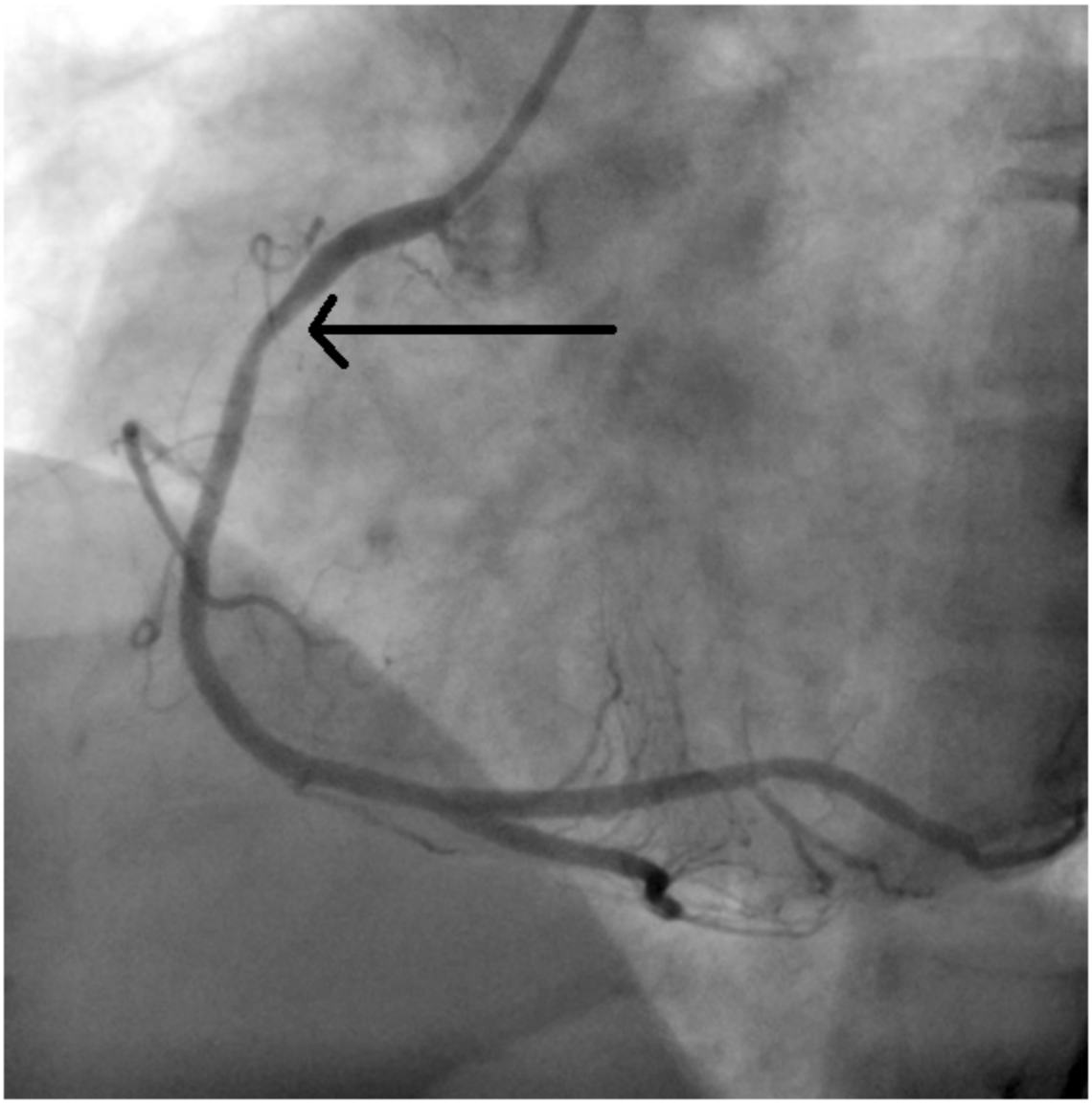


Figure 5 - A right coronary artery injection, from a patient attending the Essex Cardiothoracic Centre. Contrast injection is shown in black, filling the coronary catheter, and the coronary artery. There is a mild stenosis in the proximal segment.

1.3.4 - Fluoroscopy

The X-ray equipment can rotate 180 degrees in an anterior/posterior and lateral fashion, giving different views of the coronary arteries. Radiation injury is a known risk of exposed x-ray use.

This is more commonly seen in complex interventions, and we did not expect to see such complications during the study protocol. Injury can range from skin damage to necrosis of underlying structures (Wagner, 2007). Radiation doses are carefully monitored for staff and patients, any high dose procedures are reported to a central regulatory body.

1.4 - Percutaneous Coronary Intervention

With advances in coronary angiography, the focus of early pioneers turned to whether stenoses could be treated percutaneously, rather than with open heart surgery. The first coronary artery bypass graft was conducted in 1960, with the procedures becoming more widespread in the late 1960's (Head et al., 2013). The first percutaneous coronary intervention was conducted much later, by Andreas Gruentzig, hailed as the 'father' of coronary angioplasty (Grech, 2003) in 1977, who treated a left anterior descending artery lesion in a 38 year old male with simple balloon angioplasty.

Since then, advances in coronary intervention have meant more selective coronary catheters, coronary guidewires, balloon technology with higher pressure tolerance and lower profiles, as well as huge leaps in coronary stent technology.

1.4.4 - Balloon Angioplasty and Bare Metal Stents

Coronary stents revolutionised the treatment of coronary artery disease. The first coronary lesions were treated with plain old balloon angioplasty. While this was a landmark step is angioplasty as a whole, balloon angioplasty was compromised by acute vessel closure and re-

stenosis (Bauters et al., 1996). Coronary stents were introduced to prevent elastic recoil in the vessel, and seal dissection flaps cause by POBA, with the aim of counter acting these issues.

The very first stents to be used in man were stainless steel (BMS - Bare Metal Stent) and balloon expandable, being used predominantly in the early 1990's (Iqbal, Gunn and Serruys, 2013). As hoped, they did reduce early elastic recoil (and hence acute vessel closure), as well as restenosis (de Feyter, de Jaegere and Serruys, 1994). The early stents were not without flaws. There was a risk of stent thrombosis due to the high metallic density, and being large and technically difficult to deliver had a frequent failure rate by today's standards (de Feyter, de Jaegere and Serruys, 1994). Furthermore, even though the restenosis rate was less than POBA, it was still seen in a third of patients in early studies (de Feyter, de Jaegere and Serruys, 1994). The initial use of stents was therefore limited to acute closure or restenosis after POBA.

Two landmark trials published in 1993 BENESTENT (Serruys et al., 1994) and STRESS (Fischman et al., 1994) established BMS to be superior to POBA, driven mostly by reduced rates of revascularisation in the stenting group. This led to an exponential increase in stent use, meaning 80-90% of angioplasty cases utilised stents by the late 1990's (Serruys, Kutryk and Ong, 2006).

In these landmark trials, there still remained a significant rate of restenosis, despite BMS' superiority over POBA. The issue of elastic recoil had largely been addressed, but smooth muscle cell proliferation causing restenosis had to be addressed for medium and long term prognosis.

1.4.2 - Drug Eluting Stents

Pharmacological agents were used in an attempt to limit smooth muscle proliferation and local inflammation. Early attempts to cover stents in gold, carbon and heparin did not confer any benefits (Iqbal, Gunn and Serruys, 2013). The breakthrough came when stents were coated with the anti-proliferative agents sirolimus and paclitaxel, which were both shown to reduce smooth

muscle cell proliferation and migration (Poon et al., 1996; Axel et al., 1997). The addition of these drugs to a polymer allowed drug release over several weeks, and in turn, the first sirolimus eluting stent (CYPHER™, Cordis Medical, Milpitas, California, United States) was implanted in 1999. It became available for clinical use in 2002, followed closely by a paclitaxel eluting stent (TAXUS™, Boston Scientific, Marlborough, Massachusetts, United States). Both stents underwent numerous randomised controlled trials and proved superior to BMS in reducing rates of restenosis (Morice et al., 2002; Moses et al., 2003; Stone et al., 2004).

Since the first generation of drug eluting stents (DES), adaptations have been implemented aiming to make them more deliverable, with some incorporating differing pharmacological agents (e.g. zotarolimus, everolimus, biolimus), improved drug polymers, and thinner stent struts (Serruys et al., 2010). Evidence from meta-analyses demonstrate a benefit of second generation DES over first generation DES with regards to stent thrombosis, and repeat revascularisation rates, but not death or myocardial infarction (Park et al., 2013).

1.4.3 - Drug Eluting Stents vs. Bare Metal Stents

Drug eluting stents generally require a longer duration of antiplatelet treatment, due to the extended period of exposed stent struts. Recent data however has shown the safety in reducing antiplatelet duration in current generation DES (Windecker et al., 2020), providing an apparent safe alternative. In some clinical situations, bleeding is a potential issue, or more urgent cessation of antiplatelet medication is required. Here, a risk benefit decision needs to be made, individual to the patient and clinical situation. Shorter lesions (<20mm) with a larger vessel diameter (>3mm), appear to have similar outcomes when comparing BMS to DES in some studies.

Patients with diabetes mellitus are at risk of accelerated restenosis, and data supports the use of DES in this subgroup. The use of DES was associated with lower rates of mortality, myocardial infarction and revascularisation when compared to BMS (Garg et al., 2008). This stance has been

supported by large meta-analyses (Bangalore et al., 2012), regardless of vessel size or lesion length.

1.5 - Risks of Percutaneous Coronary Intervention

Percutaneous coronary intervention, by necessity requires a diagnostic coronary angiogram to visualise the lesion for treatment. Therefore, the baseline risks of coronary angiography are inherent in the procedure (approximately 1 in 1000). Instrumentation of an artery with coronary guidewires and balloons plus subsequent stent implantation brings about additional risks (quoted 1 in 100 during patient consenting process). The risks are described in detail in Appendix B.

Mentioning risk is important, as it forms a critical part of the decision making process regarding the treatment of a coronary lesion. This in turn has led to the use of tools to assess the significance of a stenosis and whether there is a need to put patients at risk of a PCI procedure.

1.6 - Identifying Significant Lesions in Stable Coronary Artery Disease

The focus of onward discussion will be the patient demographic for this study - chronic coronary syndrome. The decision to treat a lesion is based on two questions:

1. Does the patient have an indication for invasive treatment of their coronary artery disease?

2. Do the benefits of invasive treatment, outweigh the risks?

The severity of a stenosis on coronary angiogram correlates poorly with coronary physiology (Adjedj et al., 2017). This is known as angiographic ambiguity. Physiological evidence of ischaemia is usually necessary in the decision making process. Even with evidence of ischaemia however, decisions are not binary.

Data from recent trials, ISCHEMIA (ISCHEMIA Trial Research Group et al., 2018) and ORBITA (Al-Lamee et al., 2018) suggest no significant difference in optimal medical therapy plus invasive treatment for proven ischaemia or angina symptoms over optimal medical therapy alone. This is still not widely accepted, as earlier trials outlined below demonstrate benefit. Treatment is tailored to the individual, taking into account multiple factors. To complicate matters further, there are multiple modalities of ischaemia assessment (invasive and non-invasive).

1.7 - Non-Invasive Ischaemia Assessment

Although not the focus of this research, non-invasive ischaemia tests are clinically relevant. These tests should not be affected by hydrostatic effect as they do assess stenosis within a closed fluid system. This has important implications if hydrostatic effect is found to be a true confounding factor during this research, as such tests may be a viable alternative.

In the United Kingdom, non-invasive ischaemia assessment is still widely used. Exercise treadmill ECG was widely used but has largely been phased out. In recent times, stress echocardiography, myocardial perfusion scanning, and stress cardiac MRI (CMR) have gained popularity. A negative test for either of these modalities is a good prognostic indicator of future cardiac events (Smulders et al., 2017) whilst being extremely safe.

The above modalities look for ischaemia during cardiac stress. CT coronary angiography (CTCA) is a well-known imaging modality that provides anatomical data instead. It has a strong negative predictive value of 97-99% (Budoff et al., 2008). Although CTCA is not strictly an

ischaemia test, algorithms have been recently implemented to use the anatomical images CT provides to produce a measure of ischaemia non-invasively, known as CT FFR.

1.7.1 - CT FFR

Previous studies have shown that CT FFR correlates well with invasive FFR (r = 0.82) (Nørgaard et al., 2014) although discordance is still approximately 15%. Such studies use computer generated fluid dynamic models to generate a non-invasive FFR value. Such models aim to factor in the effects of hyperaemia, microvascular resistance and cardiac output. Inevitably, CT FFR uses generic parameters of heart, systemic and microcirculation, superimposed onto patient specific coronary CT images to produce a CT FFR (Taylor, Fonte and Min, 2013). This assumes patients 'fit' into these generic parameters, and ignore other variables such as LVEDP, wedge pressure, hyperaemic response and hydrostatic effect.

The PROMISE trial (Lu et al., 2017) took patients who proceeded to invasive coronary angiography from a standard CT coronary angiogram, and correlated a CT FFR <0.8 with coronary revascularisation or major adverse cardiac events (MACE). Patients with a CT FFR of <0.8 were more likely to have revascularisation or MACE compared with CT FFR >0.8. Also those with CT FFR <0.8 were significantly more likely to receive revascularisation when compared to severe stenosis on CTA alone. Lastly, it was suggested that CT FFR may reduce the number of referrals for invasive angiography nearly half, using <0.8 as a threshold. It is noteworthy that of all patients screened for PROMISE, approximately half had to be excluded for multiple reasons, including inadequate imaging.

1.8 - Invasive Ischaemia Assessment

Fractional flow reserve (FFR) is the most widely used invasive physiology tool in clinical cardiology. Newer resting indices such as instantaneous wave free ratio (iFR) have gained

popularity over recent years. In acute presentations of coronary artery disease (ACS), the risk of revascularisation is often outweighed by the risk of leaving a vulnerable plaque untreated. In chronic coronary syndromes, ischaemia assessment forms a vital part of the decision to treat.

1.8.1 - History of Invasive Coronary Physiology

Many types of intracoronary indices exist, and have been studied, dating back to 1974 when Gould proposed a measurement known as coronary flow reserve (CFR), using velocity measurements. The term coronary flow reserve, can be found dating further back, to 1963 (Johnson, Kirkeeide and Gould, 2015). The term gained interest in 1974 as it linked CFR to anatomical stenosis in canine studies, and demonstrated the heart's ability to increase blood flow, versus several different severities of coronary stenosis (Gould and Lipscomb, 1974). CFR is calculated by measuring coronary flow during hyperaemia and dividing by flow at baseline. This gives a ratio above one, describing how much flow can be augmented, when there is myocardial demand. The first study in 1974 even hinted that a CFR of less than 1.5 may be an indication for bypass surgery, suggesting a clinical use in decision making. CFR was studied in 1997, in the DEBATE trial, showing CFR had a modest predictive value for patients who would benefit from coronary angioplasty based on a CFR of less than 2.5 (Serruys et al., 1997).

CFR use fell in the late 90's when pressure-based systems such as FFR became more available. Even with advances in doppler technology, pressure-based systems are quicker and more robust to use compared to doppler based systems, leading to a significant rise in their popularity.

Fractional flow reserve, a pressure-based measurement, was first described experimentally in 1993 by Pijls and De Bruyne (Pijls et al., 1993). Pressure based indices before FFR often used resting conditions and measured pressure gradients across a stenosis. The concept was simple; a stenosis creates a pressure difference between the proximal section of the artery, and the section distal to the stenosis. The difference is known as the gradient and indicates the severity of the stenosis. Pd / Pa is often described as a ratio between 0 and 1.Grüntzig applied this concept in 1979 on 32 patients who underwent percutaneous balloon angioplasty (Grüntzig, Senning and Siegenthaler, 1979). Wijns also conducted similar research in 1985 (Wijns et al., 1985). Resting

indices have been superseded by FFR, but have made a re-appearance in recent research, and will be described separately. Figure 6 demonstrates a resting stenosis measurement, known as Pd (distal pressure) over Pa (aortic / proximal pressure).

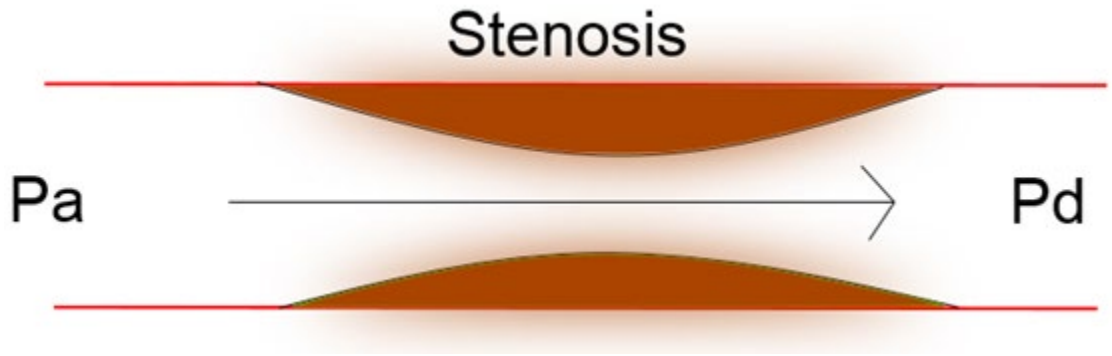


Figure 6 - demonstration of Pa and Pd. Pd / Pa gives a ratio which is used to assess stenosis severity

A major breakthrough came with the introduction of coronary vasodilators, culminating in the use of adenosine in 1990 (Wilson et al., 1990) and in turn FFR. These agents induce hyperaemia, which is critical for lesion assessment. Adenosine and hyperaemia, induce a closer physiological state to exercise, than a resting state. Furthermore, coronary autoregulation maintains coronary flow over a wide blood pressure range by adjustment of coronary resistance (mostly from the microcirculation). Using vasodilatory agents, reduces resistance to a steady minimal state, allowing us to isolate the stenosis and assess a change in pressure gradients, once autoregulation is inhibited (Johnson, Kirkeeide and Gould, 2015; Blows and Redwood, 2007). This is the functional basis of fractional flow reserve.

1.8.2 - The Theory of Fractional Flow Reserve

FFR was first reported in the literature in 1993, building on previous work of coronary flow reserve (Pijls et al., 1993). The model was initially validated in dogs, and later validated in human coronary arteries in 1994 (De Bruyne et al., 1994).

The aim of FFR is to ascertain whether a stenosis is flow limiting, using pressure-based measurements (instead of flow). CFR had been well validated at this point and the underlying concept of both is similar. They both use maximal flow as an indication of stenosis severity. CFR uses flow-based measurements to provide information on how much an artery can augment flow compared to baseline, in the presence of a coronary stenosis. Less flow, suggests a more significant stenosis. FFR on the other hand uses pressure-based measurements during maximal flow or hyperaemia, distal to a stenosis, and compares it to a pre-stenotic measurement. It is Pd over Pa, as demonstrated in figure 6, during the administration of a vasodilator (adenosine) to produce maximal and steady state hyperaemia.

FFR is thought to have advantages over CFR in multiple ways. Velocity based measurements are less robust, and take longer to acquire than pressure based measurements (Pijls et al., 1993). Furthermore, CFR utilises two different states of physiology (baseline and hyperaemia) as a ratio against each other. This means a CFR result could be due to alterations in either state, not necessarily just one. Furthermore, the overall physiological state of the patient has an effect on CFR calculations, with variable factors including blood pressure and heart rate (Gould, Kirkeeide and Buchi, 1990). FFR is thought to be more reproducible with these issues and provide a more isolated measurement for the stenosis in question.

1.8.3 - Pressure and Flow

The coronary circulation has a strict autoregulatory system. A reduction in pressure, is not proportional to a reduction in myocardial blood flow, due to changes in vascular resistance in the

coronary bed (Ramanathan and Skinner, 2005). This concept is described in physical principles and follows the same concept as Ohm's law (Figure 7).

$$V = I \times R$$

$$\text{Voltage} = \text{Current} \times \text{Resistance}$$

Figure 7 - Ohm's law. Voltage is the product of current, multiplied by resistance.

Ohm's law can be applied to the cardiovascular system. Voltage is replaced by pressure and current by flow. The result is shown in Figure 8.

$$\text{Pressure} = \text{Flow} \times \text{Resistance}$$

$$P = Q \times R$$

Figure 8 - Ohm's law, applied to the cardiovascular system. This forms the basis of autoregulation.

Autoregulation can be explained using the equation in Figure 8. If pressure drops, and flow is to remain constant, resistance must decrease, and vice versa. However, when maximal hyperaemia is applied, resistance is assumed to me minimal and constant, inhibiting autoregulation. In turn, a change in pressure becomes proportional to a change in flow (Figure 9).

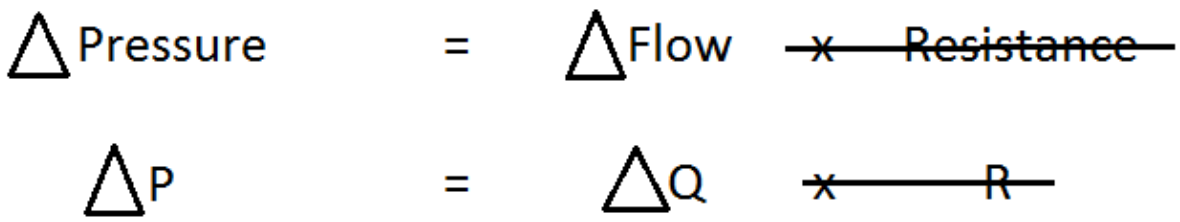


Figure 9 - at maximal hyperaemia, when resistance is minimal and constant, a change in pressure can be said to be proportional to a change in flow. Triangles represent the sum of change

In the coronary circulation therefore, FFR measures 'flow' (actually measuring mean pressure) beyond a stenosis (Pd), and compares it to flow before a stenosis (Pa). The proximal pressure is recorded either in the aorta or ostial left main stem (Pijls et al., 1996). This gives the FFR_{myo} which provides information regarding flow to the myocardium beyond the stenosis (Figure 10). In the originally described formula, venous pressure is factored into the pressure reading (taken from the right atrium), so provide a more accurate assessment of the stenosis.

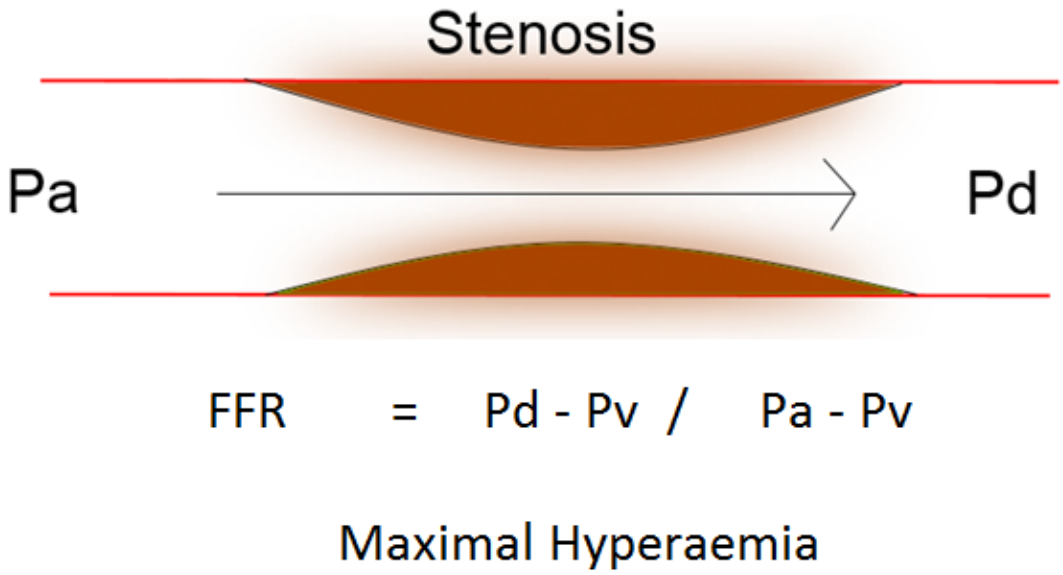


Figure 10 - Calculation of FFR- diagrammatic representation of FFR measurement beyond a stenosis. Pd = distal mean pressure, Pa = distal aortic/proximal pressure, Pv = venous pressure from right atrium. FFR = fractional flow reserve.

In current clinical practice, with the majority of cases being carried out radially, and right atrial pressure requiring femoral vein puncture, venous readings are rarely recorded. Recently, the effect of right atrial pressure on FFR calculation has been shown to be minimal (Toth et al., 2016). In Pijls original paper in 1993, he described a method to calculate FFR_{cor} . This FFR at coronary level, which factors collateral pressure into the equation, and removes it. This involves measuring wedge pressure, which is not routine practice. A wedge pressure is the measured pressure within a coronary artery when a coronary balloon is inflated to stop antegrade flow (Figure 11). The resulting pressure comes solely from collateral vessels. Calculating FFR_{myo} is then truly the sum of pressure anterogradely through the stenosis, and collaterals from other arteries, contributing to pressure distal to the stenosis.

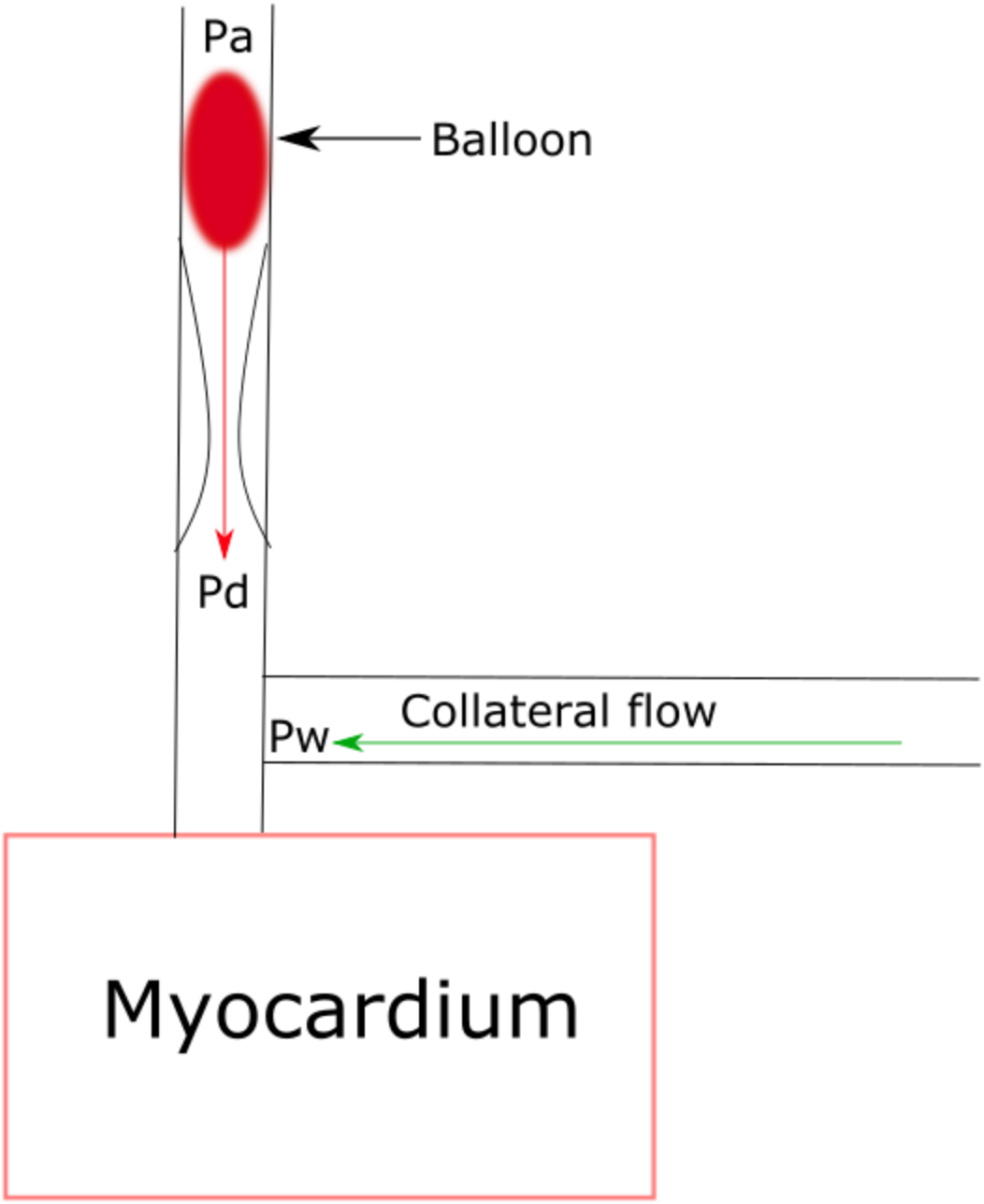


Figure 11 - Original FFR Model - Representation of wedge pressure with a balloon (marked) inflated to impede antegrade flow. The resulting pressure distal to the stenosis, measured by a pressure wire positioned there, is now solely from collaterals. Pa = proximal pressure, Pd = distal pressure, Pw = wedge pressure.

FFR is a number between 0 and 1.0. The proximal pressure is assumed to be the maximal flow obtainable in the artery if stenosis free, and is the denominator in the equation. The value in theory, should not be above 1, which indicates the same flow beyond the stenosis, as before it, and the best achievable flow. A cut off value of 0.8 is routinely used in clinical practice, to denote a negative FFR, and a lesion which does not need treatment. Simply, one can interpret this as 80% of maximal achievable flow. Values above 1.0 are not uncommon however, which relates to several potential confounding factors in FFR measurement, the most important of which for this thesis, is hydrostatic pressure. This and other confounding factors are discussed separately.

The practicalities of measuring FFR are outlined in the chapter III. In brief, the operator must pass a physiology wire, with a pressure sensor, beyond a coronary stenosis and obtain measurements while the patient is in hyperaemia. This is usually accomplished by a continuous infusion of intravenous adenosine for 1-2 minutes. Physiology / pressure wire technology has improved through the years, encouraging widespread use in most interventional cardiology laboratories.

1.9 - Clinical Evidence Supporting FFR

Several randomised control trials have supported the use of FFR in a clinical context. Studies were conducted to test the safety of deferring lesions which had a negative FFR, and the accuracy of FFR versus conventional angiography only in lesion assessment.

1.9.1 - DEFER Study

The defer study was the first widely recognised RCT involving FFR (Bech et al., 2001) published in 2001. The unique study design used FFR to assess coronary stenosis in elective patients presenting with stable angina. Patients with negative FFR values (>0.75) were

randomised to either optimal medical therapy (OMT) (defer group), or PCI (perform group). Follow-up has recently been completed over a 15 year period (Zimmermann et al., 2015a). There was a significant reduction in the rate of myocardial infarction in the defer group, compared to the perform group (2.2% vs.10%). The rate of death was not statistically different between the two groups. This not only demonstrates that the rate of myocardial infarction is low with a negative FFR, but that treating a negative FFR lesion did not improve outcome, and may indeed worsen prognosis. This is especially relevant at 15 year follow-up, where no 'catch-up' phenomena was seen, potentially relating to restenosis of the stent.

1.9.2 - FAME Study

The FAME study, published in 2009 (Tonino et al., 2009) aimed to compare angiography guided PCI with physiology guide PCI for the first time. Coronary angiography was the standard method to which decisions regarding coronary stenting was made. 1005 patients were randomised to either angiographically guided stenting, or FFR guided stenting based on a positive result (FFR <0.8). The study population had multi-vessel coronary artery disease with an average of 2.7 lesions per patient. The composite endpoint was of death, myocardial infarction and urgent revascularisation at 1 year follow-up. The FFR guided group has significantly less events compared to the angiography guided group (13.2% vs. 18.3%).

1.9.3 - FAME II Study

FAME II, build upon results in FAME by posing a slightly different question. Published in 2012 (De Bruyne et al., 2012), one can liken the design to DEFER, but with FFR values of <0.8. Initially, 1220 patients were assessed and of those 888 had a coronary stenosis with an FFR of <0.8. These were randomised in a 1:1 fashion to OMT or OMT+PCI and followed up for two years. The composite endpoint of death, myocardial infarction and urgent revascularisation, had

less events in the PCI group (8.1% vs. 19.5%) (De Bruyne et al., 2014), driven mostly by the need for urgent revascularisation. The rate of death and myocardial infarction was also lower in the PCI group in a landmark analysis from 8 days to 2 years.

Five year outcome data for the FAME II trial was recently published (Xaplanteris et al., 2018a). The composite endpoint of death, myocardial infarction and urgent revascularisation, showed significant benefit favouring the PCI group, again driven by a large difference in urgent revascularisation rates (6.3% vs. 21.1%). The individual rates of death and myocardial infarction was not different between the two groups.

This demonstrates a benefit in stenting to lesions with and FFR <0.8 compared with medical therapy alone. DEFER showed no benefit in treating lesions with an FFR of >0.75. Table 1 summarised these three randomised control trials. Another study published in 2011 further demonstrated the safety of medical therapy with FFR >0.8 lesions in the proximal LAD. Survival rates were statistically similar to patients in a reference group without known coronary artery disease at 5 years (Muller et al., 2011). This adds to the compelling evidence to treat such lesions medically, given the potential associated risks with stenting.

	DEFER	FAME	FAME II
Population	Stable angina	Stable angina	Stable angina
Treatment at Randomisation	Angiogram	Angiogram	Angiogram
Arm 1	FFR >0.75 PCI	FFR guided PCI	FFR <0.8, PCI + OMT
Arm 2	FFR >0.75 Defer	Angiography guided PCI	FFR <0.8, OMT
Standard Care When Study Conducted	PCI	Angiography guided PCI	Angiography guided PCI
Outcome	Stenting FFR >0.75 - No benefit	FFR guided PCI better than angiography guided PCI	PCI + OMT better

Table 1 - summary of DEFER, FAME and FAME II. FFR -fractional flow reserve, PCI - percutaneous coronary intervention, OMT - optimal medical therapy.

1.9.4 - Registry Data

The Mayo registry, comprising of 7358 patients compared two groups of patients; those undergoing PCI without FFR guidance, and those undergoing PCI with FFR guidance (Li et al., 2013). Patients treated with FFR guidance had a significantly reduced rate of major adverse events, supporting the use of FFR in clinical decision making.

The ISIR-FFR registry comprised 5846 patients and over 8000 coronary lesions (Ahn et al., 2017). In this data set, lesions with FFR <0.75 showed significantly improved outcomes if treated with PCI compared with medical therapy. This re-iterates the findings from FAME II. Lesions above this cut off had similar outcomes if treated medically or revascularised. This is a slightly different finding to DEFER, however one appreciates this is comparing registry data to a randomised trial. Furthermore, in untreated lesions, the FFR showed an inverse linear relationship with adverse events.

1.9.5 - FFR in Current Clinical Guidelines

European Society of Cardiology guidelines were published in 2014 and give the following guidance on FFR use (Authors/Task Force members et al., 2014);

- FFR assessment for moderate coronary stenoses are indicated to measure functional consequences
- Deferral of revascularisation with an FFR >0.8 appears safe
- FFR guided PCI and OMT is superior to OMT alone with regards to need for urgent revascularisation

American guidelines, updated in 2017 (Patel et al., 2017) suggest;

- FFR may be helpful in defining the need for revascularisation
- FFR <0.8 is consistent with ischaemia
- FFR should be used in lesions with a diameter stenosis of 50-90%

1.9.6 - FFR Use in Acute Coronary Syndrome

Early data was predominantly in stable presentations of chest pain. FFR measurement at the time of acute myocardial infarction, is invalid, due to microvascular dysfunction, and falsely raised FFR values (Claeys et al., 2001). Microvascular dysfunction causes a reduction in flow through the culprit artery, and in turn reduces the pressure gradient across a stenosis. This leads to an underestimation in FFR, and hence invalidates its use.

Use of FFR in non-culprit arteries during STEMI is still an area of fierce debate. DANAMI-3-PRIMULTI was a study conducted in the context of non-culprit coronary artery disease, treated based on FFR guidance at the index admission of a STEMI, versus treatment of the culprit only (Engstrøm et al., 2015). Patients who had complete revascularisation based on FFR had a significant reduction in the need for repeat revascularisation.

The Compare-Acute study (Chin et al., 2017), had a very similar study design to DANAMI-3-PRIMULTI, and showed similar results with a reduction in MACE, driven mostly by reduced revascularisation in the FFR guided PCI group. Interestingly, investigators also found that nearly half of lesions deemed significant on angiography, were physiologically negative when assessed by FFR. This supports the concept that FFR reduces unnecessary revascularisation when used to aid treatment decision.

1.10 - Resting Indices

Recently, novel resting measures of stenosis severity have gained increasing popularity. They can provide an assessment of ischaemia quickly and without the need for adenosine. Instantaneous wave free ratio (iFR) was the first of the novel resting indices and used coronary pressure distal to the stenosis with proximal coronary pressure in the wave free period of the cardiac cycle, located in diastole (Figure 12). It has been compared to FFR in a randomised control trial DEFINE-FLAIR (Davies et al., 2017). With regards to major adverse cardiac events

at 1 year, it was shown to be non-inferior to FFR in guiding treatment strategy, with fewer adverse procedural symptoms and shorter procedural time.

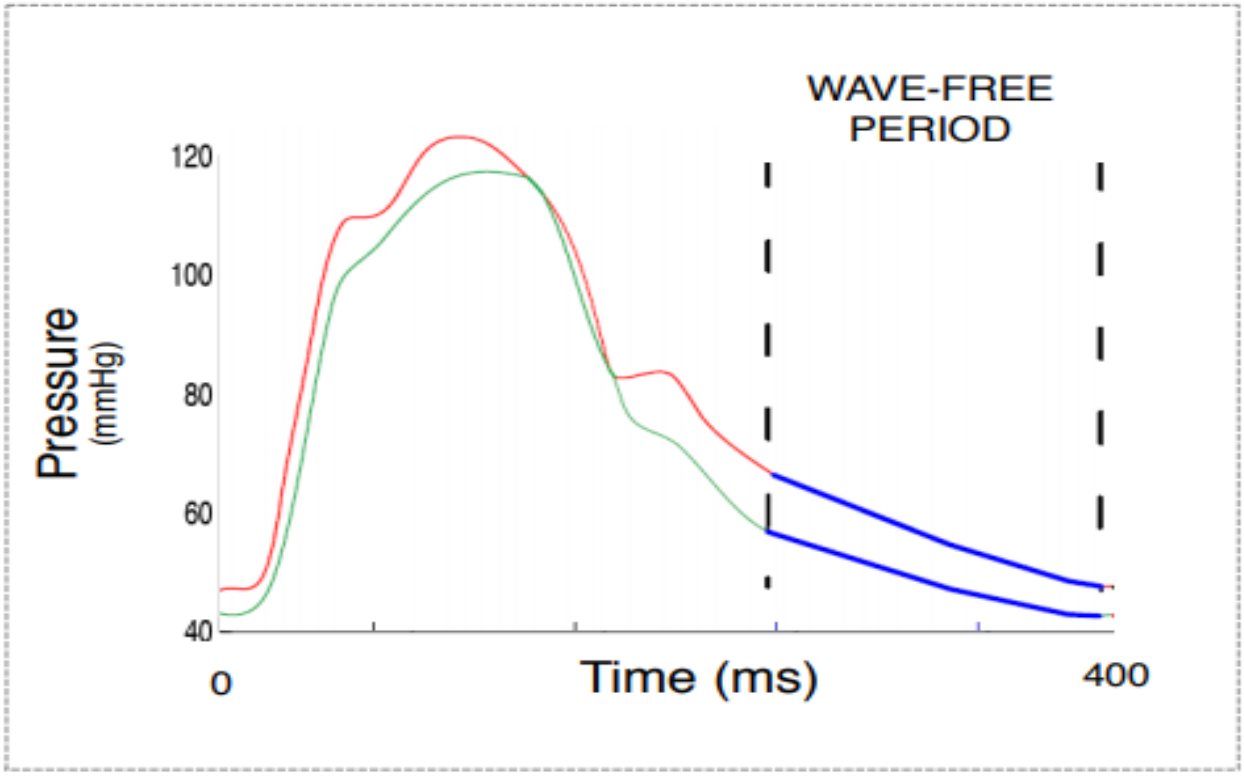


Figure 12 - The Wave Free Period- in which iFR is calculated (Pd/Pa).
(IFR calculation.pdf: Sukhjinder.nijjer (https://commons.wikimedia.org/wiki/FileIiFR calculation.pdf, https://creativecommons.org/licenses/by-sa/3.0/legalcode)

The discovery of iFR led to expansion in scientific investigation. The wave free period was specifically of interest, as it was believed to be physiologically identical to hyperaemia, without needing adenosine. Resistance in the wave free period was thought to be minimal and constant, to the same magnitude as with central infusion of adenosine. The VERIFY study (Berry et al.,

2013) however showed that iFR was significantly influenced by introduction of hyperaemia, and correlated weakly with FFR casting doubt upon its clinical validity.

Using data from the VERIFY-2 study (Hennigan et al., 2016), a further study questioned the specific timing of the wave free period. Pd/Pa measurements were taken during the whole of diastole, the middle 50% of diastole and the midpoint of diastole, with readings compared to iFR. All of these resting indices (known as varying diastolic pressure ratios (DPR) produced almost identical results to iFR with correlation values above 0.99. It appeared therefore that the wave free period did not differ significantly from other periods of diastole, as the results were essentially identical.

Furthermore, recent data has shown that taking the lowest Pd/Pa value across the whole cardiac cycle (systole and diastole) would again produce almost identical results to iFR. The VALIDATE-RFR study (Svanerud et al., 2018) produced a new index, RFR, with correlation values above 0.99 when compared to iFR. Furthermore, the lowest Pd/Pa value was outside of diastole in 12.2% of all cardiac cycles, and 32.4% of cardiac cycles in the right coronary artery. This means physiologically significant stenoses may be missed by focusing purely on the diastolic portion of the cardiac cycle.

1.11 - Pitfalls of Pressure Derived Indices

Venous pressure was factored into the original FFR equation. In routine clinical practice with the increasing popularity of radial access, venous puncture to acquire right atrial pressure, has become increasingly uncommon. Recent studies have shown that even in the presence of significantly raised right atrial pressure, the impact on FFR is negligible (Toth et al., 2016). This holds true even in the context of a CTO (Karamasis et al., 2018).

In current clinical practice, wedge pressure is not factored into FFR calculation to produce FFR_{cor} . In patients with extensive collaterals, FFR may be inaccurate.

Gender has been linked to a difference in FFR values, dating back as far as FAME and it's sub-studies (Kim et al., 2012).The general explanation is thought to be due to microvascular dysfunction. Another theory is that the female heart is smaller with less myocardial mass to subtend. This in turn leads to a higher FFR on average in females when compared with males.

The current haemodynamic state of the patient can alter pressure derived indices. Tachycardia, and raised left ventricular end diastolic pressure (LVEDP) may increase microvascular resistance and in turn FFR (Spaan et al., 2006). Furthermore patient's with microvascular dysfunction may not respond to pharmacological vasodilatation, leading to falsely elevated FFR measurements (van de Hoef et al., 2013).

The amount of mass subtended by a coronary artery is linked to fractional flow reserve, with higher myocardial mass being more likely to produce a positive pressure derived value (Leone et al., 2013b). This is due to increased flow, due to more myocardium, and in turn a reduction in pressure.

Finally, one must not forget the technical and practical issues in measuring pressure derived indices. There is a distinct learning curve when first introduced to a new catheter laboratory and various human or technical errors, may alter recordings. One hopes these will be minimised with time and experience, but good clinical practice is paramount. Technical points include:

- Adequate administration of vasodilators
- Flushing of the guide catheter and coronary artery with saline to clear contrast
- Correct normalisation of the pressure wire in the proximal vessel
- Selection of an appropriate guide catheter for the artery in question, to avoid wedging and pressure drop.
- Recognition of submaximal hyperaemia.

Lastly, the effect of hydrostatic pressure is negated in clinical practice. Hydrostatic pressure is present due to the vertical distance between the pressure wire in the coronary artery, and the guide catheter in the aorta/ostial vessel. The pressure at these points is not the same if vertically they lie at different levels, producing a potentially important confounding factor.

1.12 - Hydrostatic Pressure

Hydrostatic pressure is the pressure exerted by fluid in a confined space. In relation to coronary physiology, coronary arteries are a close fluid system, with the fluid being blood. Hydrostatic pressure in coronary vessels is therefore blood pressure.

This pressure forms the basis of invasive physiology measurements used so frequently in the catheterisation laboratory. Measurements are taken in the distal vessel, across a stenosis, and compared with pressure at the origin of the vessel or aorta. This, as described, forms the basis of FFR calculation, the gold standard technique for stenosis assessment for decades.

According to the physical laws of fluid dynamics, hydrostatic pressure changes due to the vertical point of measurement in a cylindrical tube, due to the force of gravity (Härle et al., 2017a). Figure 13 explains this in diagrammatic fashion.

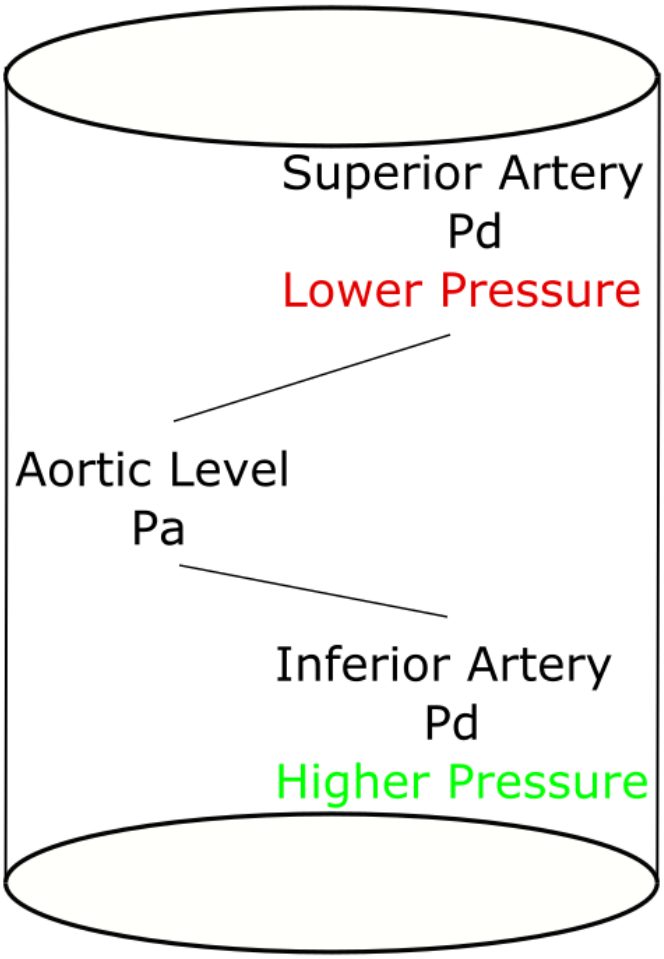


Figure 13 - Close Fluid Model of the Coronary Circulation- A cylindrical tube, demonstrating aortic level and the position of superior or inferior coronary arteries, with the effect on pressure. Pa - proximal pressure, Pd - distal pressure.

If an artery takes a superior course from the aorta, pressure measured in a superior position will be lower than it is at the aorta, purely due to gravitational effect. The opposite is true for an inferior artery, with pressure being higher. Therefore, in a completely disease free vessel lying superiorly to the aorta, with the distal pressure sensor above aortic level, Pd/Pa will be less than 1.0. The physiology assessment is already skewed, before a stenosis is introduced. With inferiorly positioned vessels compared to the aorta, Pd will be higher than Pa, and Pd/Pa will be

greater than 1.0. Only when the measuring point is at aortic level, will hydrostatic pressure not affect measurement. This is seldom the case in clinical medicine.

If one now considers the same stenosis in a coronary artery, the final Pd/Pa measurement will be lower in a superior artery, due to a lower starting value, and therefore more likely to be abnormal. It is possible that we are therefore over-estimating some lesions (superior lying arteries) and underestimating others (inferior lying arteries)

Although this concept has been acknowledged as a potential confounding factor in FFR measurement, it has largely been dismissed, as the magnitude of effect is thought to be too small to be of clinical relevance.

1.12.1 - Magnitude of Effect

Pascal's law dictates hydrostatic effect with the following equation;

Hydrostatic pressure = Fluid Density x Gravity x Height Difference

(Pascal's) (kg/m^3) (9.8ms/2) (m)

An elegant paper recently published by Härle et al (Härle et al., 2017a) used a pressure simulator to calculate the effect in a coronary model. The calculated effect was 0.77mmHg per cm of height variation. An important consideration is that this coronary model used 0.9% saline solution as the fluid. Blood has higher density, and an anticipated change would be closer to 0.8mmHg per cm.

From the equation, fluid density and gravity are constant, the sole variable being height difference between two measurement points. To power the study adequately, I had to know the anticipated magnitude of effect. This meant calculating the potential height difference between distal coronaries artery and their origin. Data from CT coronary angiography was used to estimate this height difference in one hundred patients, and is expanded upon later in this

chapter, and in chapter II. One can accurately map the route of each coronary artery and measure the vertical height difference from the aorta using CT.

1.12.2 - Hydrostatic Effect in Clinical Literature

Relevant data in this area is sparse. Although the concept of hydrostatic pressure within coronary arteries is noted in medical text books, and even by the manufacturers of pressure wires, it is dismissed as a non-significant factor during clinical measurement. At the time of study conception, no study had explored this in vivo.

Hydrostatic effects on blood pressure have been observed in peripheral, non-invasive studies. One such study measured the pressure needed to occlude the femoral artery using an external cuff placed on a patient's thigh (Sieljacks et al., 2018). This was measured supine and then in a seated position. When supine, the femoral artery is much closer to aortic level, compared to seated, where clearly it lies below. There was an observed increase in pressure needed to occlude the artery by 29 mmHg on average, when measured in a seated position.

Further supporting evidence comes from physiology studies including normal or reference vessels. In one such studies, FFR results of above 1.0 were noticed, predominantly in reference vessels and circumflex arteries (Nijjer et al., 2016). This supports hydrostatic theory, as the circumflex artery lies predominantly inferior to the aorta leading to an FFR above 1.0.

In a group of patients with moderate coronary artery stenoses, measurements in posterior arteries produced significantly higher FFR results than anterior vessels (0.87 vs. 0.79) (Härle et al., 2017c). All compared vessels had very similar coronary stenosis severity (61.6% vs. 62.5%). This could be explained by the difference in height between distal and proximal sensors and hence hydrostatic effect. The results included iFR, which followed the same trend, as expected for a pressure-based index.

Registry data follows this trend. In nearly four thousand patients on a registry data set, there was a clear mismatch in angiographically moderate lesions in the LAD and correlation with invasive FFR (Nakamura et al., 2014). The CVIT-DEFER registry demonstrated LAD lesions were statistically more likely to yield a positive FFR result (<0.80). The opposite was true for Cx and

RCA lesions, which were more likely to yield a negative result. There was no difference in left main stem lesions. A further study of 643 patients yielded the same results (Cho et al., 2014). This further supports hydrostatic pressure theory. The authors of both studies however suggest that the mismatch seen was related to the amount of myocardium supplied by the LAD compared to other vessels. Hydrostatic effect was not mentioned.

A study from 2017 in moderate coronary stenoses correlated IMR values to mismatch in invasive FFR and angiography. Lower IMR values were linked to lower FFR values and vice versa (Yonetsu et al., 2017). As in previous studies, mismatch was also seen in LAD lesions, yielding more positive results in angiographically less severe lesions. The authors again suggested subtended myocardium and microcirculatory dysfunction as the explanation.

The current leading figure in coronary hydrostatic pressure is Tobias Härle, a German cardiologist. His elegant study on potential effects of hydrostatic pressure in coronary vessels demonstrated two things (Härle et al., 2017a). Firstly, CT data quantified the vertical height differences between distal coronary vessels and their ostia, when supine. It is worthwhile noting that this study group consisted of predominantly elderly patients with aortic stenosis and may not be a true representation of the general cardiac patient base. Following this, a novel dynamic pressure simulator was used to predict the effect of coronary anatomy on FFR measurements. Indeed, this model confirmed that when the distal pressure sensor was placed at a different height to the proximal sensor, in a completely normal vessel (saline filled tube) with no stenosis, FFR measurements diverged from 1.0. FFR was >1.0 when the distal sensor was moved below the proximal sensor, and <1.0 when raised above.

No in vivo trials at study conception have been conducted.

1.13 - Research Hypotheses and Pre-Work

To test and build on hydrostatic pressure theory in vivo, I would alter the position of the patient on the angiography table from supine, to prone. Turning the patient on the angiography table would be an ideal way to prove hydrostatic pressure in vivo. Manoeuvring from prone to supine

keeps the aorta at an almost identical vertical level, but reverses distal coronary vessel position completely (Figure 14). This had never been done previously. Superior vessels become inferior and vice versa. The delta change one would see in vivo is therefore equal to the vertical height difference between superior, and inferior position, not solely the height change to the aorta. The aorta becomes the 'axis' around which superior and inferior measurements are taken.

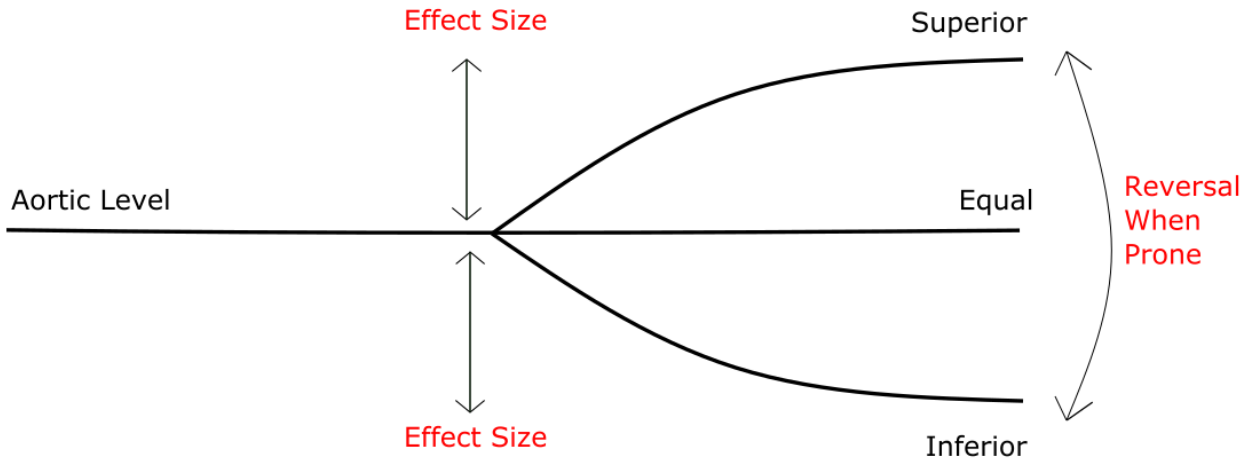


Figure 14 - Superior vs. Inferior Coronary Arteries- Illustration of superior and inferior distal pressure points versus aortic pressure. The effect size is dictated via vertical height shown with the arrows.

In clinical practice, the hydrostatic effect on wire measurement in a superior or inferior artery will be approximately half of the observed change between prone and supine measurement.

If the wire position is kept constant by strict study protocol, the only variable becomes the vertical height of the artery we are interrogating. Furthermore, the patient acts as their own control, meaning measurements are matched to their specific physiology and directly comparable.

The study hypothesis is then divided into two separate points:

- Pressure based measurements (FFR, iFR, Pd/Pa) will significantly differ between supine and prone measurements.
- Velocity based measurements will not change between supine and prone measurements (due to autoregulation).

To elaborate on the latter point, the observed change in pressure I aim to see, should not convert into an increase or decrease in flow through the stenosis. The study group of patients will have an intact autoregulatory system, meaning the change in pressure is compensated for by the physiological mechanisms mediated by the coronary microcirculation. The focus is on the physiological tools that use pressure as their primary measure, and how hydrostatic pressure can impact their results.

1.13.1 - CT Coronary Angiogram Pre-work

The data from CT coronary angiography is critical to preliminary study work. It was of great importance that I understood the anatomy of each coronary artery, and the vertical pathways they took. There are inevitably differences in individual patient's anatomy. However, the knowledge of the most common position in the vertical plane was essential for correct placement of the pressure sensor during angiography.

Quantitative data was needed to accurately calculate the height difference between the distal vessel and the proximal vessel and in turn the expected effect on FFR. This would guide study power calculation and the number of participants required in vivo. Data was collected using CT coronary angiography.

1.14 - CT Coronary Angiography (CTCA)

CT coronary angiography builds upon conventional CT scanning to produce a non-invasive method of imaging the coronary arteries. The first CT scanner was invented by Godfrey Hounsfield, with the first patient scanned in 1971, visualising the brain (Rubin, 2014). CT scanning uses x-ray to take multiple images from differing angles, which are then reconstructed by computer software, to give a final set of images.

Imaging of the coronary arteries became technically feasible in the late 90's (Donnelly, Higginson and Hanley, 2005). In current medical practice, cardiac CT can aid diagnosis in multiple clinical scenarios. An example of a cardiac CT scan is shown in figure 15.

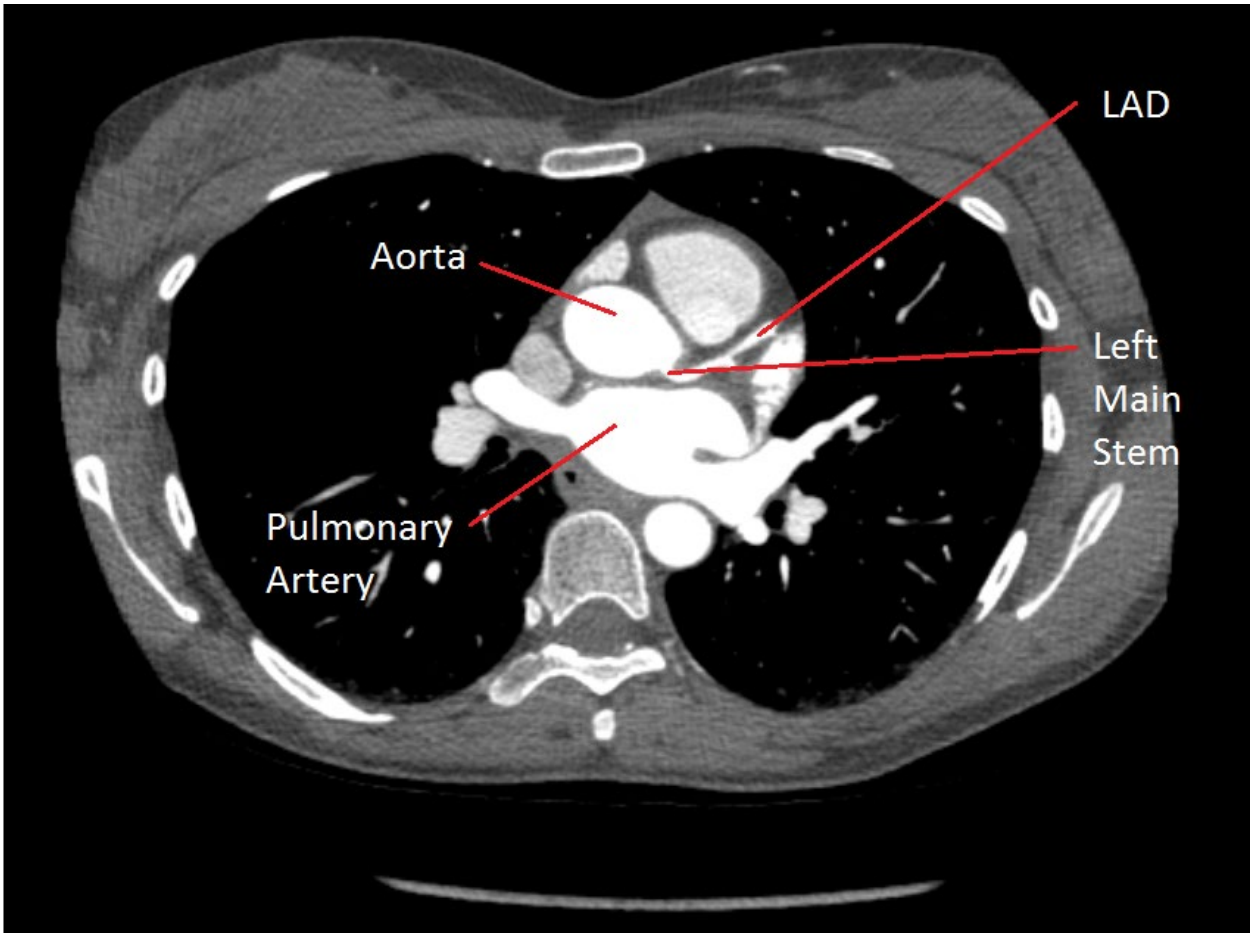


Figure 15 - Cardiac CT Showing Coronary Anatomy. LAD = left anterior descending artery. Permission for image use obtained.

In current NICE (National Institute for Health and Care Excellence) guidelines, coronary CT is the first line diagnostic test for typical and atypical angina (Chest pain of recent onset: assessment and diagnosis | Guidance and guidelines | NICE, 2018). CTCA has a high negative predictive value for the exclusion of significant coronary stenosis in stable coronary artery disease (Budoff et al., 2008, Meijboom et al., 2008). Studies have also supported the use of CTCA in ACS in lower risk patients, potentially reducing length of stay (Hoffmann et al., 2012).There is also some evidence that CTCA can identify 'vulnerable' plaques, at risk of rupture and causing acute coronary syndrome (Sun and Xu, 2014). There is still some variability in reporting of these plaques, which can make diagnosis challenging.

Although invasive angiography is still regarded as the gold standard for coronary imaging, CTCA may have some subtle advantages. Angiography provides detailed luminal assessment, whereas CTCA highlights coronary anatomy and extra luminal details. This can include non-atherosclerotic abnormalities and incidental findings, occurring in up to 4.4% of scans in some studies (Knickelbine et al., 2009). Abnormalities detected can include anomalous coronary artery origins, coronary artery fistulas, coronary artery aneurysms, coronary dissection, coronary vasculitis.

Finally, extra-coronary diagnosis can be made, including aortic stenosis, hypertrophic cardiomyopathy, and pericarditis (Kanaganayagam et al., 2014). Overall CTCA can also identify extra-cardiac abnormalities, such as aortic disease, pulmonary emboli and lung disease.

1.14.1 - Limitations of CT Coronary Angiography

A major limitation of CTCA is the image disruption caused by calcification. Whilst CTCA has a high negative predictive value, calcium deposits within the artery can lead to over estimation of coronary atheroma, in turn reducing positive predictive value (Sun, Choo and Ng, 2012). Patients with high calcium score are particularly at risk of such issues, as demonstrated by clinical trials (Budoff et al., 2008)

CT images need to be acquired in a short time frame with minimal motion artefact, meaning adequate heart rate control (<70bpm) for a satisfactory diastolic period, and adequate breath holding from the patient. Obtaining such conditions is sometimes not possible, and can be further compounded by arrhythmias such as atrial fibrillation (Clayton, Roobottom and Morgan-Hughes, 2015).

Radiation dose has steadily been falling with advances in technology. It is however still a consideration. The average dose can rage widely but a recent study of 1341 CTCA, found an average dose of 5.9mSv (Castellano et al., 2017). This is higher than the standard coronary angiography, which is thought to be approximately 3mSV (Einstein et al., 2007).

Intravenous contrast medium is injected during CTCA and there are associated risks with introduction of these agents. The volume of contrast used is less than coronary angiography, but may pose a problem in patients with significant renal impairment.

1.15 - Feasibility of in Vivo Research

The function of cardiac CT imaging with relation to this research, was to understand the height differences between certain points within the coronary vasculature and the aorta or ostial vessel. This provides information on the magnitude of hydrostatic pressure, whether an *in vivo* study is feasible, and the sample size needed to support it.

1.15.1 - Current Relevant Literature

During the data collection period, a paper by Härle et al was published focusing on the same subject matter (Härle et al., 2017a). This elegant paper used CT coronary angiography to map coronary anatomy, in a group of patients predominantly suffering from severe aortic stenosis, and awaiting TAVI (transcatheter aortic valve implantation). The vertical height variations

between various points in the coronary tree were calculated. A dynamic pressure simulator was also used separately, to demonstrate how height variations could alter FFR using 0.9 % saline as the fluid in the circuit.

Data from Härle is compared with my own in chapter II.

1.15.2 - Calculating Hydrostatic Effect from Vertical Measurements

The hydrostatic effect has been demonstrated by Härle to be 0.77 mmHg/cm. This was using 0.9% saline solution in a hydrostatic simulator. 0.9% saline is less dense that blood, and the effect is thought to be closer to 0.8 mmHg/cm. This will be the conversion rate used herein.

Figure 16 demonstrates how a calculation for hydrostatic pressure effect on a single point in an artery will take place.

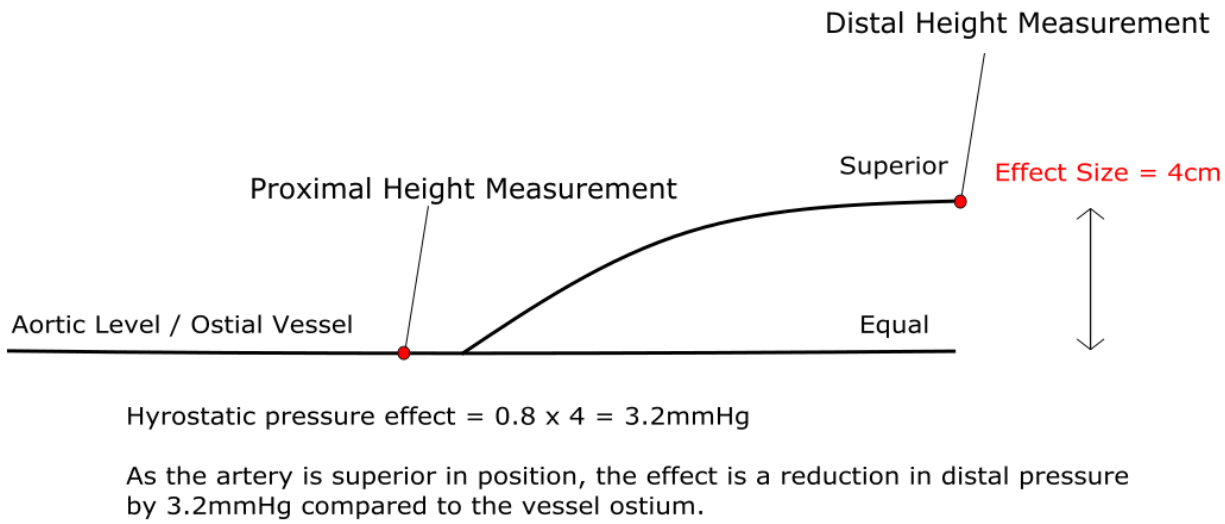


Figure 16 - Estimated Hydrostatic Effect - example of a superiorly positioned artery and the calculated effect on hydrostatic pressure. Distal red dot shows where the pressure wire will be placed, and the proximal red dot demonstrates the position of proximal pressure measurement.

Figure 16 demonstrates a scenario where a superiorly positioned artery has a distal point of measurement 4 cm higher than the proximal point (in a supine patient). One can assume this is the LAD. The pressure difference due to height alone between the ostium of the artery, and the distal portion of the artery is 3.2 mmHg. As the artery is superior, the effect is a reduction in pressure at the distal point in the artery.

Therefore, if the proximal pressure is 100 mmHg, the distal artery will have a pressure of 96.8 mmHg. If this was under hyperaemic conditions, the FFR would be 96.8 / 100, or 0.97 to two decimal places. If this whole scenario is reversed in the case of an inferiorly positioned artery, the resulting FFR would be 1.03.

1.15.3 - The Clinical Effect on FFR

We anticipated the effect on distal pressure (4-6 cm between origin and distal artery from literature and data in Chapter II) to be 3-5 mmHg, depending on the vessel. This is the change in Pd. However, it is appreciated that FFR is Pd/Pa at maximal hyperaemia, and that Pa can also change for a multitude of reasons. As Pa is the denominator in the FFR equation, a lower Pa may exaggerate the effect Pd has on Pa and vice versa. A table showing this effect is shown in Table 2. In pre-study preparation and study sample size calculation, we assume a Pa pressure of 100mmHg.

Pa Pressure	Pd Pressure	Pd/Pa	Corrected Pd/Pa (Pd - 5)	Change in Pd/Pa
80		0.88	0.81	0.07
90		0.78	0.72	0.06
100	70	0.70	0.65	0.05
110		0.64	0.59	0.05
120		0.58	0.54	0.04

Table 2 - the effect of a change in Pd of -0.05 on Pd/Pa with various systemic/Pa. As Pa pressure rises, the effect a change in Pd has (and in turn hydrostatic pressure), lessens.

This is of clinical relevance when calculating FFR due to the use of adenosine. Adenosine is a necessary step in FFR calculation, as it induces stable state hyperaemia. A side effect however is inevitably a drop in Pa pressure, which may lead to an amplification in the effect of hydrostatic pressure change measured in the distal vessel.

1.15.4 - The Effect on Resting Indices

The transtenotic gradient for hyperaemic indices, must reach 20 mmHg (assuming a Pa of 100) to be classed as significant (FFR <0.8). A change of 5mmHg is therefore 25% of the transtenotic gradient required to class a lesion as significant. The resting indices however (Pd/Pa and iFR), require a transtenotic gradient of less than half of this, with a negative iFR being classed as >0.92 for example. A 5mmHg change here is therefore relatively much larger, accounting for over 50% of the transtenotic gradient.

In clinical terms therefore, the hydrostatic effect may have a much larger effect on the classification of resting indices, due to the smaller magnitude of transtenotic gradient used in their measurement.

1.15.5 - Clinical Relevance and Mathematical Model

FFR uses a threshold (0.8) to determine the significance of a coronary lesion. The potential changes that hydrostatic pressure has on FFR may cause some values to 'cross' the threshold once corrected. To demonstrate this phenomenon, we aim to use data from CT coronary angiography to provide a correction factor for hydrostatic pressure. This will be applied to a mathematical model of 200 randomly generated FFR values ranging from 0.75 - 0.85. One may then determine how many of these values cross the threshold of 0.8 and change classification from positive to negative or vice versa due to hydrostatic effect.

1.15.6 – Research Questions, Aims and Objectives

The main research question is whether hydrostatic effect is significant confounder when using invasive pressure-based measures of stenosis assessment

The aim of this research is to quantify the magnitude of effect hydrostatic pressure exerts on the coronary circulation in each coronary artery. Once magnitude is known, one can quantify the extent of clinical inaccuracy when using pressure-based indices to assess the severity of a stenosis.

The research objectives are;

1) To map coronary anatomy using CT coronary angiogram and predict hydrostatic effect using coronary height data
2) To see if CT data is accurate in vivo, using a new research protocol comparing prone and supine measures of coronary physiology across the same stenosis
3) To measure coronary flow in prone and supine patient position and compare it to pressure measurements across the same stenosis

Chapter II - Methods, Results and Interpretation from CT Coronary Angiography

Data from this chapter has been published in a peer reviewed journal (Al-Janabi et al., 2019). *For the full manuscript, please see appendix G.*

This chapter describes the methodology and corresponding results of data collected from CT coronary angiograms retrospectively. The data was used to inform the research team if the clinical magnitude of hydrostatic effect is measureable and demonstrable in vivo

Data was retrospectively collected from 100 CT coronary angiograms conducted at the Essex Cardiothoracic Centre from August 2016 to April 2017.

2.1 - Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients referred for assessment of suspected angina

Exclusion Criteria

- Previous coronary artery bypass grafting
- Left dominant coronary circulation
- Poor image acquisition or visualisation of the coronary arteries
- Upper rim of the CT table not visible (reference point for measurement)

2.2 - CT Coronary Angiogram

The CT coronary angiogram was conducted by trained radiographers at the Essex Cardiothoracic Centre using a 64 slice CT scanner. All patients had adequate breath holding, with a heart rate of less than 80 beats per minute. Intravenous metoprolol was used to achieve adequate heart rate control if necessary.

Vertical Height Measurement

There were several predefined measurement points in the coronary tree;

Left System

1. Left coronary ostium
2. Ostial left anterior descending (LAD)
3. Distal LAD - at its highest point
4. Distal circumflex (Cx) - at its lowest point

Right System

1. Right coronary ostium
2. Right coronary artery bifurcation
3. Distal posterior descending artery (PDA) - at its highest point
4. Distal posterior left ventricular artery (PLV) - at its lowest point

The upper rim of the CT table was used as a fixed position, by which the vertical height of these points were measured. Figure 17 demonstrates a measurement taken from the left main stem. The

CT table is curved, so the lowest point is the reference point.

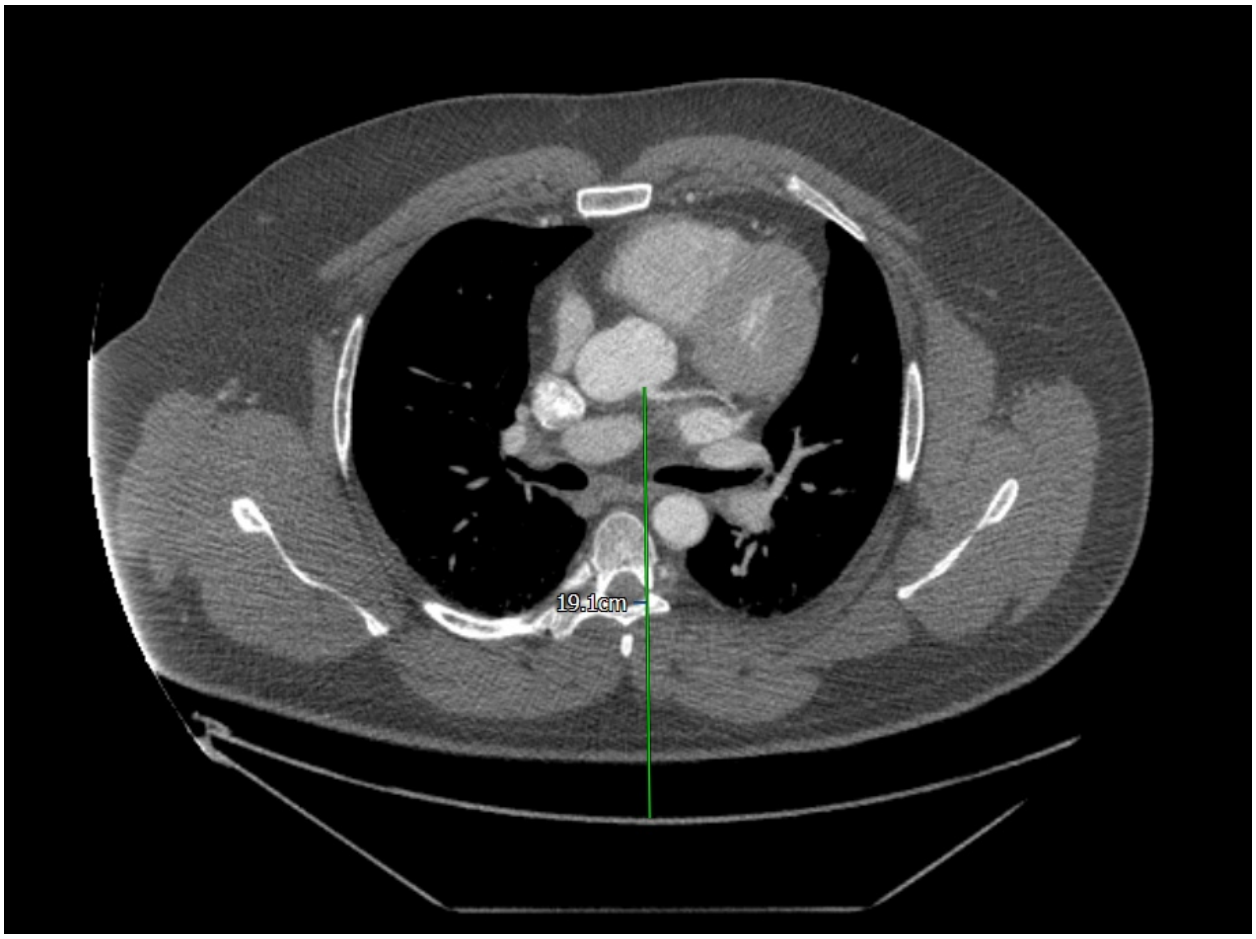


Figure 17 - Height Measurement Using Coronary CT - demonstration of a vertical measurement between the rim of the CT table, and the left main, stem using an electronic measuring calliper. The image is a transverse section.

Agfa IMPAX™ was used to view and measure distance on a hospital workstation. Measurements were taken using a contrast enhanced transverse view of the heart. The furthest point where contrast penetrated was the measurement point for distal recordings. Subtracting height values would then give the height difference two desired points.

2.3 - FFR Mathematical Model

The height in centimetres multiplied by 0.8 provided hydrostatic effect in mmHg. This change for each measurement point will be factored into 100 randomly generated FFR values between 0.75 and 0.85 using Microsoft Excel ™. The resulting corrected FFR (cFFR) will be compared to the original FFR. The percentage of these values above and below the threshold of 0.8 will be compared between FFR and cFFR to determine percentage discordance.

2.4 - Statistical Analysis

Continuous variables are expressed as mean values plus or minus standard deviation. Categorical variables are described as numbers and percentages. Statistical significance of coronary height variations was calculated using the Student t test.

2.5 - Results

2.5.1 - Patient Demographics

Patient demographics are summarised in Table 3.

Characteristic	Number (± SD)

Age	55.9 (± 11.2)
Female	68
Current smoker	12
Ex-smoker	19
Hypertension	33
Hypercholesterolaemia	25
Family History	24
Ejection Fraction	54.8% (±14.6)

Table 3 - CT Data Patient Demographics.

Two circumflex measurements and five PLV measurements were un-recordable. 15% of measurements in the PDA were un-recordable due to poor contrast visualisation.

2.5.2 - Vertical Height Measurements

Table 4 summarises the distance from the upper rim of the CT table to the specific point in the

artery. After the LCA and RCA ostium, each subsequent measurement in the left or right system is compared to the respective ostium for statistical significance. The only non significant measurement was ostial LAD, when compared to left main stem / LCA ostium.

Measurement Point	Mean height from Upper Rim of CT Table (mm) (Standard Deviation in mm)	P Value compared to vessel ostium
LCA Ostium	170.0 ±19.6	N/A
LAD Ostium	167.9 (±19.6)	0.06
Distal LAD	222.5 (± 28.3)	<0.0001
Distal Cx	136.4 (± 20.4)	<0.0001
RCA Ostium	193.8 (± 21.1)	N/A
RCA bifurcation	175.6 (± 28.3)	<0.0001
Distal PDA	212.1 (±-30.7)	<0.0001
Distal PLV	136.4 (±-26.1)	<0.0001

Table 4 - CT Height Data. Multiple measurement points referenced from the upper rim of the CT table in millimetres. LCA - Left coronary artery, LAD - left anterior descending artery, Cx - Circumflex artery, RCA - right coronary artery, PDA - posterior descending artery, PLV - posterior left ventricular artery. The results are presented as mean ± standard deviation in mm.

Figure 18 demonstrates the height from the respective ostium, to the measurement point. For LAD ostium, distal LAD and distal Cx, this is the left coronary artery ostium or left main stem. For RCA bifurcation, distal PDA and distal PLV, this is the right coronary artery ostium.

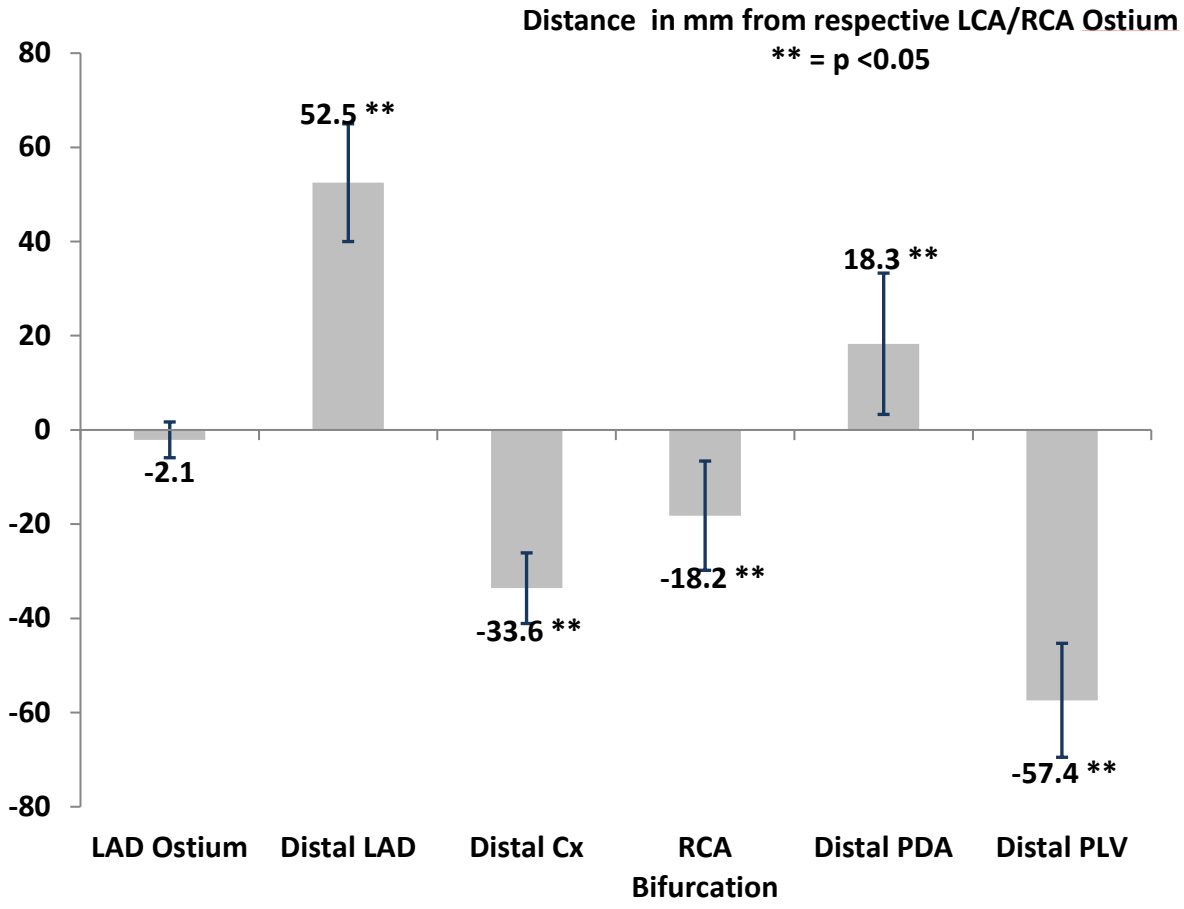


Figure 18 - Coronary Height Data - Graphical presentation of specific measurement points to their respective ostium. LAD = left anterior descending artery, Cx = circumflex, RCA = right coronary artery, PDA = posterior descending artery, PLV = posterior left ventricular.

2.5.3 - Effect on FFR

Table 5 below shows the height variation converted into pressure difference using a 0.8mmHg/cm conversion factor for each measurement point. The resulting change in FFR or cFFR is demonstrated in the far right column as compared with an FFR of 1.0.

Measurement Point	Height from respective coronary ostium (mm)	Height effect on distal pressure (Pd) - mmHg	Correction Factor	FFR	cFFR assuming Pa of 100
LAD Ostium	+2.1	-0.2	+0.002	1.0	**1.0**

Distal LAD	+52.5	-4.2	+0.04	1.0	**1.04**
Distal Cx	-33.6	+2.7	-0.3	1.0	**0.97**
RCA bifurcation	-18.2	+1.5	-0.02	1.0	**0.98**
Distal PDA	+18.3	-1.5	+0.02	1.0	**1.02**
Distal PLV	-57.4	+4.6	-0.05	1.0	**0.95**

Table 5 - CT Heights to Ostium and Effect On Pressure - The height of measurement points within a coronary artery, in relation to their respective coronary ostium and in turn the hydrostatic pressure effect. The two columns on the right dictates from physical principles, the effect of this height difference on the Pd pressure sensor and FFR given a Pa of 100. The resulting is the corrected FFR (cFFR).

2.5.4 - FFR and cFFR Discordance

Table 6 shows discordance between FFR and cFFR with regards to values crossing a threshold of 0.8.

Vessel point (+cFFR	% FFR below 0.8	% FFR above 0.8	% corrected FFR below 0.8	% corrected FFR above 0.8	% Crossing 0.8

correction)					
Distal LAD (+0.04)			6	94	**42.5%**
Distal Cx (-0.03)			72	28	**26.5%**
Distal PLV (-0.05)	45.5	55.5	92	8	**46.5%**
Distal PDA (+0.02)			30.5	69.5	**15%**

Table 6 - cFFR Values Crossing Ischaemic Threshold. The percentage of patients with 'negative' or 'positive' FFR results before and after hydrostatic correction in 100 random FFR values between 0.75 and 0.85. Substantial change occurs when hydrostatic pressure is corrected for. The furthest column on the right shows the percentage of FFR values that cross from positive to negative, or vice versa.

2.6 - Discussion and Interpretation

The findings can be summarised into three points;

1. There are statistically significant height variations between distal coronary vessels and their respective ostium.

2. Depending on the point of measurement, there is a potential change in FFR of 0.02-0.05, when hydrostatic pressure is corrected for.

3. 15% to 46.5% of FFR values between 0.75 and 0.85 re-classified across a treatment threshold of 0.8 when correcting for hydrostatic pressure effect.

Our patient demographic consisted of younger female patients. 33% of patients had an echocardiogram at the time of scanning, with preserved ejection fractions on average (54.8%). Before the introduction of updated NICE guidelines in stable chest pain (Chest pain of recent onset: assessment and diagnosis | Guidance and guidelines | NICE, 2018), CT coronary angiography was used in patients with low to intermediate risk of having coronary artery disease. This may explain the trend in demographic toward younger female patients.

2.6.1 - Height Variations

All measured points were statistically significant when compared to their respective ostium, except for the ostial LAD.

The vertical course of arteries followed expected patterns from known coronary anatomy in all cases. No patient was found to have anomalous coronary anatomy. The LCA ostium was 23.8mm lower than the RCA ostium. The average height measurements from the CT table to the distal PLV and distal Cx were equal. Compared to the respective ostium however, the PLV had a greater distance, due to the more superior position of the RCA ostium.

It is important to note that the most distal point in the artery is not always the most superior or inferior. An example of this would be in patients who have a 'wrap around' LAD. Here, the LAD reaches the left ventricular apex, and the most superior point in its course, before wrapping

around the apex and travelling inferiorly for a distance. This has been described in medical literature and can occur in up to half of patients (Kobayashi et al., 2015a).

Although not measured specifically, side branches tended to follow the same vertical course as the main vessel they branched from. An example would be the obtuse marginal branches of the circumflex (OM). These would bifurcate and often became as inferior as the main branch, albeit in a more medial horizontal plane. This is demonstrated in Figure 19. The same applies to the diagonal branches of the LAD.

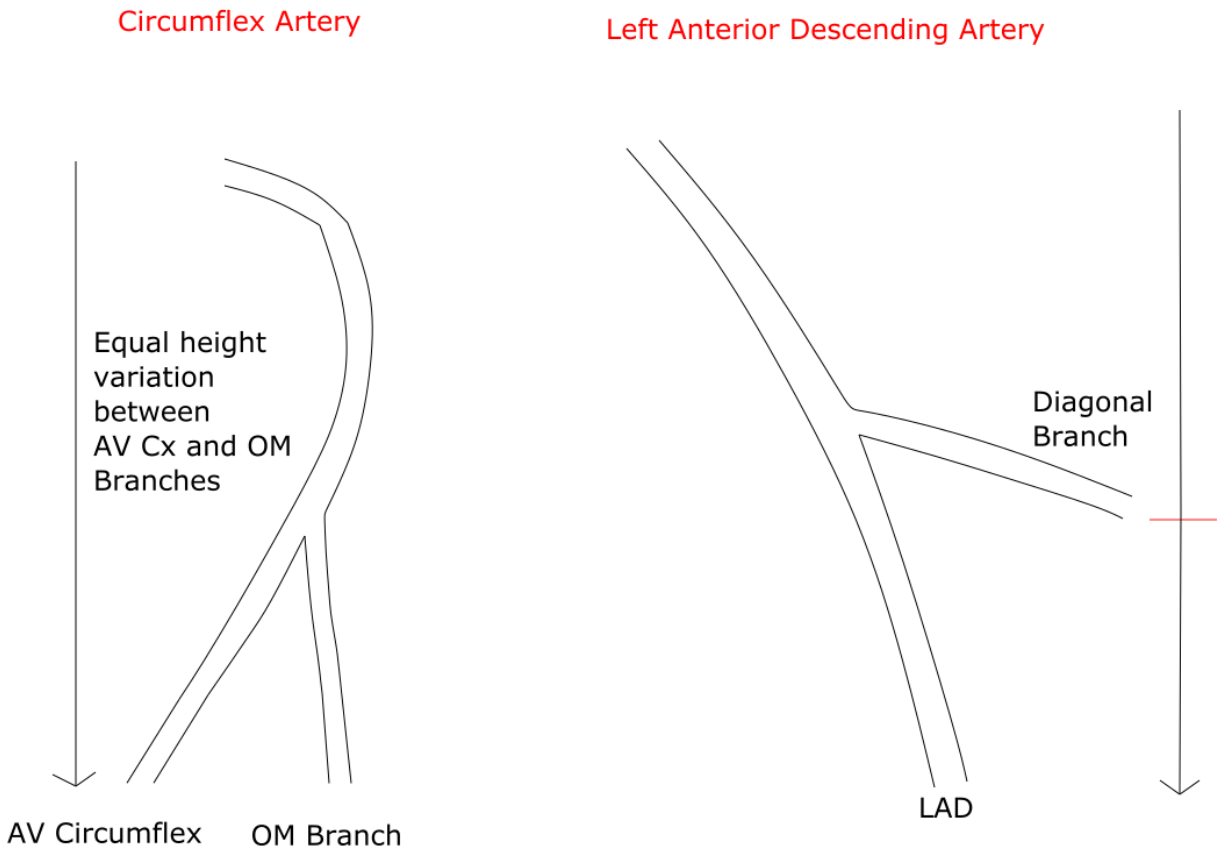


Figure 19 - Coronary Branch Points - Illustration of branching points of the circumflex (Cx) and left anterior descending artery (LAD). The obtuse marginal (OM) branches of the circumflex would often end as inferiorly as the circumflex AV (atrioventricular) branch, meaning equal distal measurements in each branch, and potentially hydrostatic effect. The diagonal branches of

the LAD would take a more horizontal course, and not reach the same vertical distance as the LAD itself.

2.6.2 - Al-Janabi vs.Härle Data

Härle et al published similar CT data recently in an older cohort of patient awaiting TAVI. A comparison of the two data sets are summarised in Table 7 below.

Measurement Point	Al-Janabi Data	Härle Data	Difference
LMS to RCA Ostium	23.8 mm	25 mm	1.2 mm
LMS to Distal LAD	52.5 mm	49 mm	3.5 mm
LMS to Distal Cx	33.6 mm	39 mm	5.4 mm
Ostial RCA to Distal PLV	57.4 mm	26 mm	31.4 mm
Ostial RCA to Distal PDA	18.3 mm	38 mm	19.7 mm

Distal PDA to Distal PLV	75.7 mm	65 mm	10.7 mm

Table 7 - Al-Janabi vs. Härle CT data. Height difference between various coronary points calculated using CT coronary angiography.

The measurements between LMS and RCA ostium, LMS to distal LAD and LMS to distal Cx were largely similar. There were however more pronounced differences in measurements between ostial RCA and distal PLV, and ostial RCA to distal PDA. There could be several reasons for this.

Firstly, inter-observer measurement variation could play a role in part of the difference seen. Secondly, contrast penetration to the distal PDA was not clearly seen in 15% of our CT scans, meaning an underestimation of the height variation in our data for this artery. Finally, our study demographic consisted of predominantly young female patients with normal aortic valves. The demographic of Härle's group, consisted predominantly of elderly patients with severe aortic stenosis. The calcification of the aortic valve may alter coronary position in these patients. One may also take into consideration other factors such as patient height, which may have varied between the two groups. Unfortunately, this was not available for me to collect retrospectively.

Data from the dynamic pressure simulator in Härle's study also supported the predicted effect of changing Pa pressures. As Pa pressure fell below 100mmHg, there was a greater effect on Pd/Pa when altering Pd pressure (by changing vertical height in the simulator). The opposite was true when Pa pressure was above 100mmHg, with the same change in vertical height resulting in a lesser effect (Härle et al., 2017a). The authors state that the effect of hydrostatic pressure on FFR or Pd/Pa is inversely proportional to aortic pressure.

The mathematical model assumes a Pa pressure of 100, essentially meaning a change in Pd pressure cause the FFR to change by the same amount. A drop in distal pressure by 4mmHg, equates to a drop in FFR by 0.04, a drop in pressure by 2mmHg equates to a drop in FFR by 0.02.

Table 2 from section 1.15.3 highlighted the importance of Pa pressure variation. The lower the Pa, the greater the change in Pd will affect FFR.

This has relevance to the study protocol, as resting measurements will also be collected. There may indeed be a difference between hydrostatic pressure effect in resting indices (i.e. resting Pd/Pa/iFR) and FFR, as resting indices will not have the effect of adenosine reducing blood pressure and therefore a higher Pa value.

2.6.3 - FFR Magnitude of Effect

The magnitude of change (0.02-0.05) may seem small in relation to a possible FFR reading of 0-1.0. However, lesions can frequently circle the threshold of treatment (currently accepted as 0.8 for FFR), meaning slight variations may impact clinical decision making (Montalescot et al., 2013). If one accepts a binary cut-off point, applying correction factors for height seen a substantial number of values change their classification from positive FFR values (<0.8) to negative, and vice versa. This alone could lead to a significant change in treatment for patients.

Many operators agree that treatment of a coronary stenosis is not a binary decision and takes into account other clinical factors. The effect of hydrostatic effect on an artery, may need to be one of these identifiable factors.

2.6.4 - Potential Impact on Clinical Practice

A Pd/Pa above 1.0 has anecdotally been noticed at our institution by multiple operators, usually in the circumflex artery. This observation is also described in the medical literature, especially in

mildly diseased or normal arteries (Nijjer et al., 2016). This is the result of the pressure sensor on the wire, lying inferiorly to the proximal pressure sensor. Pd is therefore greater than Pa, and the resulting value is greater than 1.0.

Furthermore, the effect of hydrostatic pressure is seen when comparing similar stenoses in superior and inferior arteries. Arteries that are positioned inferiorly had higher average FFR and iFR values than those positioned superiorly, despite similar stenosis severities between the two groups (Härle et al., 2017a; Davies et al., 2017) . This is shown below (Table 8).

Artery Position When Supine	Stenosis %	FFR	iFR
Superior	61.6	0.79*	0.86*
Inferior	62.5	0.87*	0.94*

Table 8 - Superior vs. Inferior Stenosis Position - effect on iFR and FFR. Superior vs. Inferior anatomically positioned arteries in a group of 214 coronary stenoses. The % stenoses were very similar but FFR and iFR measurements were significantly higher in those arteries positioned inferiorly, supporting the theory of hydrostatic pressure effects.

In daily practice therefore, the position of the wire in the distal coronary artery may have clinical importance, and potentially affect the FFR by up to 0.05, assuming a Pa pressure of 100.

2.6.5 - PDA vs. PLV Wire Placement - A Clinical Case Example

PDA to PLV distance was shown to be relatively large in both Härle's data and my own (65mm and 75.7mm respectively). These branches bifurcate from the main RCA at the crux. Wire position in either branch is usually an arbitrary decision in a stenosis at or proximal to the crux. Pressure recordings may therefore differ based on the branch chosen due to hydrostatic pressure effect across the same stenosis. A procedure that follows was conducted at the Essex Cardiothoracic Centre, and demonstrates such a scenario.

A 73 year old man presents with exertional angina. His angiogram is shown below in figure 20.

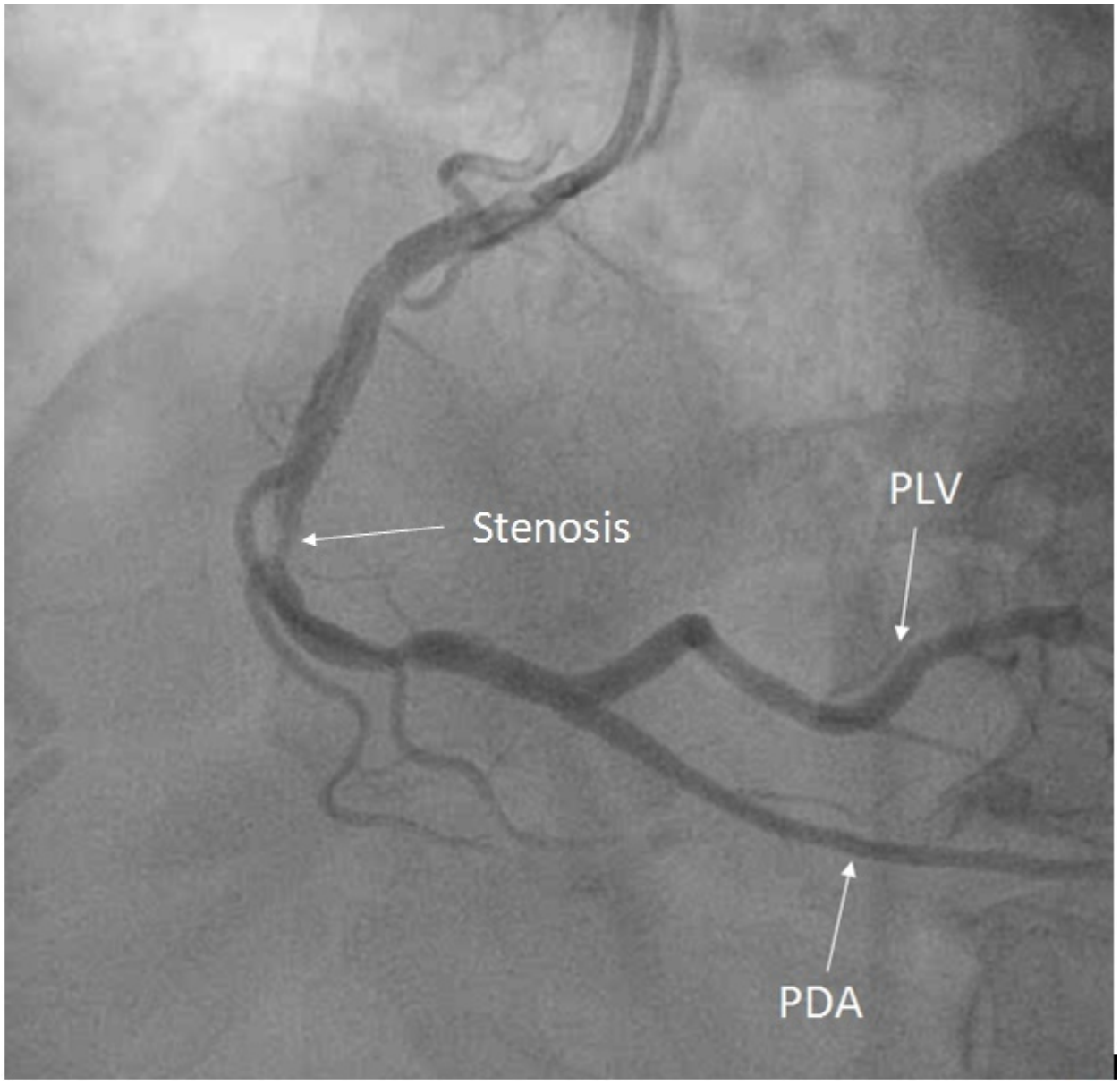


Figure 20 - Case Study - mid RCA lesion in a 73 year old male with exertional angina. The stenosis, PLV (posterior left ventricular artery) and PDA (posterior descending artery) are marked with arrows.

The stenosis is situated approximately 30 mm from the crux/bifurcation. The pressure wire could be placed in either PLV or PDA. For clinical clarification, FFR and doppler velocity measurements were taken in the distal PLV, and distal PDA and subsequently compared. Table 9 summarises the results below.

Measurement point	FFR	Hyperaemic Flow (cm/s)
PDA	0.75	17.1
PLV	0.8	19.1

Table 9 - Pressure and Flow Case Study Data. FFR (fractional flow reserve) and doppler flow measurements across the right coronary artery stenosis, with the physiology wire placed in the PDA (posterior descending artery) and PLV (posterior left ventricular artery).

FFR was technically negative when the wire is positioned in the PLV (0.8). When moved to the PDA, the FFR is positive (0.75) suggesting the need for treatment. The PDA is superior to the PLV, giving a lower distal pressure and in turn a lower FFR value. Doppler flow did not change significantly and falls within the error rate of the doppler measuring technology (Davies et al., 2006).

2.7 - Limitations

2.7.1 - Patient Demographic

The patient demographics were clearly of a specific group. The average age was 56 with 68% being female. This represents selection bias regarding those patients put forward for a CT coronary angiogram in the first instance. Before the update from NICE (Stable angina: management | Guidance and guidelines | NICE, 2018), CT coronary angiography was used in

predominantly low to intermediate risk patients, as shown in Figure 21 below (BrJCardiol, 2018).

Estimated likelihood of CAD		
10–29%	**30–60%**	**61–90%**
Offer CT calcium scoring	Offer non-invasive functional imaging	Offer invasive coronary angiography
Outcome depends on CT score 0; investigate other causes of chest pain 1–400; offer 64-slice CT coronary angiography >400; follow pathway for 61–90% likelihood of CAD	If reversible myocardial ischaemia is uncertain, offer invasive coronary angiography	Offer non-invasive functional imaging if invasive testing not appropriate
If significant CAD uncertain		
Offer non-invasive functional imaging		

Based on data from NICE clinical guideline 95[20]
Key: CAD = coronary artery disease; CT = computed tomography

Figure 21- 2018 NICE Guidelines for Stable Angina - the likelihood of CAD versus investigation modality. As show, patients scoring low for coronary artery disease risk, were often investigated with CT coronary angiography (from NICE guidelines CG95).

It is expected the group of patients in the study will be a different demographic with more coronary artery disease, and predominantly male. This may have an effect on coronary height variations, as Härle et al showed sex was a predictor of distance between maximal height measurements in the coronary tree (Härle et al., 2017a). The maximum measured height difference was greater in men, and interestingly also in those with reduced ejection fractions. This may be associated with ventricular dilation, although this was not specifically commented upon. In our demographic, composed predominantly of women, the average height variations may be somewhat underestimated.

2.7.2 - Coronary Visualisation

A proportion of CT scans in the data acquisition period could not be analysed due to poor coronary visualisation. The predominant reason for this was inadequate contrast penetration to all distal vessels. This may lead to underestimation of the maximal height difference. It must be noted that in clinical practice, the distal vessel seen on CT scan may be too distal for wire placement, and therefore is less important.

Coronary calcification did not affect measurement of distal vessel height in this study population.

2.7.3 - Measurement Point

Measurements were taken at the most distally visualised point in the artery. In clinical practice, the wire may not be placed as distally due to operator preference.

Human error may also lead to variations in the maximal height measurements. Despite the greatest care, it is not unreasonable that two separate researchers may have obtained slightly different results, using the same scans. The CT table is also slightly curved, meaning great care had to be taken to use the correct reference point each time when measuring the coronary arteries. Furthermore, the measurement point in the coronary artery was the central point in the lumen, which may lead to small reproducibility errors.

Whilst the vertical height deviation of a coronary artery from its ostium are gradual, it would have been useful to map the rate of change in height, with the horizontal distance from the ostium. Further data points to incorporate this would have been useful in retrospect.

2.7.4 - Mathematical Model

Microsoft Excel™ was used to generate 200 random numbers between 0.75 and 0.85. 45.5% were below 0.8, and 55.5% were above. The distribution was not equal purely due to chance.

The model only factors in a single variable to a change in FFR, when in reality, hydrostatic pressure is a single potential variable. Whilst independent of stenosis severity, and position in the artery, hydrostatic pressure effects may be affected by patient factors such as heart rate and systemic blood pressure. This is also the case for FFR measurements in general.

Hydrostatic pressure calculation uses a conversion factor of 0.8 mmHg/cm of vertical height. This is extrapolated from Härle's paper where a dynamic pressure simulator found the conversion rate to be 0.77 mmHg/cm using 0.9% saline. *In vivo*, where blood is the fluid, the assumed conversion rate will be higher, owing to blood's higher density, hence 0.8 mmHg is used in the model. This is the best estimate known at this time, and hence could be subject to change, potentially affecting the calculations within the model.

Finally, the Pa pressure for all calculations is assumed to be 100 mmHg. At maximal hyperaemia, Pa pressure will undoubtedly fall, possibly below 100 mmHg, meaning a greater effect when Pd is altered or corrected for due to hydrostatic pressure. The opposite is true if Pa pressure is above 100 mmHg, with a lesser effect from hydrostatic pressure altering Pd.

2.8 - Conclusions

The distal point in all coronary arteries vary significantly in vertical height from their ostium, yet in clinical practice they are assumed to be 'level'. The effect of this height variation is a difference in intracoronary pressure between the ostium and distal vessel due to hydrostatic forces. Alterations in distal pressure lead to a change in FFR of 0.02 - 0.05 (assuming a Pa pressure of 100mmHg). Using a mathematical model and correcting for hydrostatic effect 46.5%

of FFR measurements between 0.75 and 0.85 re-classify (from positive to negative, or vice versa) across a given treatment threshold of 0.8.

Chapter III - Methods and Results from Invasive Physiology

3.1 - Method Overview

GRAVITY is a prospective observational study conducted at the Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Foundation Trust comparing supine and prone invasive coronary physiology.

Prone patient position during invasive coronary angiography is a novel concept, with no previous guidance in the medical literature. At the time of writing, no evidence existed of instrumentation of an artery in a prone patient. I designed the study and wrote the protocol and supporting documents, obtained ethical permission and screened and recruited all patients. I collected all physiological data during angiography and performed subsequent analysis. The first patient was successfully studied at the Essex Cardiothoracic Centre in July 2017.

There were many technical, safety and ethical considerations which were addressed with careful planning and multiple trial runs using staff as practice patients.

3.2 - Primary and Secondary Endpoints

The aim of the methodology is to capture data required to prove or disprove the end-points of the study.

Primary Endpoint

- The delta change in pressure based measurements between supine and prone measurements

Secondary Endpoint

- The delta change in velocity recordings, between supine and prone measurements

3.3 - Ethical Approval and Study Population

3.3.1 - Ethical Approval

The study protocol was given a favourable opinion by the East of England - Cambridge South Research Ethics Committee on 16th of March 2017.

3.3.2 - Clinical Study Registration

The GRAVITY study is registered on the clinical database website ClinicalTrials.gov (identifier: NCT03097172).

3.3.3 - Study Population

The study population consisted of patients with coronary artery disease of 'moderate severity' referred to our institution for further assessment of coronary artery severity in the form of a 'pressure wire'. All were elective day case patients loaded with aspirin and clopidogrel in preparation for possible stent implantation. All patients were provided with written study information and the chance to ask any questions before giving written consent. They were also involved of their right to withdraw at any time, without affecting their medical care.

Inclusion and exclusion criteria are given below (Table 10), as well as a flowchart summarising the procedure (Figure 22)

Inclusion Criteria	Exclusion Criteria
1. Age > 18 years of age	1. Previous CABG with any patent grafts
2. Anginal symptoms or evidence of myocardial ischaemia	2. Significant left main stem stenosis
3. Stenosis >50% on coronary angiogram or CT coronary angiogram	3. Haemodynamic Instability
4. Participant is willing and able to give informed consent	4. Unable to consent
5. Eligible for PCI	5. Unable to receive dual antiplatelet therapy

6. Contraindication to adenosine

7. Recent acute coronary syndrome (ACS) (<48 hours)

8. Pregnancy

9. Unable to lie prone

10. Severe valvular heart disease or cardiomyopathy

11. Severe renal dysfunction (eGFR <30mls/min)

Table 10 - Inclusion and exclusion criteria. PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, ACS = acute coronary syndrome, CT = computed tomography.

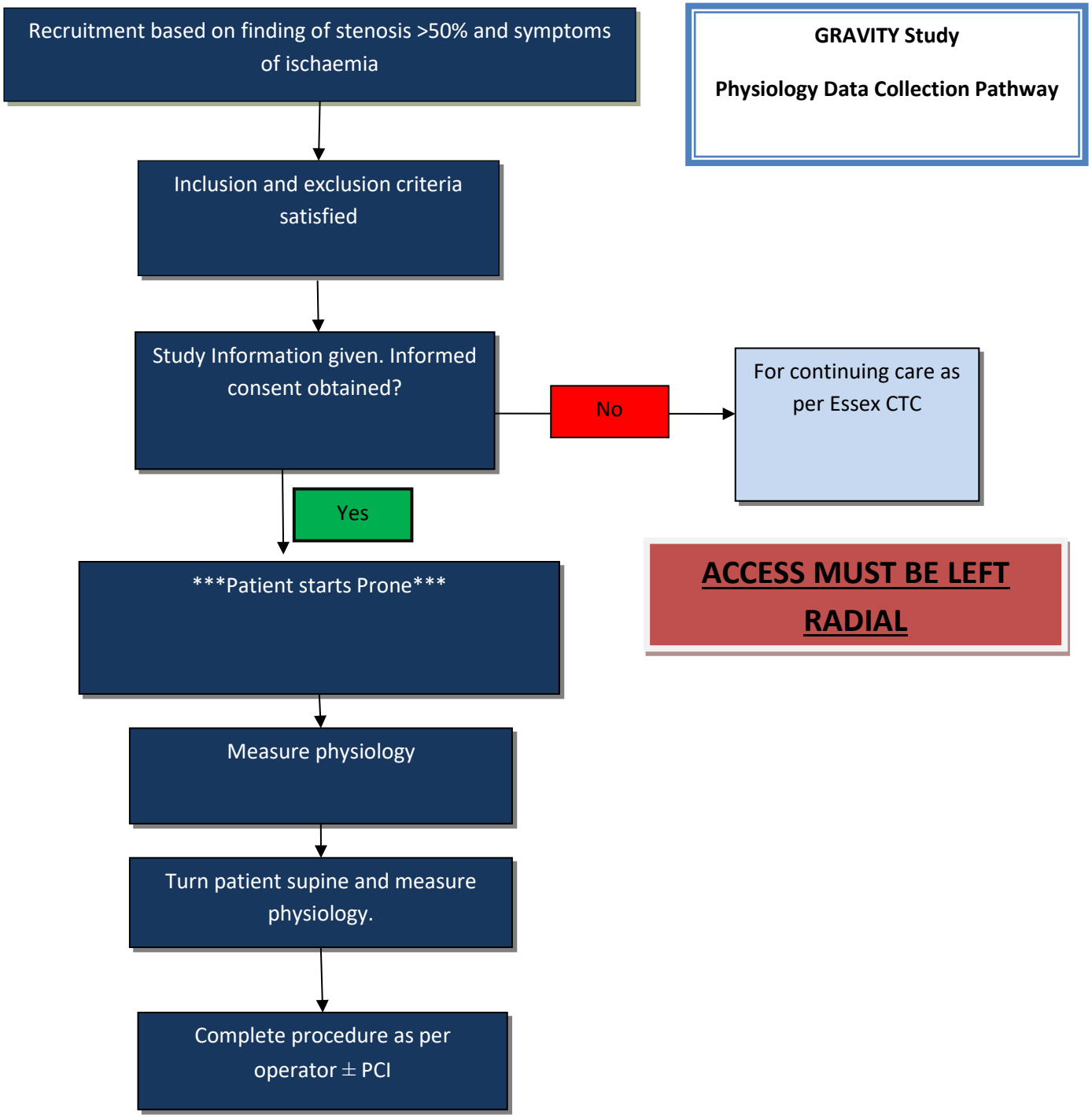


Figure 22 - Patient Flowchart

3.4 - Sample Size Calculation and Statistical Analysis

Sample size was calculated for 80% power, and for a p value of <0.05, using a paired T-test to meet the primary endpoint. GPower3™ statistical software calculator was used for the power calculation (Faul et al., 2007).

In our study, a standard deviation of the difference in the mean of 0.04 is used for FFR, as has been for previous studies assessing change in coronary artery physiology (Ladwiniec et al., 2015). The minimum difference we expect to see between prone and supine physiology measurements using the mean is 0.06. This calculated minimum difference is extrapolated from CT coronary data (See Data from Chapter II), where the smallest height difference (Circumflex artery) equates to a 0.03 change in one position. When the patient is turned from prone to supine, this number will in theory double, meaning a total change of 0.06.

UsingGPower3™, for a two tailed, matched T-test, with 80% power and a 5% error rate, the minimum sample size required is 6. As three coronary arteries are being included, 6 measurements per artery, equates to 18 patients overall as a minimum. Ethical approval was obtained for 30 patients in total, with regular data review during recruitment. The calculation from GPower3™ is shown below in Figure 23.

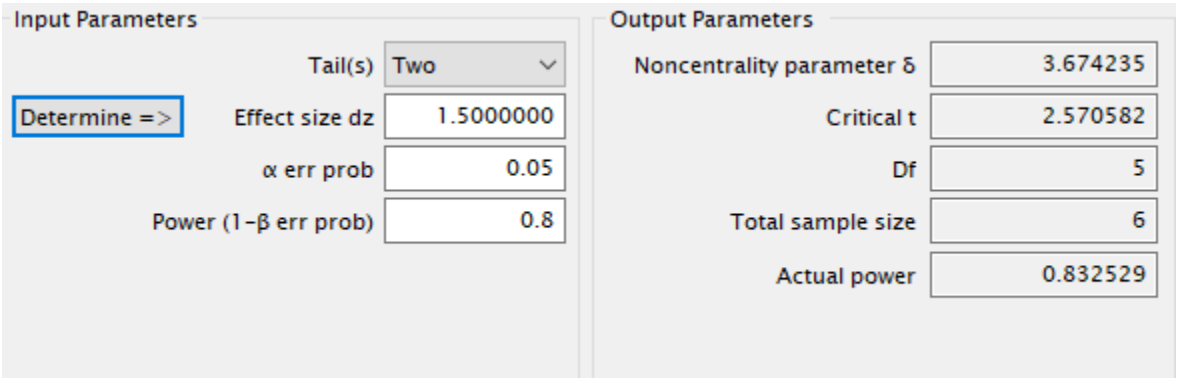


Figure 23 - Power Calculation - using GPower3™. Effect size was calculated using difference between the means of matches pairs (0.06) and standard deviation (0.04).

Continuous variables are presented as means with standard deviation. Categorical variables are presented as numbers and percentages. Delta change in measurements between prone and supine position are given a positive delta if the direction of change is as expected based on physical principles. A negative value is given if against. Correlation between height differences and delta change in pressure-based indices was assessed by Spearman's correlation/

All statistics were calculated using IBM SPSS® statistics software.

3.5 - Study Challenges

Supine standard measurements are a daily occurrence at our institution. Prone position is completely novel, and as such was carefully planned.

3.5.1 - Vascular access

Safe femoral access is not possible when prone. Left radial access was chosen as the most simple and safe site.

|The sheath is inserted with the patient prone and wrist pronated at the standard right side of the X-ray table. (Figure 24 and 25).

Figure 24 - Prone Positioning - The left arm is being draped and readied for arterial puncture. ECG leads are already attached. Permission for use from all involved.

Figure 25 - Prone Positioning 2- Patient being positioned prone, with two members of the team on each side for safety.

3.5.2 - Turning Manoeuvre

Prone positioning has been used for ventilated patients suffering from acute respiratory distress syndrome (ARDS) (Kallet, 2015). Intensive care staff kindly offered training to catheter laboratory staff.

The patient was treated as a 'sedated' patient and prompted not to assist or move the left arm (holding the radial sheath). When the study protocol required turning from prone to supine, two slide sheets are inserted under the patient and pulled in the correct direction. Two members of

staff are situated on each side of the table to ensure the patient cannot fall off the table and a central position is maintained. Before turning, all coronary catheters, physiology wires and other equipment attached are removed from the patient. Cannulae could be temporarily disconnected and reconnected once turned. ECG leads were not removed but could be adjusted if displaced during repositioning.

Displacement of the sheath was a possibility during turning, and the team had to be observant regarding this issue. A checklist of events is given in Appendix D.

3.5.3 - Procedural Considerations

Once the patient is in a prone position, the procedure is largely the same as in a supine position. Puncturing the left radial artery in a prone patient, with a pronated hand, is anatomically different to standard procedure. Operators had to adjust their puncture technique to compensate for this.

Secondly, the image and position of the coronary arteries were reversed. For example, the right coronary artery originated on the right side of the screen (as opposed to the left side in standard angiography - Figure 26).

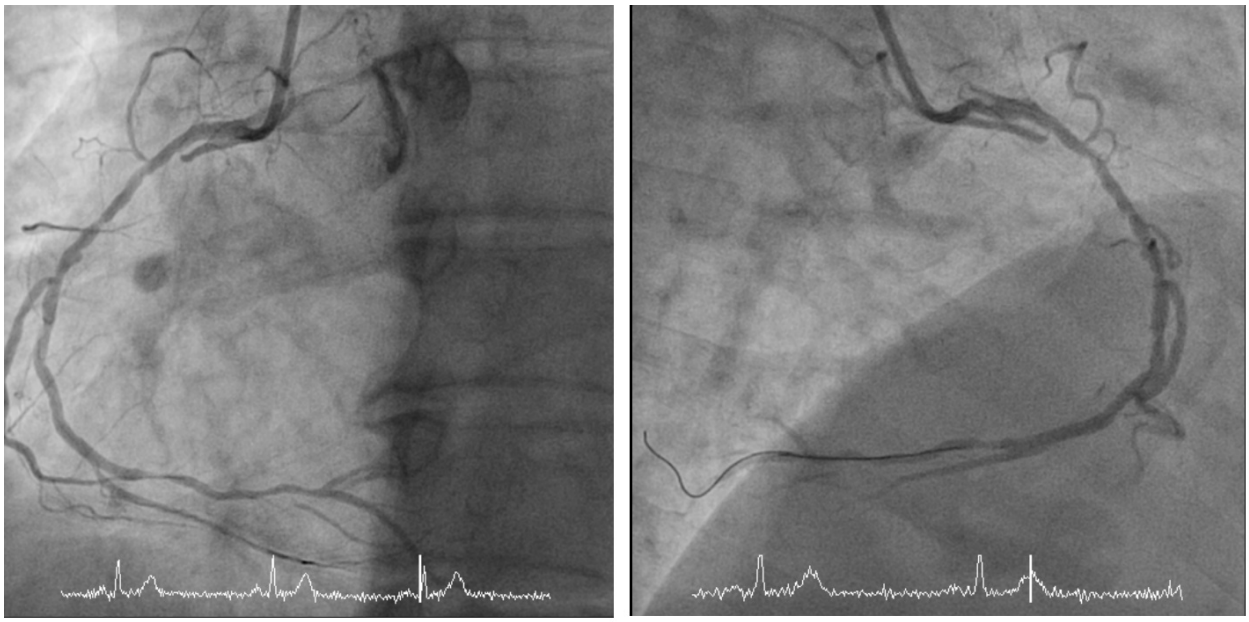


Figure 26 - Prone Angiographic Projection - Standard angiographic appearance of the right coronary artery in a supine patient on the left. On the right, the right coronary artery is seen in a prone patient with the origin appearing from the opposite side of the screen.

Cranial and caudal views were also reversed. Therefore, the operators and radiographer had to reverse normal projection positions to visualise specific arteries (Appendix E).

There were other technical considerations. Firstly, accessory equipment such as ECG's and cannulae had to be tested to make sure their length was adequate when a patient was prone. Oxygen nasal cannula and masks were also tested to ensure oxygen delivery was safe and uncompromised in the prone position.

3.5.4 - Safety and Practical Considerations

Our utmost consideration was for the safety and comfort of our patients. Pillows and hand gel cushions were placed to ensure optimal comfort during the procedure. As part of the pre-

screening, patients were asked of any difficulties lying prone and any measures that could be taken to ease this. In some cases, the patient was asked to lie themselves prone outside in recovery before the procedure, to try and anticipate any issues with lying in this position.

Nausea is sometimes experienced during angiography. Being prone actually reduced the risk of aspiration and made management of vomiting somewhat easier.

Defibrillation pads could be placed anterior and posterior or posterior and lateral or (instead of anterior and lateral) when the patient was prone. If defibrillation did not restore spontaneous circulation, chest compressions would be inefficient when prone. The team would therefore perform a turning manoeuvre in the event of a cardiac arrest requiring CPR. The estimated delay in turning is 10-20 seconds at maximum.

Asystole or severe bradycardia is a transient phenomenon occurring in approximately 5% of cases (Landau et al., 1994). Causes include contrast injection, medication or temporary occlusion of a coronary artery. If this occurred, the patient would be positioned supine immediately.

3.6 - Study Protocol

3.6.1 - Prone Component

Once arterial access is gained via the left radial artery (and verapamil or nitrate has been given intra-arterially to avoid vasospasm), a standard guidewire with overlying 6 French catheter of the operators choice, is passed into the aortic root. Once the stenosis was adequately visualised, coronary physiology was measured.

3.6.2 - Physiology Wire

Pressure and velocity measurements were recorded in the coronary artery of interest. A Combowire™ made by Volcano Corporation (San Diego, California, United States) was used in all cases. This was connected to a Combomap© device, to capture the outputs from the wire.

Pressure sensors on the wire are placed at 1.5cm from the wire tip, while flow sensors are at the tip itself (Figure 27). This is critical information when normalising the wire in the coronary artery.

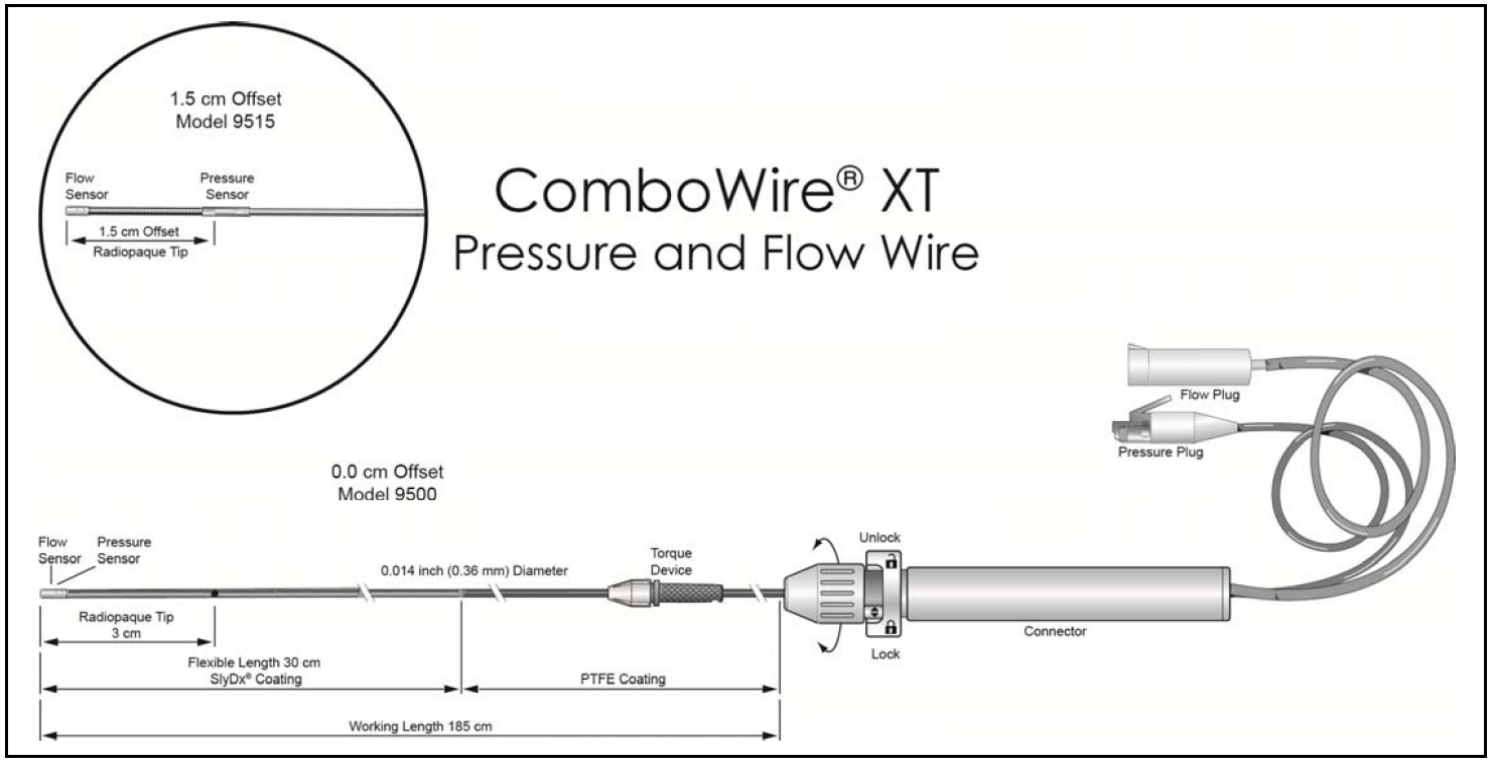


Figure 27- ComboWire - Illustration of the Combowire (Image from Volcano Corporation, San Diego, California, USA).

3.6.3 - Combomap System

Unfortunately, our integrated physiology system in the laboratory, even though manufactured by Volcano Corporation, was only compatible with a pressure wire, not a pressure and velocity wire. Therefore, a standalone unit was used, capable of measuring pressure and velocity outputs (See Figure 28). The signal was split from the lab haemodynamic unit and fed into the Combomap system.

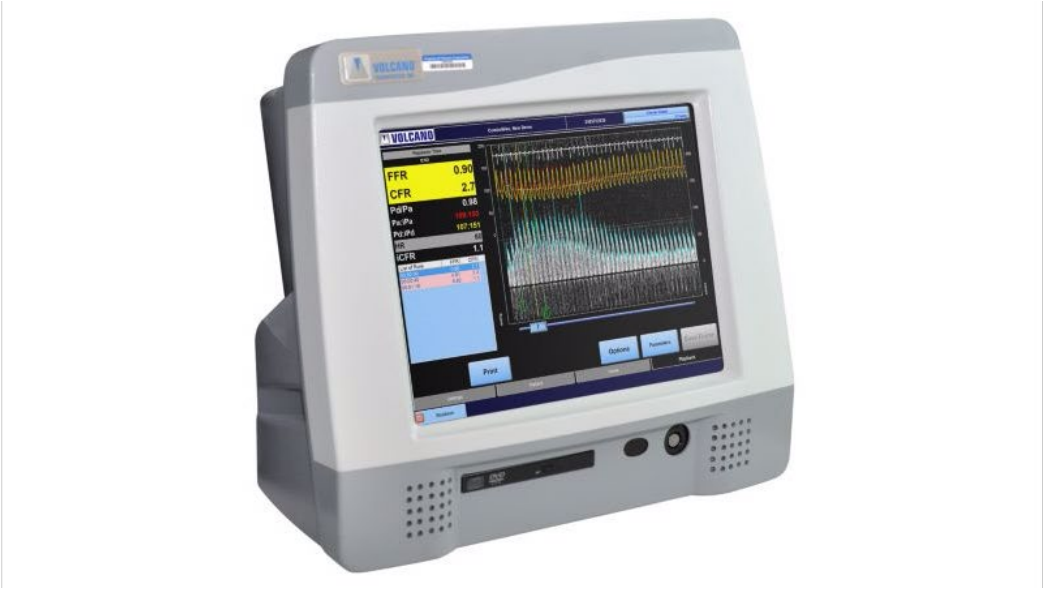


Figure 28 - Combomap System - used for physiology output data. (Image from Volcano Corporation, San Diego, California, USA).

3.6.4 - Physiology Measurements

70-100 units per kg of unfractionated Heparin is given prior to physiology wire insertion. Measurements were taken on a Combomap™ system (Volcano Corp, San Diego, California, United States) connected via a pressure and flow plug, as illustrated above. The Combomap™

system was zeroed at the same time as the laboratory invasive pressure monitoring, at the beginning of the case. Pressure is normalised at the coronary ostium. Intra coronary gylcerlytrinitrate at a dose of 250-500 micrograms is then administered followed by a saline flush of 10ml. This process has remained largely unchanged from its initial experimental publication in medical literature (Pijls et al., 1993). Figure 29 shows data collected from a patient on the Combomap™ system.

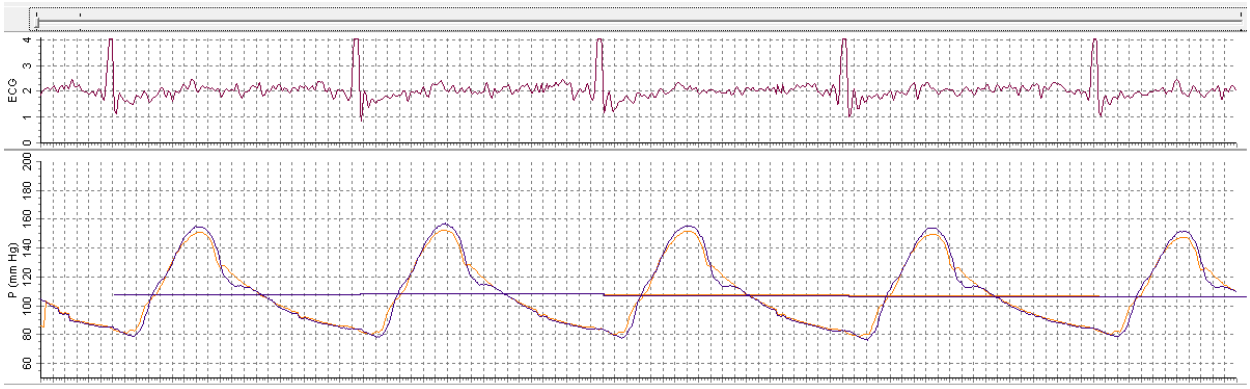


Figure 29 - Invasive Pressure Normalisation - in a GRAVITY patient. Top strip showing the patient's ECG, with some minor interference. Bottom strip showing invasive blood pressure (red line) normalised with the Combowire™ pressure readings (yellow line).

Once adequately normalised, the wire was passed beyond the stenosis, into the distal vessel. Initially the wire was placed as distally as possible. Once in position, slight adjustments in torque of the wire were made to give the clearest velocity doppler trace. Resting Pd/Pa and resting flow were measured. In some cases, it was necessary to move the wire slightly back or forward to achieve a clear velocity trace. The position was noted and fluoroscopically stored for the upcoming supine physiology measurements.

Hyperaemic measurements were taken with the intravenous infusion of 140/mcg/kg of adenosine. During hyperaemia, FFR and hyperaemic velocity measurements were obtained. Finally, a 'drift check' was conducted to ensure there was no pressure deviation from the original normalisation, ensuring the Pd/Pa was 1.0 (±0.02). Figure 30 shows a hyperaemic trace

measured on the Combomap™ system. This is the same patient as Figure 29 previously. This concludes the prone aspect of the study protocol. The patient is now turned supine.

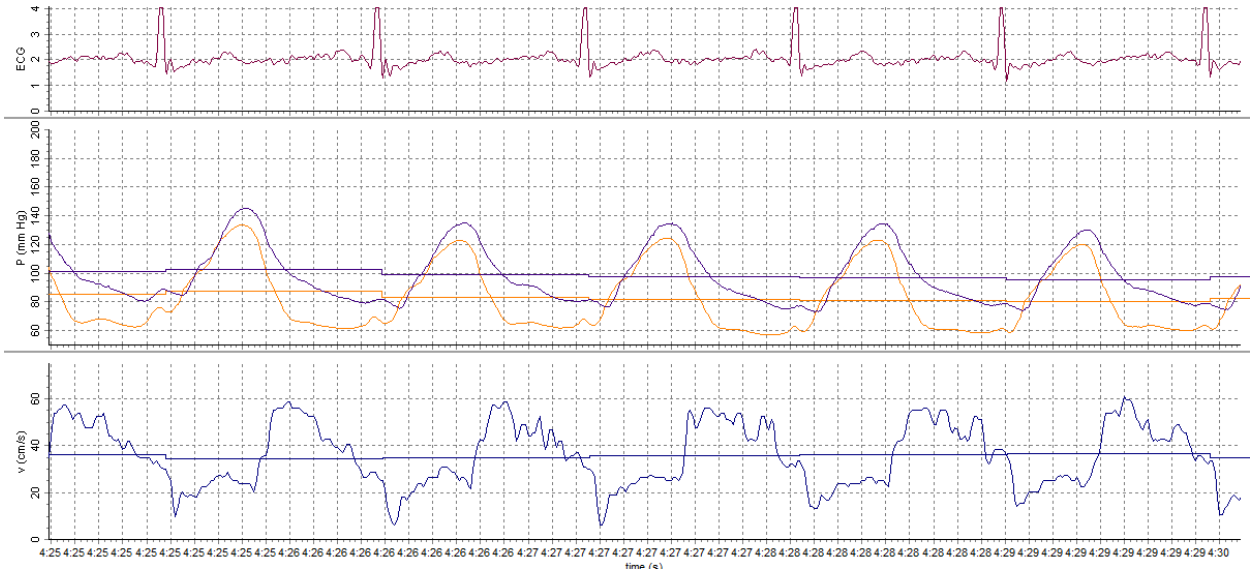


Figure 30 - Hyperaemic Pressure and Flow Measurements - from the Combomap™ system. The top strip demonstrates the ECG, middle strip shows aortic pressure (blue) versus wire pressure (yellow) in the distal vessel. The bottom strip is an outline of the hyperaemic flow in the distal vessel measured by the wire. The FFR in this vessel was 0.85 in the prone position.

3.6.5 - Supine Component

Supine protocol is identical to prone. The wire was placed as identical a position as it was during prone angiography. Side branches and anatomical landmarks were used as a guide.

The operator is given supine FFR measurements as a diagnostic aid. No input or guidance was given by the study team at any point with regards to stenting.

3.6.6 - Post Procedure and Recovery

No extra precautions were taken post procedure or during recovery. The patient was observed in recovery on a cardiac monitor over the next 4 to 6 hours. Once reviewed by clinical staff (including a post procedure ECG), the patients were allowed home the same day. Contact details were left to allow patients to liaise with the research team if there were any further issues. No follow-up procedures or investigations were organised as part of the study. Patients exited the study once angiography was complete.

3.7 - Midpoint Protocol Changes

After the tenth patient, the study team reviewed all results and implemented slight changes to the protocol, within ethical limits.

3.7.1 - Clinical Measurement Point

A second FFR measurement point was added during hyperaemia. The operator was asked to choose a point in the artery where they would clinically place the wire. For one artery therefore, a distal FFR and clinical FFR were measured. The reason for this change is to assess whether a more proximal wire position would still be significant, given the expected lesser effect of hydrostatic pressure.

In some cases, where the coronary stenosis was very distal, the distal wire position was the same as the clinical position.

3.7.2 - Left Lateral View and Vertical Height Measurement

A ninety-degree left lateral X-ray picture was taken in a subset of patients to assess vertical height from wire to aorta. This is the similar to the pre-study coronary CT height data, but directly from angiography. This change was implemented to try and identify a correlation between vertical height and the change in Pd/Pa, iFR and FFR. Figure 31 is an example of a measurement acquisition.

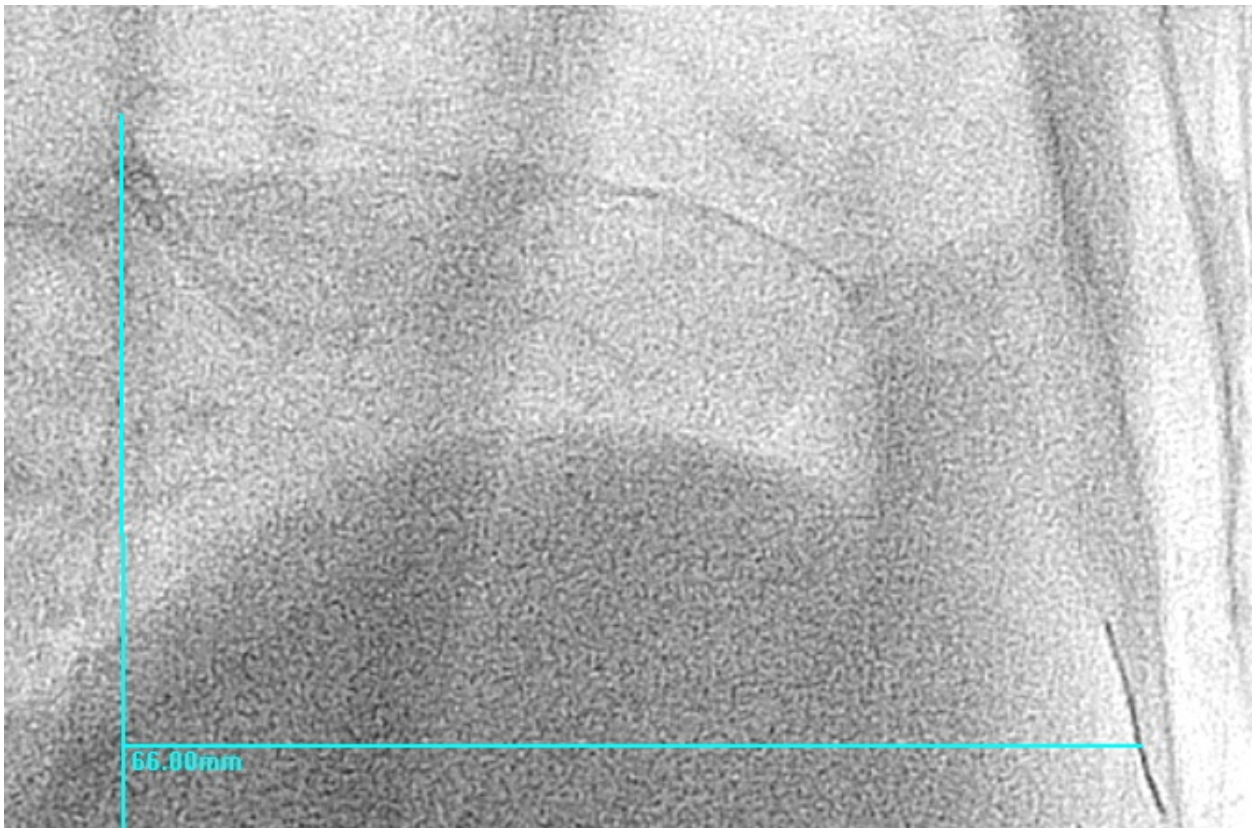


Figure 31 - Guide to Wire Measurement - in the left lateral x-ray view between the guide catheter, top left, and the sensor on the wire, bottom right.

3.8 - Data Analysis

Data was analysed using a software program called Study Manager™ (Volcano Corporation). Optimal tracings for resting and hyperaemic indices were used to obtain:

1. Resting distal pressure over aortic pressure (Pd/Pa)
2. iFR
3. Resting velocity
4. Hyperaemic Pd/Pa (also known as fractional flow reserve)
5. Hyperaemic velocity

Five cardiac cycles were averaged to give the above values (apart from iFR which required ten cycles), which were imported into an Microsoft Excel™ for further statistical analysis. Flow and pressure measurements were taken, whenever possible from the same five beat sample, as long as quality was adequate for both. Mean values were used for pressure and velocity recordings over these five beats.

Angiographic Data

QCA (Quantitative Coronary Analysis) was used to measure lesion length and stenosis percentage on a laboratory work-station. It was also used to measure aorta to wire distance.

3.9 - Statistical Analysis

Normally distributed continuous variables are presented as means with standard deviation. Categorical variables are presented as numbers and percentages. Data was compared for statistical significance using a Student's t test for matched pairs. Significance was calculated for

a p value of <0.05. Statistics were calculated using IBM SPSS® statistics software. SPSS was also used to calculate a Spearman correlation between two sets of data.

3.10 - Outcome Measures

Outcome measures were as follows:

Primary Outcomes

1. Change in pressure-based measurements (Pd/Pa, iFR and FFR) when prone and supine.

2. Change in hyperaemic flow velocity when prone and supine.

Secondary Outcomes

1. Correlation in vertical height (wire to aorta on QCA) and change in pressure-based measurements (protocol change during recruitment).

2. Change in pressure-based measurements (Pd/Pa, iFR and FFR) when the wire is position 'clinically' (protocol change during recruitment).

3.11 - Results Overview

The results in this chapter will be divided into the following sections:

1. Patient Demographics
2. Angiographic data
3. Resting Indices (Pd/Pa, iFR)
4. Hyperaemic Indices (FFR)
5. Velocity / Flow measurements

3.12 - The First Patient

The first patient was recruited on the 14th of July 2017.

3.13 - Patient Demographics

Twenty-one patients were recruited with twenty three coronary lesions, between July 2017 and August 2018. Ten LAD, seven Cx and six RCA lesions were included in analysis.

Patient demographics are summarised in table 11 below. All patients were male. Three female patients declined study participation. Two patients had two lesions assessed as part of one procedure. One with a lesion in the LAD and PDA, a second with PLV and Cx. All right coronary lesions were in a dominant vessel.

One patient suffered a physiology wire related dissection in side branch of a main vessel. This was treated conservatively with no clinical sequelae. The patient was discharged home the same day. There were no other adverse events post procedure for any recruited patient.

	Total (%)	LAD (%)	Cx (%)	RCA (%)
Total Number	23 (100)	10	7	6
Age	63	65	61	63
Male	23 (100)	10(100)	7 (100)	6 (100)
Height (cm)	174	174	176	170
Smoking	1 (4)	0 (0)	1 (14)	0 (0)
Diabetes	3 (13)	1 (10)	0 (0)	2 (33)

Hypertension	10 (43)	5 (50)	1 (14)	4 (66)
Hypercholesterolaemia	11 (48)	4 (40)	3 (43)	4 (66)
Family History	2 (9)	1 (10)	0 (0)	1 (17)
Ejection Fraction	52	52	51	54
% Stenosis*	50	43**	50	63**
Complications	1 (4)	1 (10)	0	0
Adverse Events (re-admission, MI, stroke, death)	0	0	0	0

*Table 11 - Patient Demographics - In Vivo Data. Divided per artery. *Right coronary artery stenosis was significantly higher on angiographic QCA compared to the LAD.*

On average, LAD lesions were less angiographically severe compared to the overall average (58% vs. 63%) and RCA lesions were more stenosed (78% vs. 63%). The LAD was significantly less stenosed on QCA when compared to the RCA ($p<0.05$).

3.14 - Lesion Characteristics

Specific lesion data is summarised below per artery studied (Table 12). Stenosis percentage was calculated using QCA (quantitative coronary analysis).

Case Number	% Stenosis	Length (mm)	Position of Lesion
		LAD	
1	48	17.9	Proximal
4	52	10.5	Proximal
7	51	13	Proximal
9	43	21.2	Proximal
10	41	6.6	Proximal
11	10	4.1	Mid
15	43	4.5	Proximal
16	38	10.7	Mid
17	60	6.8	Proximal
18	43	8.6	Mid
Mean (± SD)	43 (±13.2)	10.4 (±5.6)	-
		Circumflex	

Case Number	% Stenosis	Length of Lesion (mm)	Position of Lesion
2	44	13.2	Mid
3	57	14	Distal
6	44	22.8	Mid
8	61	4.9	Proximal
21	46	10.5	Proximal
22	55	22.3	Mid
23	46	5.0	Mid
Mean (± SD)	50.0 (± 7.0)	13.2± 7.3)	-
Right Coronary Artery			
Case Number	% Stenosis	Length of Lesion (mm)	Position of Lesion
5	52	19.6	Mid
12	47	5.3	Distal
13	70	11.9	Mid
14	70	11.9	Proximal
19	55	12.0	Distal
20	84	5.2	Distal
Mean (± SD)	63.0 (± 14.0)	11.0 (± 5.3)	-

Table 12 - Stenosis Data for All Cases

Overall five patients of twenty three were treated with coronary stents following measurement of FFR. Three LAD lesions and two RCA lesions. Table 13 summarises this.

Case	Artery	FFR	Treatment
4	LAD	0.72	3.0 x 16 Synergy DES
5	RCA	0.62	3.5 x 20 Synergy DES
7	LAD	0.64	3.0 x 24 Synergy DES
17	LAD	0.54	2.75 x 38 Xience DES and 3x 8 Xience DES overlapping
20	RCA	0.7	2 x 18 Xience DES

Table 13 - Treated Lesions. Stent lengths are in mm.

3.15 - Guide to Wire Measurement

Guide to wire measurement for all arteries are shown in table 14 below. Using the collected height data, the estimated pressure change is estimated. Assuming a Pa pressure of 100, the mean predicted change in FFR is 0.09 in the LAD, 0.05 in the Cx and 0.05 in the RCA (figure 32).

Case Number	Artery	Guide to Wire Height (mm)	Estimated Hydrostatic Effect (mmHg)
10	LAD	66	10.6
11	LAD	52	8.4
12	PLV	33.4	5.4
13	PLV	50	8
14	PDA	11.1	1.8
15	LAD	53.5	8.6
16	LAD	42.9	6.8

17	LAD	68.1	10.8
18	LAD	65.3	10.4
19	PLV	46.5	7.4
20	PLV	20.4	3.2
21	CX	35.9	5.8
22	CX	29.3	4.6
23	CX	27.7	4.4

Table 14 - Guide to Wire Data. Measurements in mm, and the estimated hydrostatic effect. The vertical distance should double (x 2) when the patient changes position from supine to prone, as the wire is rotating around the 'axis' of the aorta. The estimated effect factors this in.

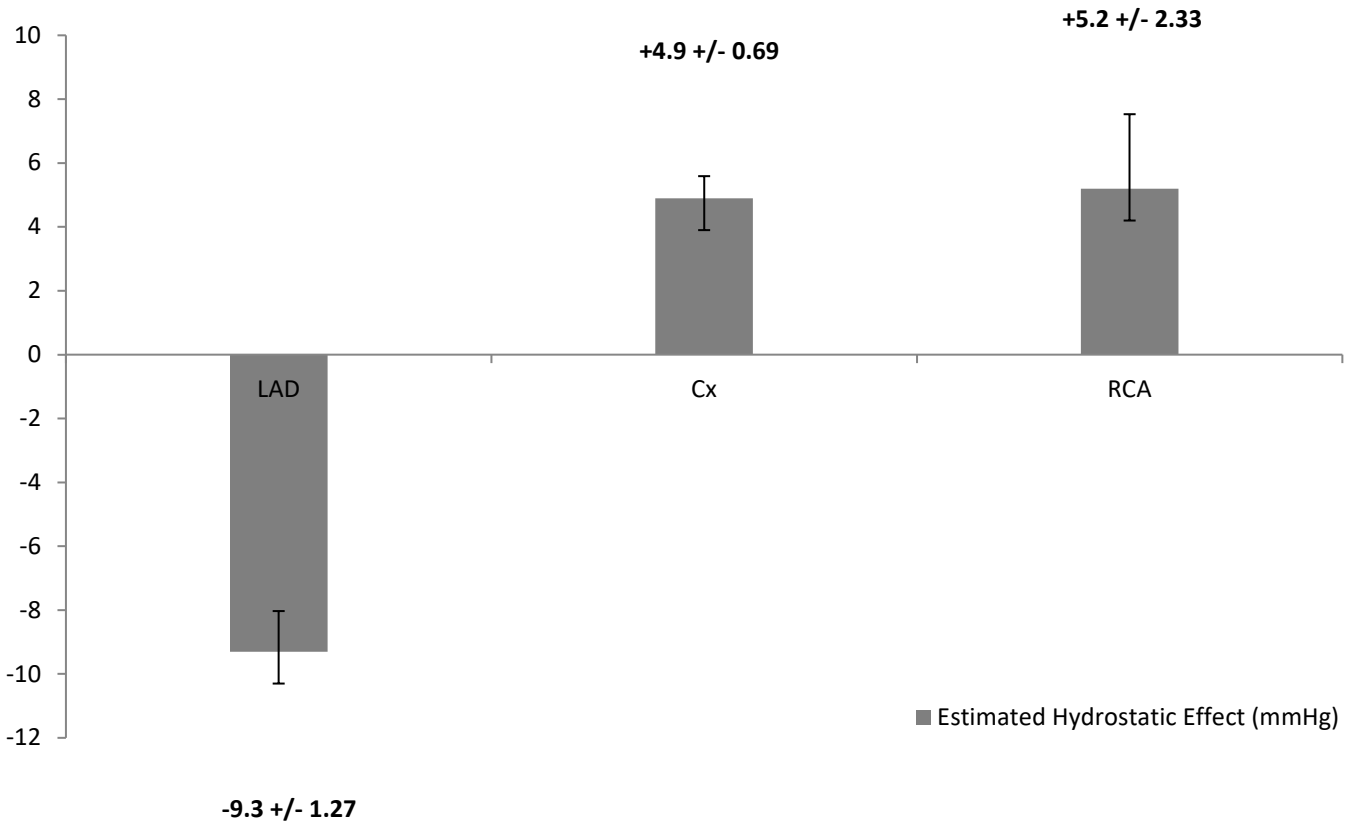


Figure 32 - Estimated Hydrostatic Effect - calculated from mean guide to wire measurement in mmHg across all coronary arteries ± *standard deviation. Mean LAD = 9.3 mmHg, Cx = 4.9 mmHg, RCA = 5.2 mmHg.*

3.16 - Pressure Based Indices

3.16.1 - Delta Change

Prone and supine pressure-based indices are compared to produce a delta change. For each artery, there is a predicted direction of change. For example, an LAD is situated inferiorly in a prone patient (pressure increases), and superiorly when supine (pressure decreases). We

therefore expect the pressure measurement to drop when moving from prone to supine and vice versa. This is the expected direction of change.

If the change seen is in the predicted direction, the calculated delta change will be allocated a positive value. A change in the opposite direction of expected change will be allocated a negative delta. This is for all pressure-based indices. A summary of the expected direction of change in all arteries is shown below in table 15.

Artery	Prone Pressure	Supine Pressure	Expected Change
LAD	Higher	Lower	Decrease
Cx	Lower	Higher	Increase
PDA	Higher	Lower	Decrease
PLV	Lower	Higher	Increase

Table 15 - Anticipated Direction of Change. This is the expected direction of change and is allocated a positive delta value.

3.16.2 - Pd/Pa

Prone versus supine data from all Pd/Pa measurements is presented table 16. The mean delta change between positions was 0.05 ($p < 0.0001$). Figure 33 shows superior versus inferior artery position Pd/Pa across all vessels. One cannot compare prone and supine positions across all vessels simultaneously, as some are inferior when prone and some superior when prone (and vice versa). Superior position is expected to produce lower pressure-based values.

Mean superior vs. inferior Pd/Pa was 0.91 vs. 0.96 respectively ($p < 0.001$). Each group of arteries was also statistically significant ($p <0.05$).

Vessel (n)	Prone Pd/Pa Mean (±SD)	Supine Pd/Pa Mean (± SD)	Delta Change Mean (±SD)	P Value
LAD (10)	0.96 (0.07)	0.88 (0.09)	0.08 (0.04)	0.0006
Circumflex (7)	0.93 (0.03)	0.98 (0.02)	0.05 (0.04)	0.009
RCA-PDA(2)	0.93 (0.03)	0.91(0.06)	0.02 (0.02)	0.032
RCA-PLV (4)	0.91 (0.07)	0.98 (0.02)	0.07 (0.05)	
All (± SD) (23)	-	-	0.05 (0.04)	<0.0001

Table 16 - Prone vs. Supine Pd/Pa. Prone mean Pd/Pa and supine mean Pd/Pa with delta change and standard deviation.

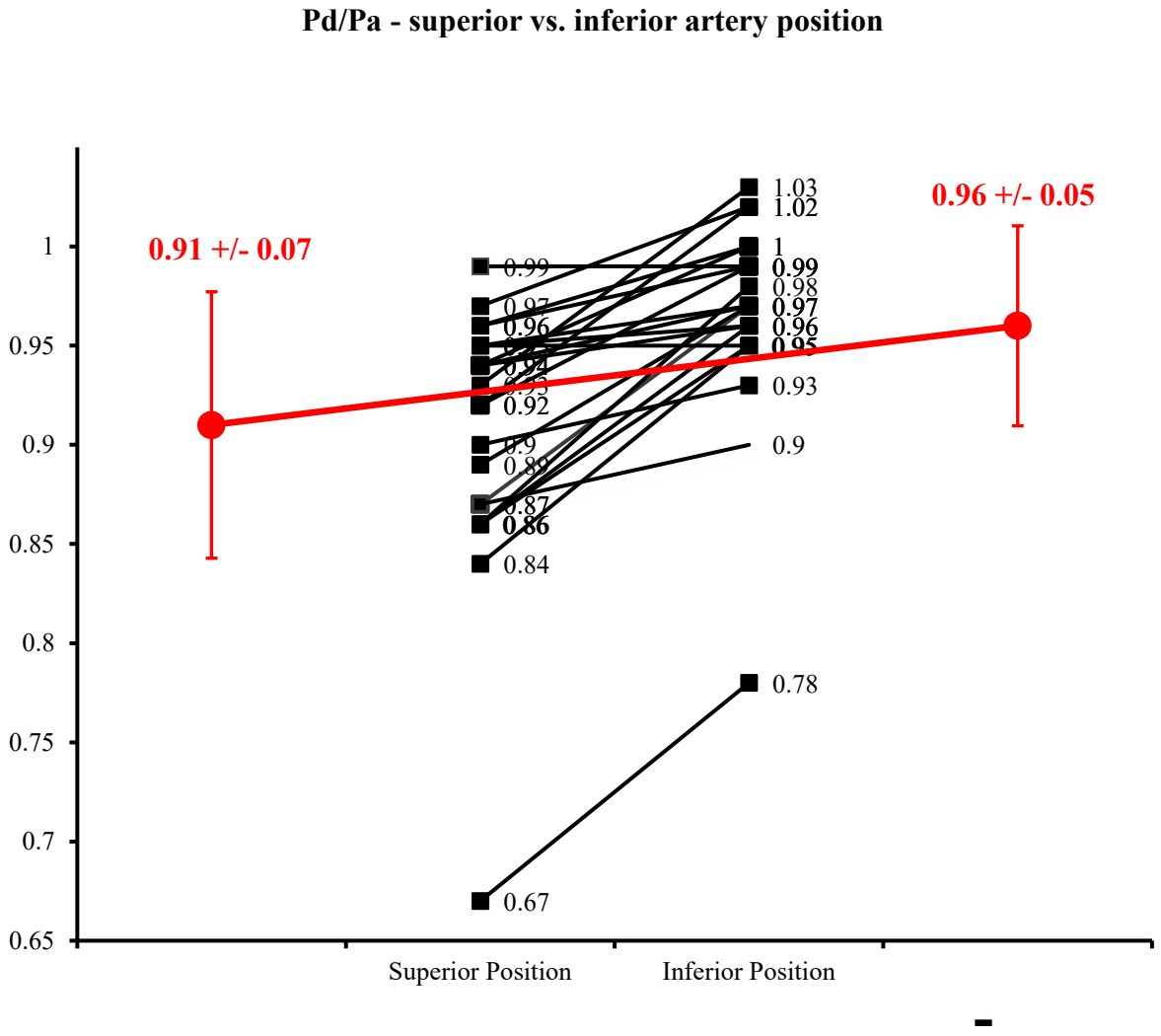


Figure 33 - Pd/Pa of Superior vs. Inferior artery position. Mean values are in red. The results are statistically significant. ($p<0.05$).

Data grouped per artery is shown below.

Left Anterior Descending Artery Measurements

Table 17 and figure 34 show Pd/Pa in all cases of LAD stenosis. Prone Pd/Pa was 0.96 vs. 0.88 when supine. The mean difference of 0.08 was statistically significant (p=0.0006)

Case Number	Prone Pd/Pa	Supine Pd/Pa	Delta Change	
1	0.99	0.99	0.00	
4	0.97	0.87	0.10	
7	0.95	0.86	0.09	
9	1.02	0.92	0.10	
10	1.03	0.93	0.09	
11	1.02	0.97	0.05	P = 0.0006
15	0.96	0.94	0.02	

16	0.97	0.95	0.02
17	0.78	0.67	0.11
18	0.95	0.84	0.11
Mean (±SD)	0.96 (0.07)	0.88 (0.09)	0.08 (0.04)

Table 17 - LAD Pd/Pa. Delta change in Pd/Pa between prone and supine positioning in the left anterior descending artery. The results are statistically significant ($p<0.05$)

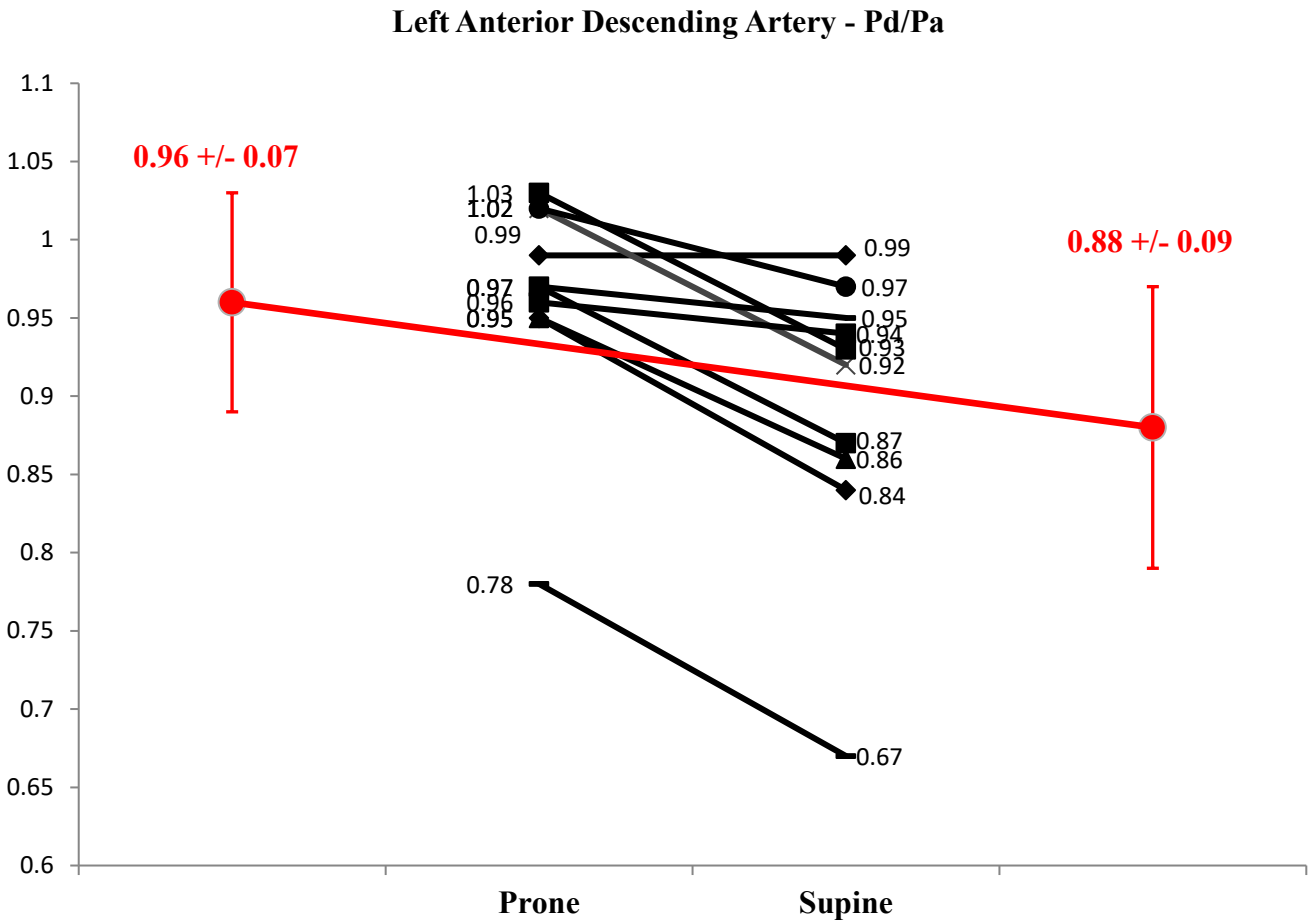


Figure 34 - LAD Pd/Pa - between prone and supine positioning. Mean values are in red. The results are statistically significant. ($p<0.05$).

Circumflex Artery Measurements

Table 18 and figure 35 compare Pd/Pa in all cases of Cx stenosis. Prone Pd/Pa was 0.93 compared to 0.98 when supine. The mean difference of 0.05 is statistically significant (p=0.009)

Case Number	Prone Pd/Pa	Supine Pd/Pa	Delta Change	
2	0.96	1.0	0.04	
3	0.96	0.99	0.03	
6	0.95	0.97	0.02	
8	0.92	0.99	0.07	
21	0.86	0.98	0.12	P = 0.009
22	0.94	0.96	0.02	
23	0.94	1.0	0.06	
Mean (±-SD)	0.93 (0.03)	0.98 (0.02)	0.05 (0.04)	

Table 18 - Cx Pd/Pa. Delta change in Pd/Pa between prone and supine positioning in the circumflex artery. All values here changed as expected. The results are statistically significant ($p<0.05$)

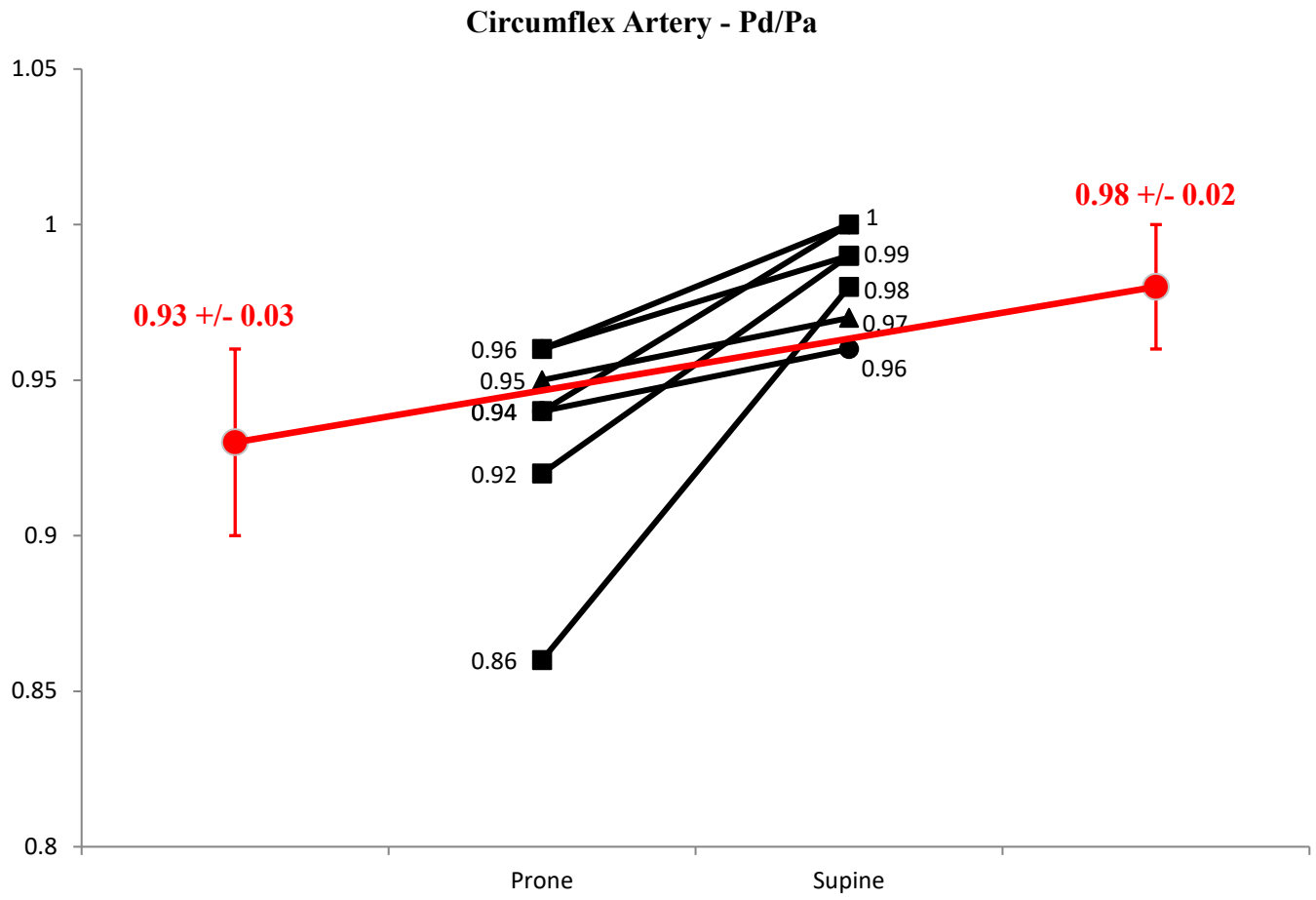


Figure 35 - Cx Pd/Pa Delta Change - between prone and supine positioning. Mean values are in red. The results are statistically significant. ($p<0.05$).

Right Coronary Artery Measurements

Table 19 and Figure 36 summarise all RCA data. The mean delta change of 0.05 was statistically significant (p=0.032).

Case Number	Prone Pd/Pa	Supine Pd/Pa	Delta Change	
5 (PDA)	0.9	0.87	0.03	
14 (PDA)	0.95	0.95	0.00	
PDA Mean (+SD)	0.93 (0.03)	0.91 (0.06)	0.02 (0.02)	
12 (PLV)	0.96	0.99	0.03	
				P = 0.032
13 (PLV)	0.86	0.96	0.10	
19 (PLV)	0.9	0.93	0.03	
20 (PLV)	0.89	0.97	0.09	
PLV Mean (±SD)	0.91 (0.07)	0.98 (0.02)	0.07 (0.05)	
PLV and PDA Mean (± SD)			0.05 (0.04)	

Table 19 - RCA Pd/Pa. Delta change in Pd/Pa between prone and supine positioning in the right coronary artery. The results are statistically significant ($p<0.05$)

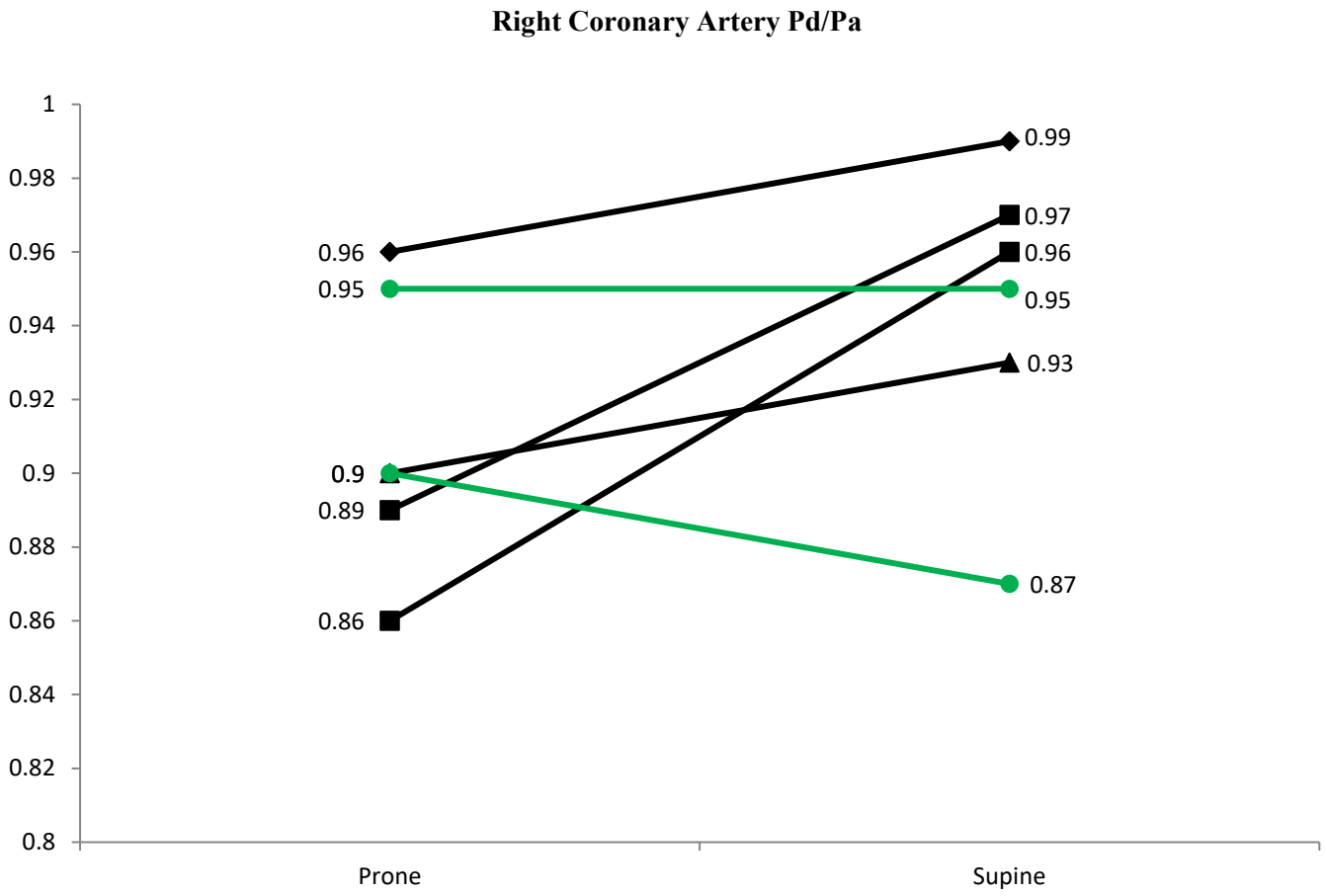


Figure 36 - RCA Pd/Pa Delta change - between prone and supine measurements is statistically significant ($p<0.05$).

3.16.3 - Instantaneous Wave Free Ratio (iFR)

iFR data across all arteries is shown in Table 20. All iFR data is shown in figure 37, which compares superior to inferior artery position. The mean delta change in iFR was 0.06 ($p < 0.0001$). One iFR measurement could not be retrospectively calculated, so data is from the

remaining 22 measurements. Mean superior vs. inferior iFR was 0.87 and 0.93 respectively. Each group of arteries was also statistically significant, bar the RCA.

Vessel (n)	Prone iFR Mean (±SD)	Supine iFR Mean (± SD)	Delta Change Mean (±SD)	P Value
LAD (10)	0.91 (0.16)	0.85 (0.14)	0.06 (0.07)	0.02*
Circumflex (7)	0.90 (0.05)	0.97 (0.03)	0.07 (0.04)	0.01*
RCA-PDA(2)	0.86 (0.09)	0.85(0.11)	0.01 (0.02)	0.19
RCA-PLV (3)**	0.87 (0.10)	0.94 (0.04)	0.07 (0.07)	
All (±SD) (22)**	-	-	0.06 (0.05)	<0.0001*

*Table 20 - Prone vs. Supine iFR. Prone mean iFR and supine mean iFR with delta change and standard deviation. * represents statistical significance. **It was not possible to calculate iFR from one RCA-PLV recording.*

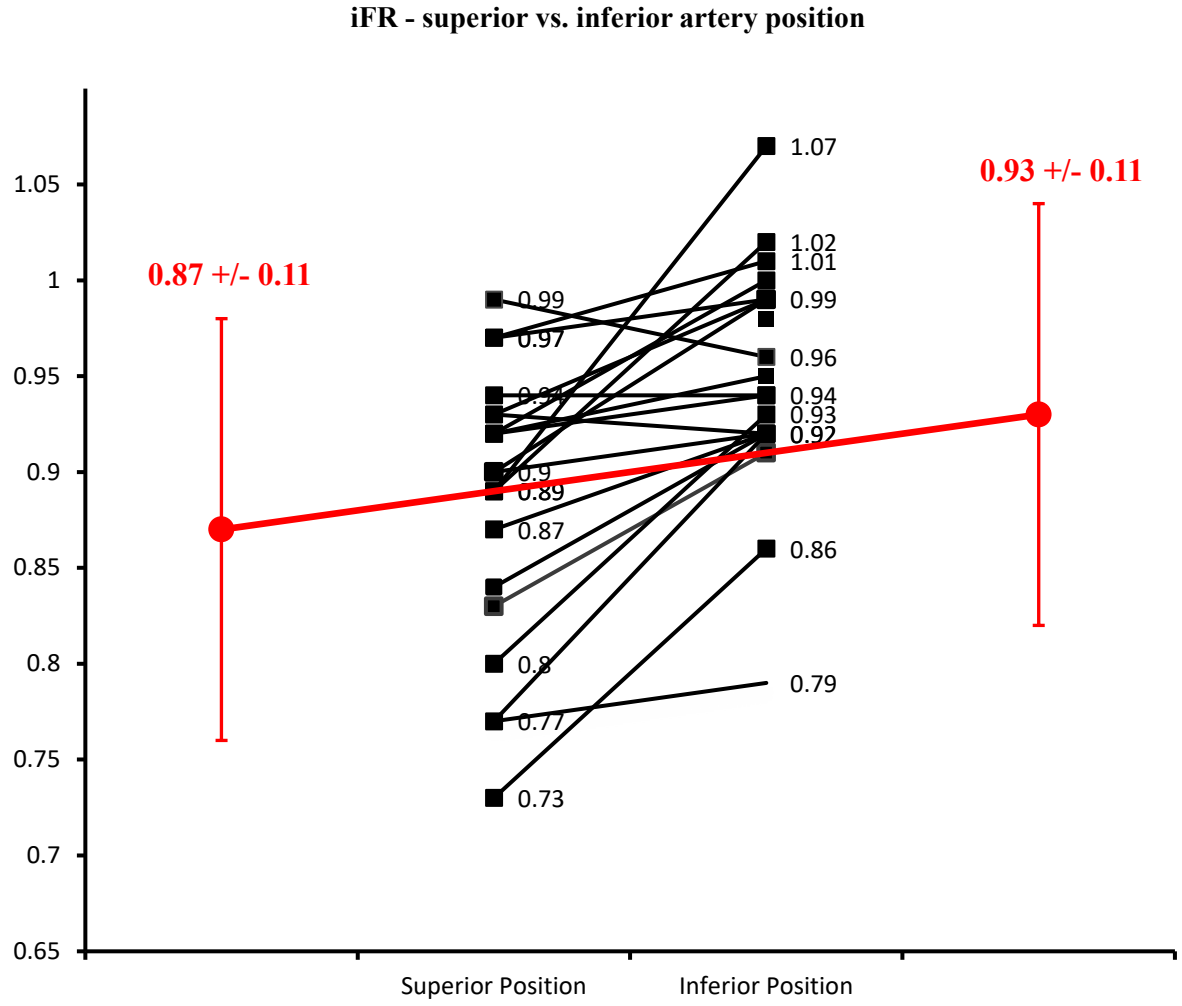


Figure 37 - Superior vs. Inferior iFR. Mean values are in red. The results are statistically significant.

Data grouped per artery is shown below.

Left Anterior Descending Artery

In the left anterior descending artery, prone vs. supine iFR was 0.91 vs. 0.85 respectively. The mean change of 0.06 was statistically significant ($p<0.05$). Table 21 and Figure 38 summarise these results.

Case Number	Prone iFR	Supine iFR	Delta Change	
1	0.96	0.99	-0.03	
4	0.91	0.83	0.08	
7	0.92	0.84	0.08	
9	1.02	0.89	0.13	
10	1.07	0.89	0.18	
11	1.01	0.97	0.04	P = 0.02
15	0.94	0.92	0.02	
16	0.94	0.94	0	

17	0.5	0.5	0
18	0.86	0.73	0.13
Mean (±SD)	0.91 (0.15)	0.85 (0.14)	0.06 (0.06)

Table 21 - LAD iFR. Delta change in iFR between prone and supine positioning in the left anterior descending artery. The results are statistically significant ($p<0.05$)

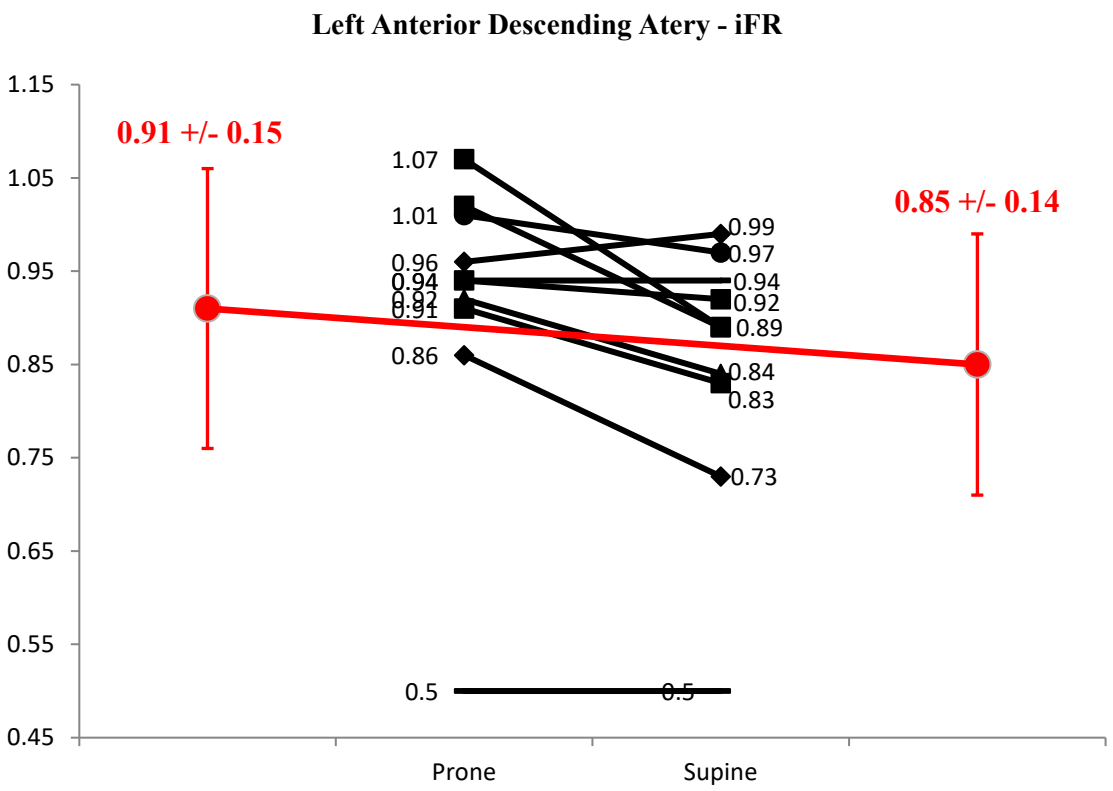


Figure 38 - LAD iFR Delta Change - between prone and supine positioning. Mean values are in red. The difference is statistically significant ($p<0.05$).

Circumflex Artery

In the circumflex artery, prone vs. supine iFR was 0.90 vs. 0.97 respectively, with the mean change of 0.07 being statistically significant ($p<0.05$). Table 22 and figure 39 summarise these results.

Case Number	Prone iFR	Supine iFR	Delta Change	
2	0.93	0.99	0.06	
3	0.97	0.98	0.01	
6	0.92	0.95	0.03	
8	0.89	0.99	0.10	
				P = 0.01
21	0.80	0.96	0.16	
22	0.90	0.92	0.02	
23	0.92	1.0	0.08	
Mean (±SD)	0.90 (0.05)	0.97 (0.03)	0.07 (0.05)	

Table 22 - Cx iFR. Delta change in iFR between prone and supine positioning in the circumflex artery. The results are statistically significant ($p<0.05$)

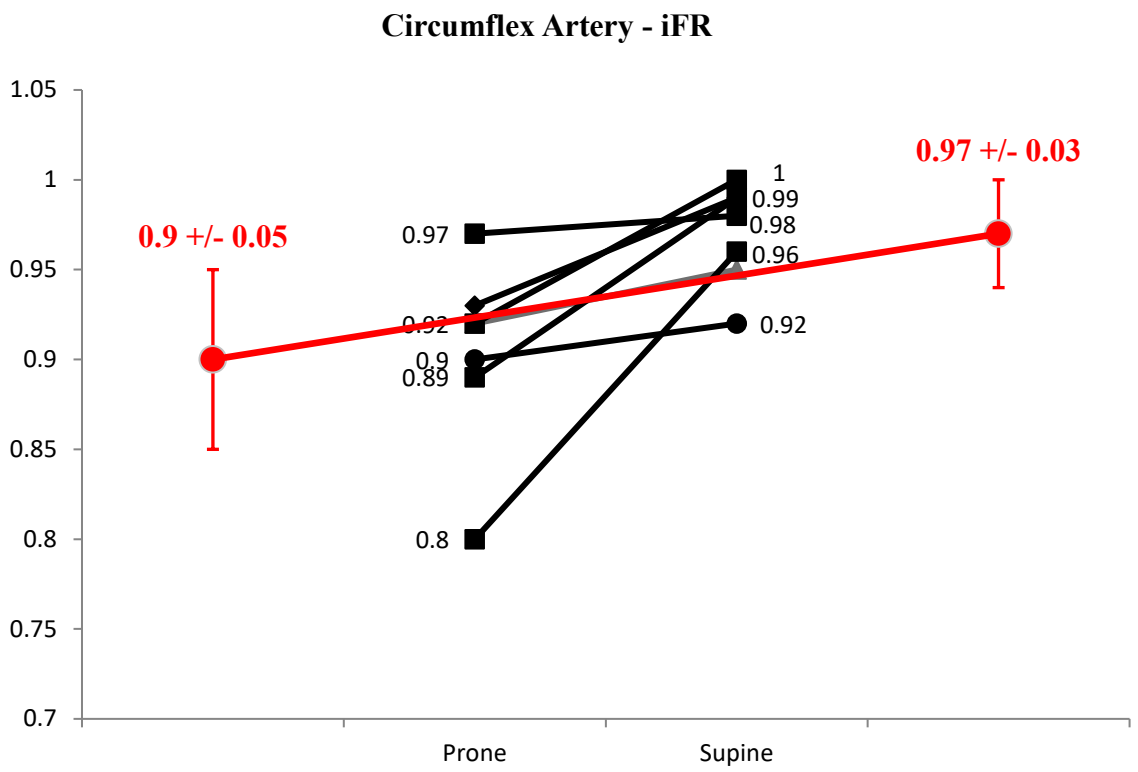


Figure 39 - Cx iFR Delta Change between prone and supine positions. Mean values are in red. Results are statistically significant (p=0.01).

Right Coronary Artery

The mean delta change of 0.04 for both PLV and PDA was not statistically significant. Table 23 and figure 40 summarise these results.

Case Number	Prone Pd/Pa	Supine Pd/Pa	Delta Change	
5 (PDA)	0.79	0.77	0.02	
14 (PDA)	0.92	0.93	-0.01	
PDA Mean (+SD)	0.85 (0.10)	0.85 (0.11)	0.00 (0.02)	
12 (PLV)	0.97	0.99	0.02	
13 (PLV)	0.77	0.92	0.15	P = 0.19
19 (PLV)	0.87	0.91	0.04	
20 (PLV)	N/A	N/A	N/A	
PLV Mean (±SD)	0.87 (0.10)	0.94 (0.04)	0.07 (0.07)	
PLV and PDA Mean (±SD)			0.04 (0.09)	

Table 23 - RCA iFR. Delta change in iFR between prone and supine positioning in the right coronary artery. The results are not statistically significant (p>0.05).

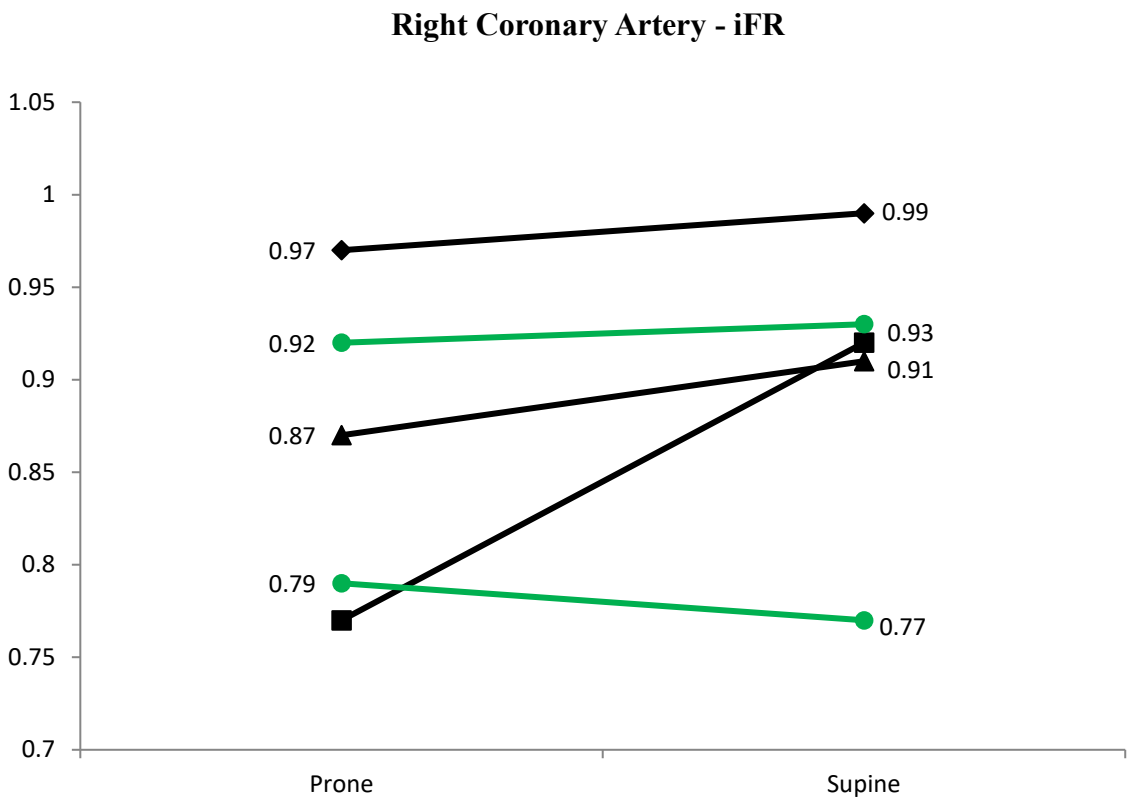


Figure 40 - RCA iFR Delta Change between prone and supine positioning. Mean difference is not statistically significant (p>0.05).

3.16.4 - Fractional Flow Reserve

Fractional flow reserve across all arteries is summarised in table 24 and figure 41. The mean change in FFR was 0.06 (p <0.0001). Superior vs. inferior FFR was 0.78 vs. 0.84 respectively. Each group of arteries was also statistically significant.

Vessel (n)	Prone FFR Mean (±SD)	Supine FFR Mean (± SD)	Delta Change Mean (±SD)	P Value
LAD (10)	0.86 (0.11)	0.77 (0.14)	0.09 (0.07)	0.003*
Circumflex (7)	0.82 (0.06)	0.87 (0.07)	0.05 (0.03)	0.006*
RCA-PDA(2)	0.75 (0.10)	0.69(0.10)	0.06 (0.02)	0.004*
RCA-PLV (4)	0.82 (0.10)	0.86 (0.08)	0.04 (0.03)	
All (± SD) (23)	-	-	0.06 (0.04)	<0.0001*

*Table 24 - Prone vs. Supine FFR. Prone mean FFR and supine mean FFR with the delta change and standard deviation. * represent statistical significance.*

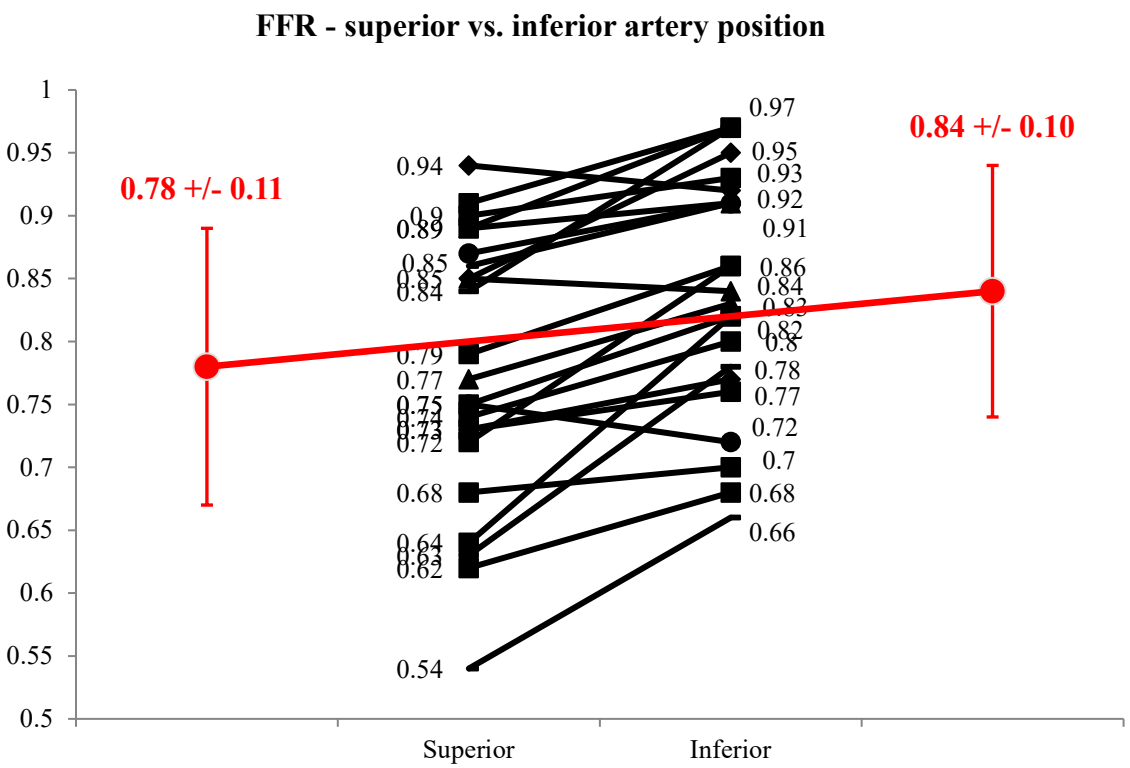


Figure 41 -FFR Delta Change - Superior vs. Inferior. Mean values are in red. Results were statistically significant - p=<0.0001.

Left Anterior Descending Artery

In the LAD, mean prone versus supine FFR was 0.86 vs. 0.77 respectively. The delta change of 0.09 was significant. Table 25 and figure 42 summarise the results.

Case Number	Prone FFR	Supine FFR	Delta Change	
1	0.92	0.94	-0.02	
4	0.86	0.72	0.10	
7	0.82	0.64	0.18	
9	0.97	0.84	0.13	
10	0.95	0.85	0.10	
11	0.97	0.91	0.06	P = 0.0027
15	0.72	0.75	-0.03	
16	0.97	0.89	0.08	
17	0.66	0.54	0.12	
18	0.78	0.63	0.15	

Mean (± SD)	0.86 (0.11)	0.77 (0.14)	0.09 (0.07)

Table 25 - LAD FFR. Delta change in FFR between prone and supine positioning in the left anterior descending artery. The results are statistically significant ($p<0.05$)

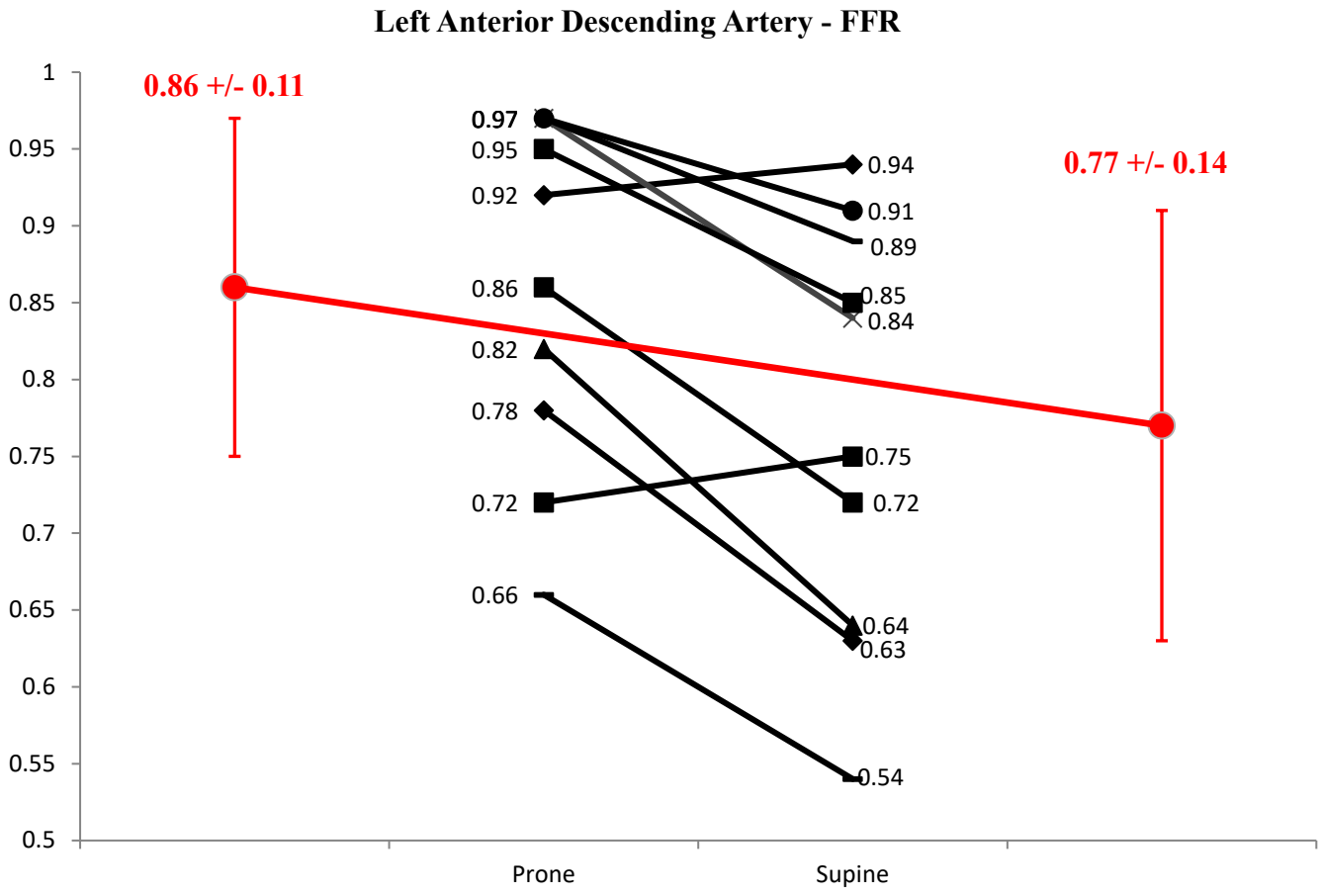


Figure 42- LAD FFR Delta Change between prone and supine positioning. Mean values are in red. The results are statistically significant ($p<0.05$)

Circumflex Artery

FFR in the circumflex artery, prone vs. supine was 0.82 vs. 0.87 respectively. This delta change was statistically significant. Table 26 and figure 43 summarise the results.

Case Number	Prone FFR	Supine FFR	Delta Change	
2	0.79	0.86	0.07	
3	0.85	0.84	-0.01	
6	0.87	0.91	0.04	
8	0.86	0.91	0.05	
21	0.77	0.83	0.06	P = 0.0056
22	0.73	0.76	0.03	
23	0.90	0.96	0.06	
Mean (± SD)	0.82 (0.06)	0.87 (0.07)	0.04 (0.03)	

Table 26 - Cx FFR. delta change in FFR between prone and supine positioning in the Circumflex artery. One delta changed the opposite direction as anticipated. Results are statistically significant (p <0.05).

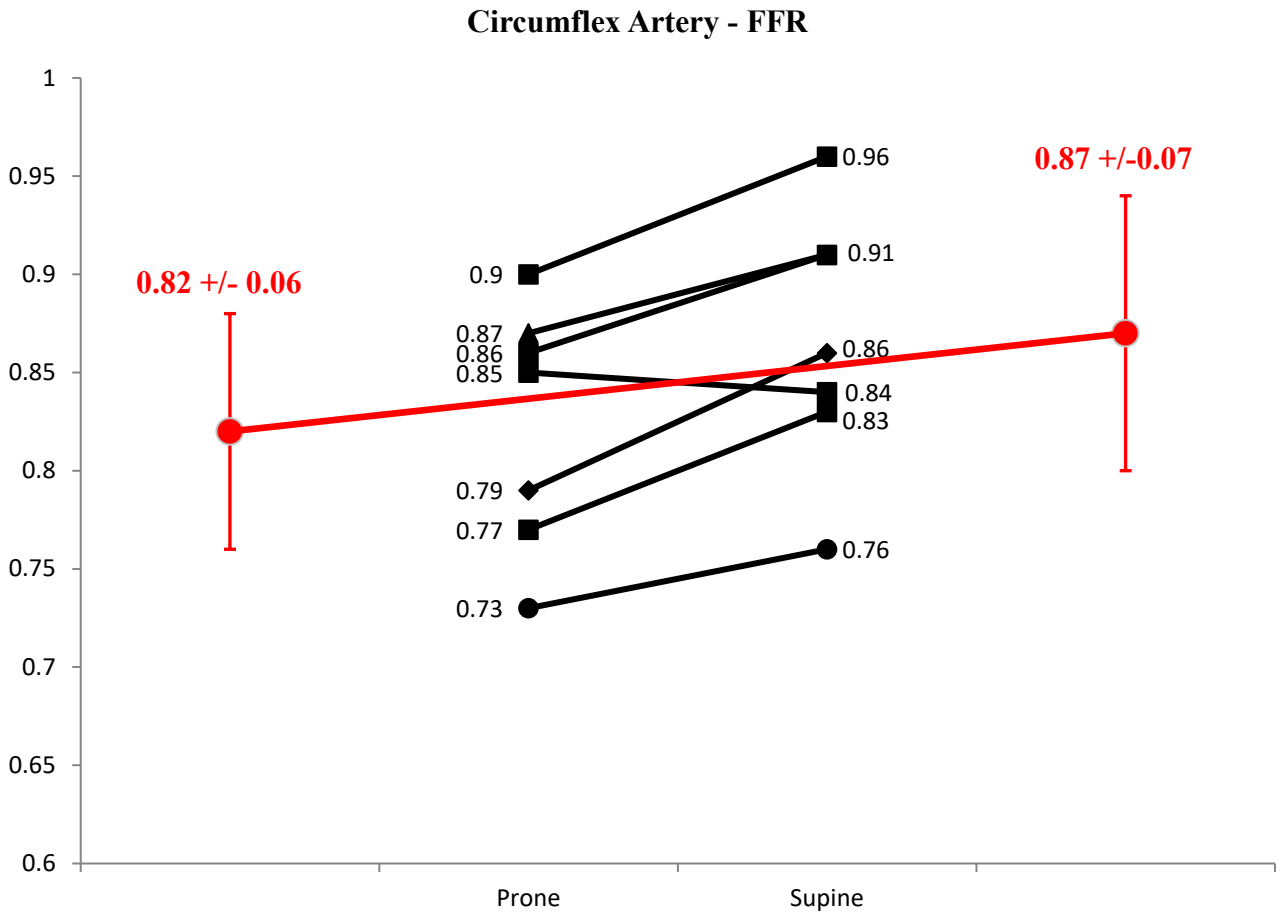


Figure 43- Cx FFR Delta Change between prone and supine positioning. Mean values are in red. The results are statistically significant (p<0.05)

Right Coronary Artery

Delta change between positions in the RCA was 0.04 ($p < 0.05$). Table 27 and figure 44 summarise the results.

Case Number	Prone FFR	Supine FFR	Delta Change	
5 (PDA)	0.68	0.62	0.06	
14 (PDA)	0.82	0.75	0.07	
PDA Mean (±SD(+)	0.75 (0.10)	0.69 (0.10)	0.07 (0.01)	
12 (PLV)	0.89	0.91	0.02	P = 0.004
13 (PLV)	0.74	0.80	0.06	
19 (PLV)	0.73	0.77	0.04	
20 (PLV)	0.68	0.70	0.02	

PLV Mean (± SD)	0.82 (0.10)	0.86 (0.08)	0.04 (0.03)

Table 27 - RCA FFR. Delta change in FFR between prone and supine positioning in the right coronary artery. All delta changes are in the anticipated direction. The results are statistically significant ($p<0.05$).

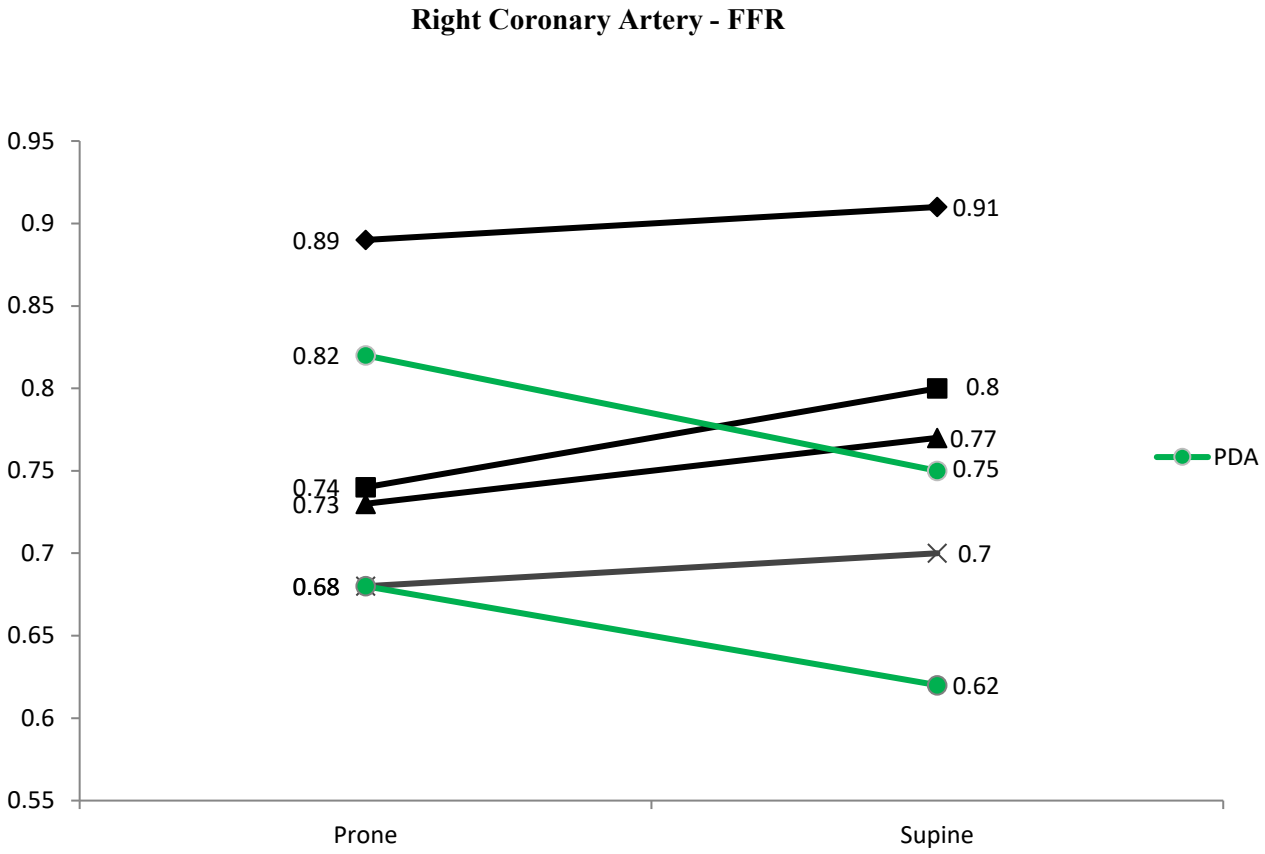


Figure 44 - RCA FFR Delta Change between prone and supine position. The results are statistically significant ($p<0.05$) when combined with PDA data.

3.16.5 - FFR Clinical Measurement Point

Left Anterior Descending Artery

Measurements at the clinical point in the LAD are shown below. Prone FFR vs. supine FFR was 0.91 vs. 0.85 respectively, giving a mean change of 0.06. These values were statistically significant ($p<0.05$). Results are summarised in table 28 and figure 45.

Case Number	Prone FFR	Supine FFR	Delta Change	
9	1.0	0.93	0.07	
10	0.98	0.93	0.05	
11	0.95	0.91	0.04	
15	0.89	0.86	0.03	P = 0.0028
16*	0.97	0.89	0.08	
17	0.66	0.54	0.12	
18*	0.92	0.89	0.03	
Mean (± SD)	0.91 (0.12)	0.85 (0.14)	0.06 (0.03)	

*Table 28 - LAD Clinical Measurement Point. Clinical measurement points for FFR. All values changed in the appropriate direction. The clinical values are statistically significant (p <0.05). *Clinical point as per distal point.*

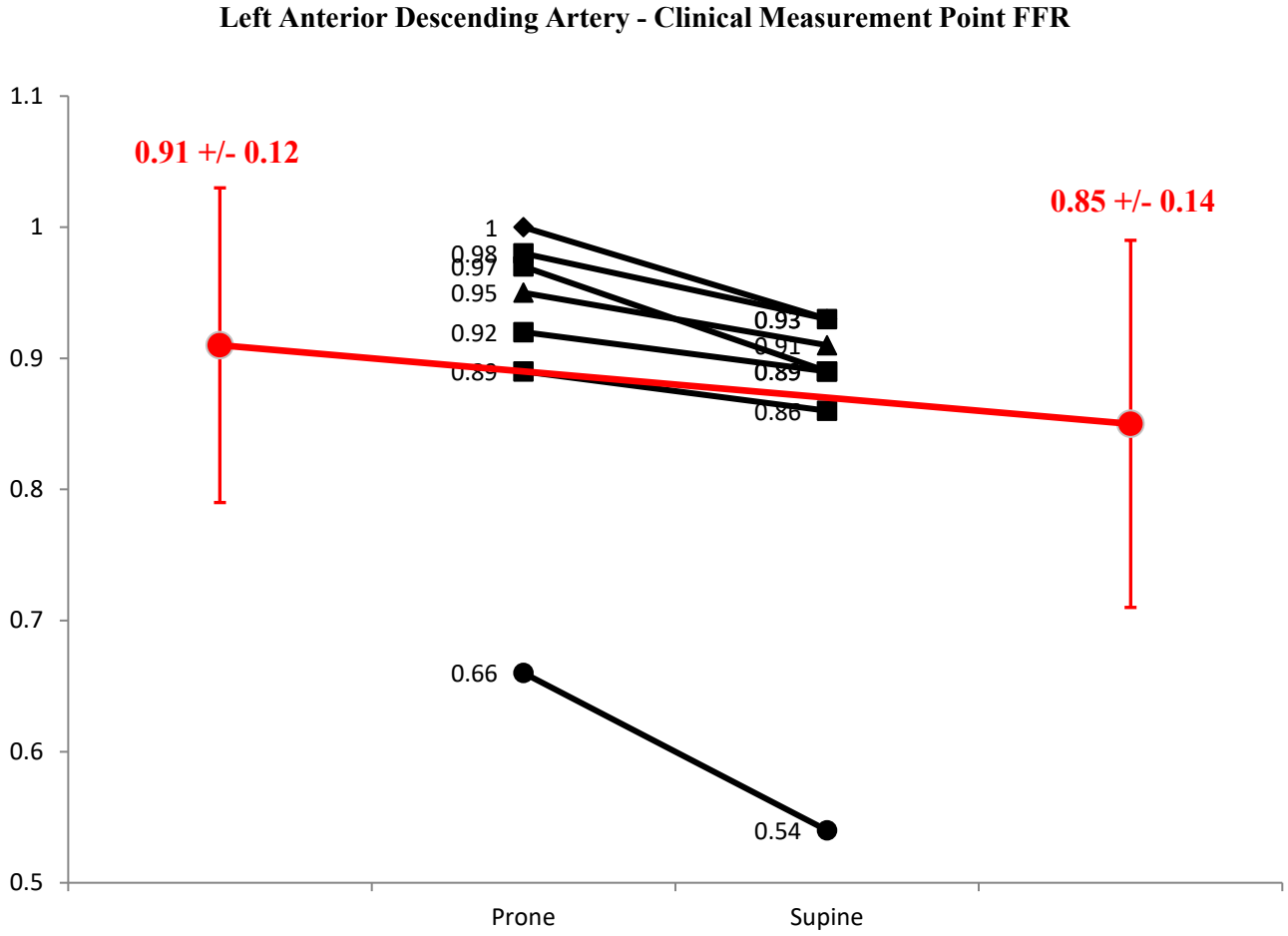


Figure 45 - LAD Clinical Measurement Point. Mean values in red. Values are statistically significant ($p<0.05$).

Circumflex Artery

Only three cases were recorded at the clinical point which is insufficient for adequate statistical power. The results were not significant (Table 29).

Case Number	Prone FFR	Supine FFR	Delta Change	
21	0.90	0.89	-0.01	
22	0.89	0.91	0.02	
23	0.94	0.99	0.05	P = 0.37
Mean (± SD)	0.91 (0.03)	0.93 (0.05)	0.02 (0.03)	

Table 29 - Cx Clinical Measurement Point

Posterior Descending Artery

Only one result was obtained for the PDA. The clinical FFR did not change and remained at 0.8 in both positions.

Posterior Left Ventricular Artery

Four cases are available for comparison of clinical measurement points in the PLV, which is

insufficient for adequate statistical power (Table 30). The results were not significant statistically ($p<0.05$).

Case Number	Prone FFR	Supine FFR	Delta Change	
12	0.91	0.99	0.08	
13	0.79	0.79	0.00	
19	0.76	0.75	-0.01	P = 0.35
20	0.68	0.70	0.02	
Mean (± SD)	0.79 (0.10)	0.81 (0.13)	0.02 (0.04)	

Table 30 - RCA Clinical Measurement Point

3.17 - Summary of Pressure Based Measurements

To summarise the data for Pd/Pa, iFR and FFR;

1. There is a statistically significant difference in prone versus supine position for Pd/Pa (delta change 0.05) across all arteries and also when grouped per artery ($p<0.05$).

2. There is a statistically significant difference in prone versus supine FFR (delta change 0.06) across all arteries and also when grouped per artery ($p<0.05$)

3. There is a statistically significant difference in prone versus supine iFR (delta change 0.06) ($p <0.05$) across all arteries.

4. All 23 measurements for Pd/Pa changed in the expected direction, apart from two measurements, which did not change.

5. All but two iFR measurements changed in the anticipated direction

6. All but three FFR measurements changed in the anticipated direction.

7. There is a statistically significant difference in prone versus supine clinical FFR measurement in the LAD only ($p<0.05$) The RCA and Cx measurements were not adequately powered.

3.18 - Stenosis Re-classification

When correcting iFR and FFR by a magnitude of 0.06 (the mean delta change across all measurements), 36% of iFR and 26% of FFR measurements re-classify from positive to negative, or vice versa across a predefined threshold. This is shown in table 31.

Index	Total Number	N Crossing Threshold	% Crossing Threshold
iFR (<0.89)	22	8	36%
FFR (<0.80)	23	6	26%

Table 31 - Stenosis Re-classification. Percentage of values crossing iFR and FFR threshold, once corrected for hydrostatic pressure effects.

3.19 - Doppler Measurements

Combined and grouped mean doppler velocity between prone and supine positions at rest and hyperaemia were not statistically significant (Table 32 and 33). Resting doppler flow superior vs. inferior was 17cm/s vs. 15cm/s and 29cm/s vs. 28cm/s at hyperaemia. At rest, the mean delta change was 1.6cm/s ($p = 0.31$) and at hyperaemia -0.9cm/s ($p = 0.85$).

RESTING FLOW				
Vessel (n)	**Prone Velocity Mean (±SD) - cm/s**	**Supine Velocity Mean (± SD) - cm/s**	**Delta Change Velocity Mean (±SD) - cm/s**	**P Value**
LAD (10)	15.8 (4.2)	15.4 (3.8)	0.4 (2.9)	0.71
Circumflex (7)	16.8 (5.4)	21.3 (6.7)	4.5 (7.0)	0.15
RCA -PDA(2)	13.8 (3.4)	12.6 (1.7)	1.2 (1.7)	0.58
RCA-PLV (4)	11.8 (2.9)	11.5 (2.7)	-0.3 (3.1)	
All (23)	-	-	1.6	0.31

Table 32- Prone vs. Supine Resting Doppler Flow. There were no statistical differences across all arteries between the positions.

HYPERAEMIC FLOW				
Vessel (n)	**Prone Velocity Mean (±SD) - cm/s**	**Supine Velocity Mean (± SD) - cm/s**	**Delta Change Velocity Mean (±SD) - cm/s**	**P Value**
LAD (10)	30.6 (9.7)	30.4 (14.1)	0.2 (12.1)	0.96
Circumflex (7)	31.5 (7.3)	33.5 (11.4)	-2 (10.9)	0.64
RCA -PDA(2)	30.0 (4.3)	20.9 (5.0)	0.1 (1.1)	0.84
RCA-PLV (4)	18.9 (5.5)	19.4 (3.7)	0.5 (3.1)	
All (23)	-	-	-0.9	0.85

Table 33 - Prone vs. Supine Hyperaemic Doppler Flow. As for resting flow, there were no statistical differences across any artery between both positions.

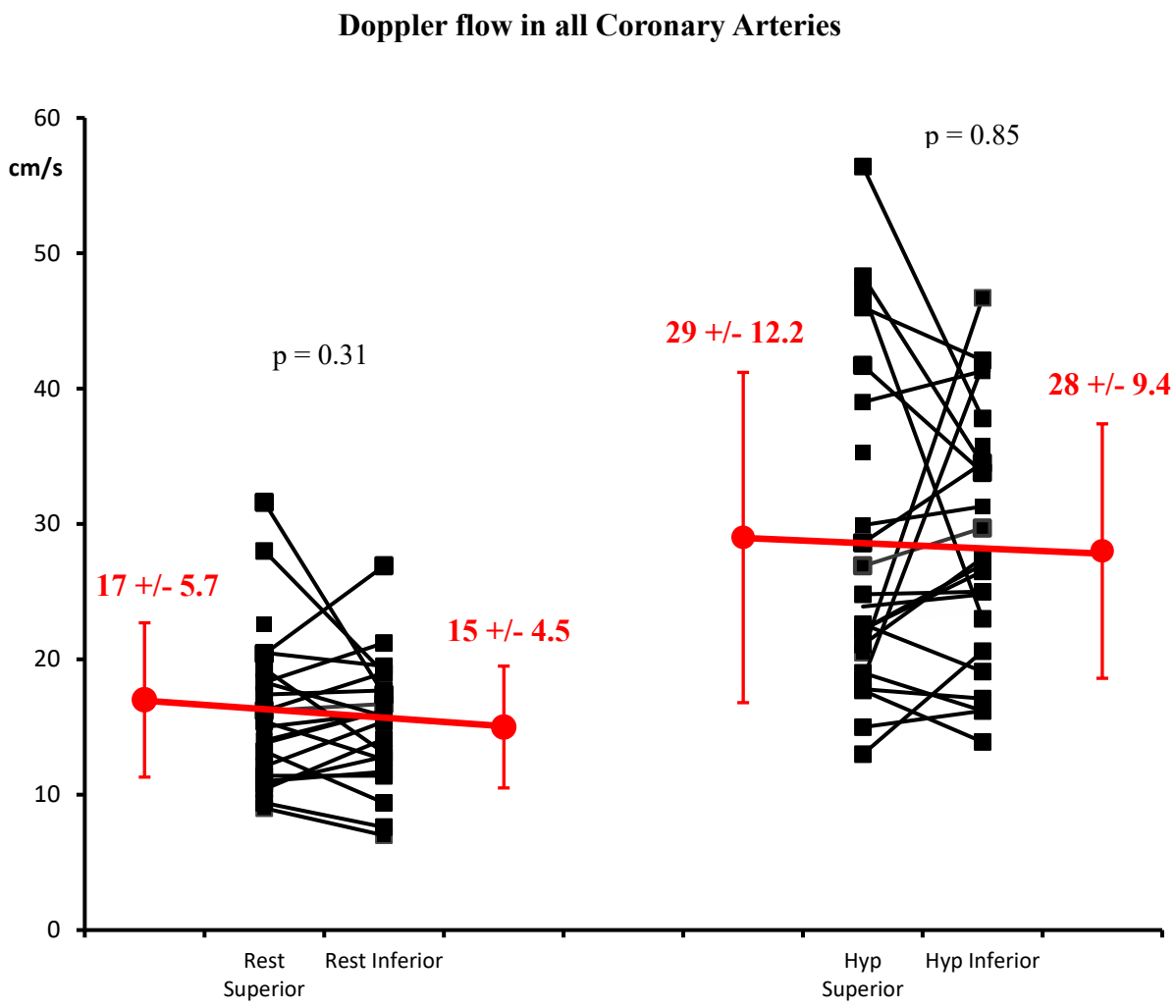


Figure 46 -Doppler Flow Data - superior versus inferior artery position, at rest and hyperaemia. There was no statistical difference between superior and inferior artery position, at rest or hyperaemia. Red lines and data labels represent mean values.

Case by case data is shown in table 34. Breakdown per artery is shown in figure 47.

Case	Resting Prone Flow (cm/s)	Resting Supine Flow (cm/s)	Delta Change (cm/s)	Hyperaemic Prone Flow (cm/s)	Hyperaemic Supine Flow (cm/s)	Delta Change (cm/s)
1	7.0	9.0	2.0	46.7	20.5	-26.2
2	15.0	16.0	1.0	39.0	41.3	2.3
3	22.6	13.2	-9.4	35.3	35.8	0.5
4	16.7	16.2	-0.5	29.7	26.9	-2.8
5	16.2	13.8	-2.4	24.8	23.9	-0.9
6	18.3	15.8	-2.5	29.9	31.3	1.4
7	16.2	14.0	-2.2	19.1	18.5	-0.6
8	31.6	17.4	-14.2	41.7	33.8	-7.9
9	15.4	12.1	-3.3	25.0	24.8	-0.2
10	17.7	17.4	-0.3	37.8	56.4	18.6
11	21.2	18.3	-2.9	34.4	48.3	13.9
12	10.4	14.1	+3.7	22.2	26.5	4.3
13	15.4	12.6	-2.8	22.6	19.1	-3.5
14	11.4	11.4	0	17.8	17.1	-0.7
15	11.7	11.0	-0.7	27.0	22.2	-4.8
16	19.5	20.5	1.0	42.1	46.0	3.9
17	13.1	19.3	6.2	16.2	19.0	2.8
18	19.0	16.2	-2.8	27.5	21.1	-6.4

19	10.8	12.8	2.0	17.7	13.9	-3.8
20	9.4	7.6	-1.8	15.0	16.2	1.2
21	13.2	9.4	-3.8	13.0	20.6	7.6
22	28.0	19.0	-9.0	47.2	23	-24.2
23	20.4	26.9	+6.5	28.6	34.5	5.9
Mean (± SD)	16.5 (5.8)	15.0 (4.3)	-1.5 (4.7)	28.7 (10.3)	27.9 (11.3)	-0.8 (9.8)

Table 34 - Per Artery Resting and Hyperaemic Doppler Flow.

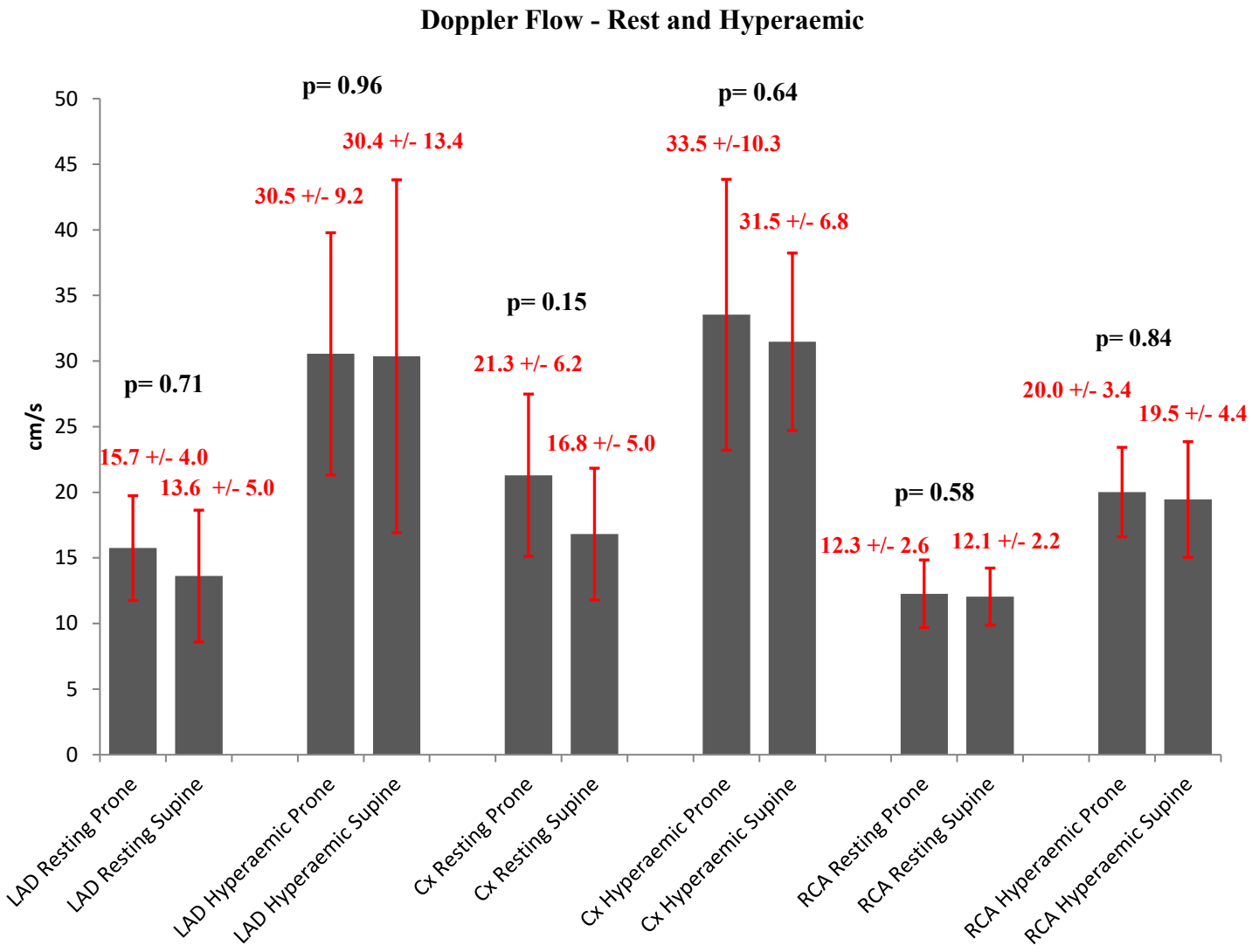


Figure 47 -Resting and Hyperaemic Doppler flow per artery - prone versus supine ± SD. Delta change in each artery is not statistically significant (p>0.05.)

3.20 - Summary of Doppler Based Measurements

In summary, the doppler based measurements demonstrated the following;

1. There was no statistical difference between prone and supine doppler measurements in the resting state, in all coronary arteries (in combination and individually).

2. There was no statistical difference between prone and supine doppler measurements during steady state hyperaemia in all coronary arteries (in combination and individually).

Results were non-significant for resting and hyperaemic measurements (p= 0.12 and 0.68 respectively).

3.21 - Guide to Wire Correlation Data

3.21.1 - Pd/Pa

Each guide to wire measurement has been correlated with the delta change in Pd/Pa for that specific stenosis. A scatter plot below is shown in figure 48. Spearman's correlation calculation is 0.493, which is not statistically significant.

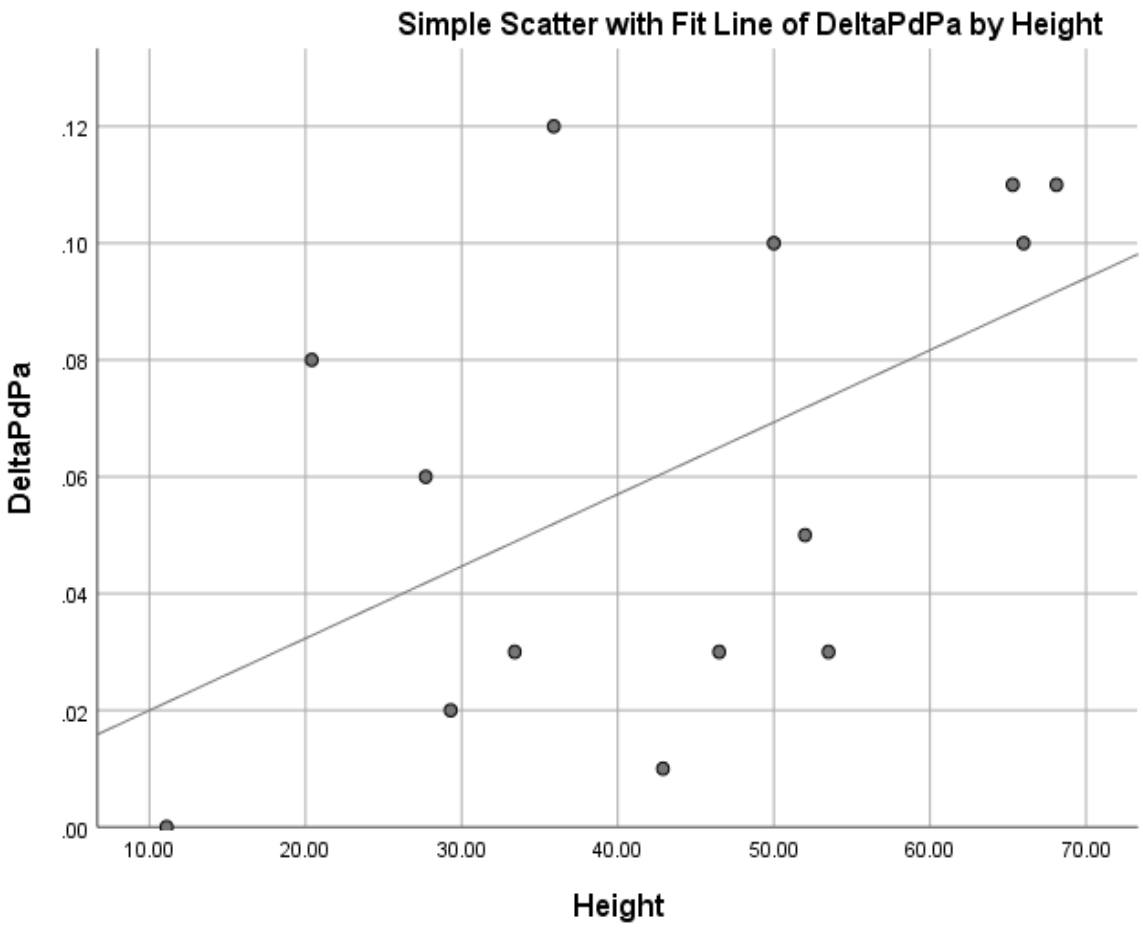


Figure 48 - Height Versus Delta Change in Pd/Pa. Spearman correlation was not significant.

3.21.2 - iFR

A Spearman's correlation value of 0.402 was obtained for iFR versus guide to wire distance. This was not statistically significant. A scatter plot demonstrates this in figure 49.

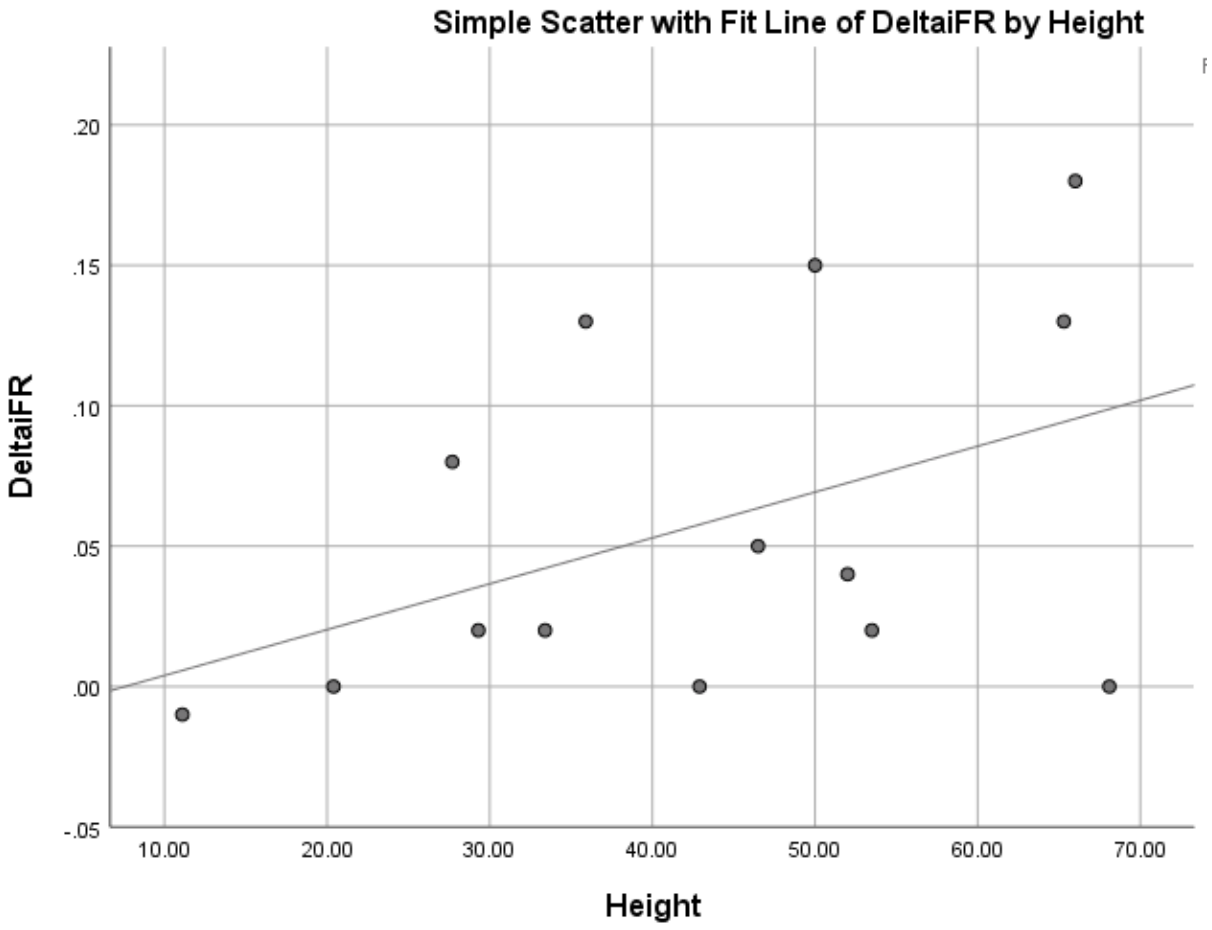


Figure 49 - Height Versus Delta Chaneg in iFR. Spearman's correlation was not significant.

3.21.3 - FFR

For FFR versus guide to wire distance resulted in a Spearman's correlation value of 0.528. This is statistically not significant. A scatter plot is shown below.

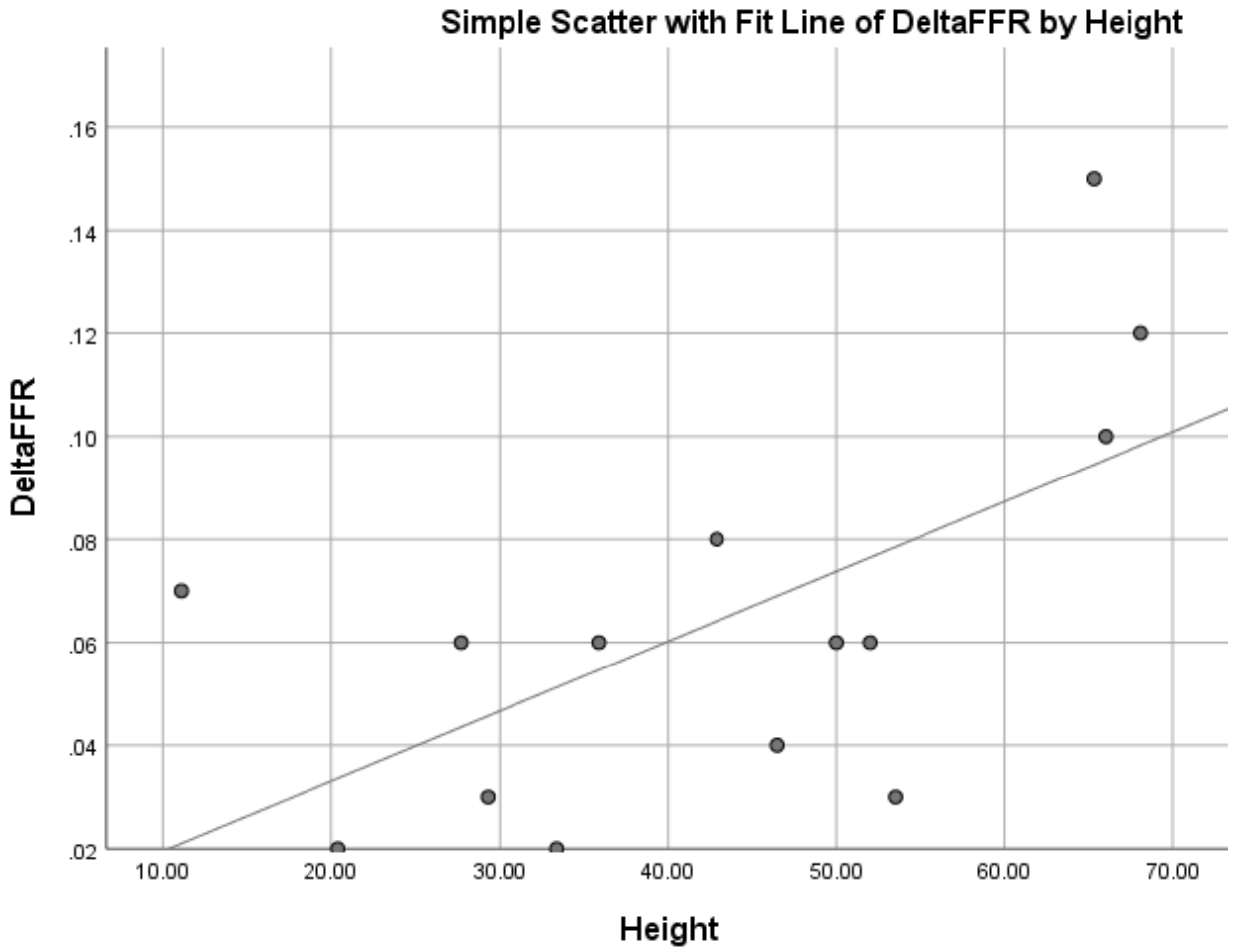


Figure 50 -Height Versus Delta Change in FFR. Spearman's correlation was not significant.

3.22 - Estimated Hydrostatic Effect versus in Vivo Effect

Guide to wire measurements from angiography were used to predict a mean hydrostatic effect as previously shown in Figure 32. Now table 35 compares the predicted mean change, to the actual mean change seen in vivo, across measurements in all three coronary arteries.

Artery	Predicted Pressure Change Based on Anatomy (mmHg)	Predicted Change in Pd/Pa, iFR and FFR	Actual Change in Pd/Pa, iFR and FFR
LAD	9.3	0.09	0.09
Cx	4.9	0.05	0.05
RCA	5.2	0.05	0.04

Table 35 - Predicted vs. Actual Hydrostatic Effect in Vivo

3.33 - Summary of All Results

1. For all lesions referred for pressure wire, stenosis severity assessed by QCA varied significantly between the LAD and RCA.

2. There was a statistically significant difference between mean prone and supine Pd/Pa across all arteries

3. There is a statistically significant difference between mean prone and supine iFR across all arteries.

4. There was a statistically significant difference between mean prone and supine FFR across all arteries.

5. There was no statistical change in mean resting or hyperaemic doppler flow between prone and supine positions across all arteries.

6. Guide catheter to wire measurements did not significantly correlate with delta change in PdPa, iFR or FFR

Chapter IV - Discussion and Interpretation

4.1 - Overview

The study hypotheses consisted of two points. The results obtained from clinical data support these points in that;

1. Pressure based measurement did significantly differ between prone and supine positions

2. Velocity based measurements did not significantly differ between prone and supine positions

Discussion topics will follow the below order;

1. Patient Demographics

2. Angiographic Data

3. Pressure-based indices

4. Doppler-based indices

5. Potential Clinical Implications

6. Study Limitations

7. Future Direction

8. Summary

4.2 - Patient Population / Demographic

The average age for recruited patients was 63 years old, and was similar between artery groups. All patients were male, with two female patients declining invitation to participate in the study. Male sex is associated with greater vertical height variations between coronary artery and aorta (Härle et al., 2017a).

Smoking and diabetes were uncommon overall, 4% and 13% of all patients, whereas hypertension and hypercholesterolaemia were more common, 43% and 48% respectively.

All patients had preserved LV function >50%. LV dilation would have likely increased hydrostatic effect, as the coronary circulation sits atop an expanding ventricle. Although this is an evidence free area, (Härle et al., 2018) showed in a subset of patients with impaired LV function, hydrostatic effect was still prominent.

No adverse events were recorded in the study population. One physiology wire related coronary dissection occurred in a side branch. The rate of iatrogenic coronary artery dissection is very low (<0.2%), and can be due to guide catheter trauma, guidewire induced injury, balloon inflation or stent implantation (Eshtehardi et al., 2010). The rate quoted during consent for wire related injury to the vessel is 1 in 500. However, data on incidence using specific physiology wires is scarce. In a study using the same physiology wire as the current research, the rate of dissection is reported to be 1 in 192 in the hands of experienced operators (Waard et al., 2018). Physiology wires with doppler measuring equipment have added weight and bulk, and almost certainly increase the risk of coronary injury. Along with time and cost implications, this adds to the reasons such measures of invasive coronary physiology have been phased out of clinical practice. There is now more than ever a reliance on pressure-based equipment due to its safety

and efficiency. This reliance and widespread use heighten the importance of recognising hydrostatic pressure effect as true confounder.

4.3 - Angiographic Data

A larger number of patients were referred for pressure wire assessments in LAD lesions. The referrer's reasons for this have not been recorded, but is likely due to the anatomical importance of the LAD and the myocardial mass supplied (Kim et al., 2016).

4.3.1 - Stenosis Percentage

Despite the increased number of referrals for LAD lesions, stenosis as measured by QCA was numerically less than the Cx artery and significantly less when compared to RCA lesions. The burden of myocardial ischaemia is linked to the benefit seen with revascularisation in that territory (Reynolds Harmony R., Picard Michael H. and Hochman Judith S., 2015). This in turn could lead to referrals for pressure wire assessment in lesions which are not as severe, but in clinically important arteries. Visual assessment however does not correspond strongly with QCA (Adjedj et al., 2017). QCA has reasonable diagnostic accuracy when compared to FFR as a gold standard but has less reliable outcome data (Budoff et al., 2016).

Lesion length was similar in all artery groups. Previously, studies have shown a strong correlation with lesion length and FFR (López-Palop et al., 2013). Lesion length may be one of the strongest predictors of a functionally significant stenosis.

4.3.2 - Position of Stenosis

Of all twenty three lesions, 10 were classified as proximal (first third of the vessel), 9 were classified as mid (middle third of vessel), and 4 as distal (final third of vessel). Vertical height variation from the ostial vessel generally increases in a gradual fashion along the length of the vessel (chapter II). Lesions in the proximal and mid vessel may not alter pressure-based indices substantially, as the hydrostatic effect is limited by the vertical height at the point of measurement. This concept led the research team to take more proximal measurements after a results review (clinical measurement point data).

Looking at the seven clinical measurement points taken in the LAD specifically, four lesions were proximal and three were in the mid vessel. Two of the lesions in the mid vessel used the same point in the vessel for clinical (as per operator decision) and study measurement points. The mean delta change was 0.06 across these seven lesions. This is clinically very re-assuring, as in routine practice, physiological measurements may not be taken as distally as stipulated in the study protocol. This subset of results shows that even when the wire is positioned more proximally, hydrostatic effect is still relevant.

4.3.3 - Guide to Wire Measurement Correlation

Guide to wire measurements did not show a significant correlation with delta change in Pd/Pa, iFR or FFR per lesion, but did show a trend towards positive correlation. However, the overall mean guide to wire distance measured on QCA, almost exactly predicted mean FFR delta change in vivo per artery group (Table 35).

Guide to wire measurements in this research had inaccuracy. A single LAO measurement, taken when prone, was multiplied by two to give an estimated additive hydrostatic effect from the supine component. In retrospect, a more accurate method would have been an additional LAO measurement when supine, in addition to the prone measurement QCA also has inherent error in

measurement (Wunderlich et al., 1998) which may have impacted subsequent correlation analysis. The fluoroscopic angle also varied and may not have been exactly 90 degrees LAO in each case. Lastly, purely based on patient position, the LAO 90 may not have captured a purely perpendicular view of the coronary tree.

After study recruitment and during data analysis, a study by Härle et al investigated the effect of hydrostatic pressure in vivo (Härle et al., 2018), following on from the previous work on hydrostatic pressure models (Härle et al., 2017a). This was the first published study in vivo to focus on hydrostatic effect. His group measured FFR in the standard supine position, and compared FFR measurements with the patient positioned on the right and then left lateral position. This work was published after this study's data collection period.

This is a similar clinical study to the current research, despite different patient positions, and pressure-based measurements only (no doppler flow). Härle's study showed a significant correlation between height and FFR change in positions (with a Spearman's correlation value of 0.694 versus our value of 0.528). With regards to Pd/Pa, Härle's data also showed a significant correlation with height (0.604 versus our data of 0.493. QCA was used to measure height between the guide catheter and the wire in each position, giving a more accurate correlation than the current study.

Härle also demonstrated, in a similar way to the current research, that the differences seen in Pd/Pa, iFR and FFR between supine, left and right sided patient positions, could be abolished by adjusting for hydrostatic pressure via mean height measurements on angiography (Härle et al., 2018).

An interesting point is the moderate to good correlation per lesion, but an almost exact prediction on mean hydrostatic effect per artery group from mean height per artery group measured on QCA. This is difficult to explain, but height may not be the only confounding variable in pressure-based indices during patient position change.

Prone positioning has been used as a strategy to treat ARDS for decades. Recently, prone positioning has been trailed in patients with COVID-19 (Sartini et al., 2020). When prone, the weight of the heart, lungs and abdominal viscera is lifted off the dorsal lung regions, aiding ventilation to these areas (Scholten et al., 2017). The weight of the heart itself is thought to add

3-5cm H_2O (5.5 to 9.3mmHg) of pressure to the underlying tissue (Malbouisson et al., 2000). It is not known whether this adds to, and to what magnitude it affects, the hydrostatic pressure effect within coronary arteries. If we believe to moderate correlation of vertical height to delta change in pressure-based indices, the physical weight of the heart could be a substantial contributor. In turn, those with dilated ventricles, may have a greater mass effect as well as greater height deviation of coronary arteries from the aorta. Both may present as a significant change in hydrostatic pressure compared to supine positioning.

4.4 - Pressure Results

Pd/Pa, iFR and FFR measurements changed significantly when comparing prone and supine measurements. The direction of delta change supported physical principles, with inferior readings measuring higher than superior readings in the vast majority of cases.

4.4.1 - Pressure Based Values > 1.0

Across Pd/Pa, iFR and FFR readings, there were numerous instances of recordings above 1.0. If pressure is truly proportional to flow, as pressure-based indices imply, a value above 1.0 suggests greater flow distal to a stenosis than at the ostial vessel. This is unlikely to be true and is a potential pitfall of using a pressure-based measurements as a surrogate for flow.

In supine patients, this is phenomenon is normally seen in mildly disease vessels, and usually the circumflex artery. Observation of this phenomenon has been recognised by other authors in the medical literature (Nijjer et al., 2016), but the potential impact on day to day use of pressure based indices, has largely been overlooked. Readings above 1.0 suggest an inherent error in measurement before the addition of a stenosis, leading to inaccuracy.

The novel aspect of this research is that recordings over 1.0 were frequently seen in the LAD when prone. In this instance, the LAD has assumed the position of a circumflex artery (i.e. inferior to the aorta) in a standard supine patient. On the contrary, the LAD in a supine patient would have a resting value below 1.0, even in a completely disease-free vessel. Again, there is inherent error and resting inaccuracy of measurements, due to hydrostatic effect. This error is present in all pressure-based methods of assessing coronary stenoses.

4.4.2 - Pd/Pa

Resting Pd/Pa has been validated against FFR in large volume trials and has an overall accuracy of 80% when compared to FFR. This is comparable to newer resting indices such as iFR (Jeremias et al., 2014). The binary 'cut off' point for Pd/Pa is usually 0.9 - 0.92. A change of up to 0.11 as seen in some Pd/Pa measurements, could drastically alter decision making in a proportion of patients. It is noteworthy that resting Pd/Pa is not routinely used to guide treatment alone, especially with iFR and other novel resting indices readily available.

All Pd/Pa recordings altered in the expected direction based on hydrostatic theory.

4.4.3 - iFR

iFR measurements were calculated retrospectively from raw data. One iFR result could not be retrospectively calculated, as the raw data trace was too short. Therefore 22 results in total were available for analysis. RCA iFR was the only subgroup in which statistical significance was not reached, as only five cases were available. All other subgroups of arteries amongst Pd/Pa, iFR and FFR showed statistical significance when comparing prone and supine measurements.

4.4.4 - FFR and Hyperaemia

Hyperaemia is a distinct variable between FFR and iFR or Pd/Pa. On average the Pa pressure did vary between resting measurements and hyperaemia. Furthermore, supine Pa pressure was lower than prone Pa pressure. Table 36 summarises the differences.

Measurement	Prone Pa (mmHg)	Supine Pa (mmHg)
Pd/Pa and iFR	97	92
FFR	95	89

Table 36 - Pa Pressure During Prone and Supine Pd/Pa, iFR and FFR.

As described in section 1.15.3, the Pa pressure is directly related to the hydrostatic effect on Pd/Pa and FFR. A lower Pa pressure amplifies the effect of pressure change in the artery when calculating Pd/Pa for FFR by directly altering the denominator in the equation. For example, a change in Pd of 5mmHg leads to a change in Pd/Pa of 0.07 at a Pa pressure of 80 mmHg, but only 0.04 at 120 mmHg. This could be a potential explanation for the difference in FFR delta, and Pd/Pa delta.

Adenosine infusion and hyperaemia is the cause for a drop in Pa when comparing resting indices and FFR. The cause of a lower supine Pa compared to prone Pa is uncertain and likely multi-factorial. As per study protocol, prone measurements were performed first, followed by supine measurements after the turning manoeuvre. Therefore, supine measurements, would have

potentially had two doses of intravenous nitrates and adenosine. The patient would have also been exposed to an increasing length of time on the angiography table, potentially leading to greater intravascular depletion.

One may expect a small variation due to inherent error rates in equipment. FFR has been shown to be a highly reproducible measure. Nevertheless, studies analysing paired tests in the same artery and stenosis demonstrate a standard deviation of 0.02 between measurements (Johnson et al., 2015) in 190 patients. This applies to the current research as the same artery was measured twice in differing patient positions.

4.5 - Supporting Evidence in the Clinical Literature

Härle and his group conducted the first published in vivo study with left and right lateral positioning (Härle et al., 2018). This has already been discussed with relation to guide to wire correlation with change in FFR in section 4.3.3. The study was published during this research's data collection period.

In 30 coronary stenoses, there were statistically significant changes in Pd/Pa, iFR and FFR when comparing supine measurements, to left and right lateral patient position. No velocity of flow-based measurements were conducted. Pressure based indices produced larger values when inferior to the aorta, compared to superior in the same artery, across the same stenosis. This was statistically significant for Pd/Pa, iFR and FFR. These findings mirror our own, despite different patient positions. Table 37 summarises and compares the data between Härle's group, and the current research.

Measure	Härle Data Delta Change	Al-Janabi Data Delta Change
Pd/Pa	0.037	0.05
iFR	0.043	0.06
FFR	0.045	0.06

Table 37 - Delta Change Between Patient Position - Al-Janabi vs. Härle Data.

The magnitude of change in Härle's data is less than the current research. This can be explained by the difference in positions between both studies. One may expect a lesser hydrostatic effect when positioned laterally, compared to prone. Compared to current research, Härle's group rotated partially around the 'axis' of the aorta by 90 degrees, whereas the current research rotated 180 degrees. Intrathoracic physiology may also vary due to the varying angles of rotation.

Pd/Pa shows less change than iFR and FFR in both data sets, with iFR and FFR delta change being very similar. In Härle's data set 26.7% of FFR lesions changed classification across a binary cut-off (0.8) based on the position showing maximum delta change. This is identical to the 26% seen in the current research. iFR re-classification in Härle's data was the same at 26.7%, but higher in the current research at 36%. The magnitude of change in some stenoses would have been amplified in the current research, given the greater effect of hydrostatic pressure when prone.

Their conclusion was similar to ours. There is a clinically relevant change in pressure-based indices, affecting stenosis classification. This potentially leads to misclassification of lesions and mistreatment.

Within the last 6 months, a Japanese research group have conducted an almost identical study to ours, measuring Pd/Pa and FFR in 27 lesions in the prone and supine positions (Kawaguchi et

al., 2019). Their study starting recruitment two months after ours (September 2017) and produced very similar results. A comparison with our results is shown below in Table 38.

Measurement	Al-Janabi Data Delta change	Kawaguchi Data Delta change
LAD Pd/Pa	0.08	0.08
LAD FFR	0.09	0.09
Cx Pd/Pa	0.05	0.05
Cx FFR	0.05	0.05
RCA Pd/Pa	0.05	0.07
RCA FFR	0.05	0.06

Table 38 - Al-Janabi vs. Kawaguchi Data. Delta change (between prone and supine positions) in Pd/Pa and FFR in LAD, Cx and RCA.

The only differing measurements were the RCA Pd/Pa and FFR delta change. LAD and Cx measurements were identical, which is extremely re-assuring. The differences in the RCA could be due to which specific distal branch was chosen (PLV or PDA). Kawaguchi et al did not specify this in their methods, however diagrammatically, it appears the wire was positioned at bifurcation of the RCA.

Their data set did not include iFR or doppler flow velocity. The current research adds to current data by adding novel data for these parameters. Pd/Pa, is now rarely used, and including the effect on a newer resting index such as iFR is clinically relevant. Furthermore, the current research confirms that coronary flow is unchanged, which no other study has to this point. This provides supporting evidence that hydrostatic effect exists and confounds the tool of pressure based indices we use routinely during PCI.

However, the similarity between data sets shows reproducibility and a reassuringly constant confounding effect of hydrostatic pressure.

4.6 - Doppler Measurements

There was no significant change between prone and supine doppler flow across resting and hyperaemic measurements. The overall delta changes between the groups were almost zero, with a change of -1.5cm/s in resting measurements and -0.8 cm/s in hyperaemic measurements across all cases. The majority of cases had small delta changes in flow (less than 5cm/s in 16 of 23 cases). This correlates with the original theory that coronary flow will be maintained even when the pressure changes in the artery. There were some large changes in individual cases however (case 1 - 46.7cm/s prone and 20.5cm/s supine) which is difficult to fully explain.

A possible explanation is variation in the doppler signal strength. Whilst gaining experience as a research group, it was clear that small variations in rotation or horizontal movement of the wire, could lead to large doppler signal changes. Flexibility in wire positioning was limited, with the aim to match the same position in the artery between prone and supine measurements. Rotation was the major variable in gaining adequate signal. In general, the operator would attempt to get the strongest signal within 2-5 minutes of wire placement to minimise radiation and prolonged procedural times. Positional stability and the correct signal angle have been noted to be the main technical challenges with invasive doppler measurements (Newby and Fox, 2002).

Bradycardia, coronary spasm and dissection are known to be rare complications (<1%) of doppler wire use (Qian et al., 2000). Coronary doppler flow velocity has good short term

reproducibility (de Bruyne et al., 1996). Long term reproducibility is modest, as measurements are affected by heart rate, aortic pressure and luminal area (Mario, Gil and Serruys, 1995). This shouldn't have been an issue in the current study where measurements were taken within a very close time frame.

Until recently, our understanding of human coronary physiology came predominantly from animal models. In 2016, Nijjer et al, acquired extensive data from 567 coronary measurements, including trans-stenotic gradient, FFR, doppler flow, microvascular resistance and coronary flow reserve. Autoregulatory mechanisms, which maintain prone and supine doppler measurements in this research, were clearly demonstrated. As stenosis severity increases, microvascular resistance falls, caused by a vasodilatation of the microcirculation (Figure 51). Flow was kept stable and constant until a critical stenosis point is reached (85-90%). At this point, flow does fall, leading to angina at increasingly lower levels of physical activity.

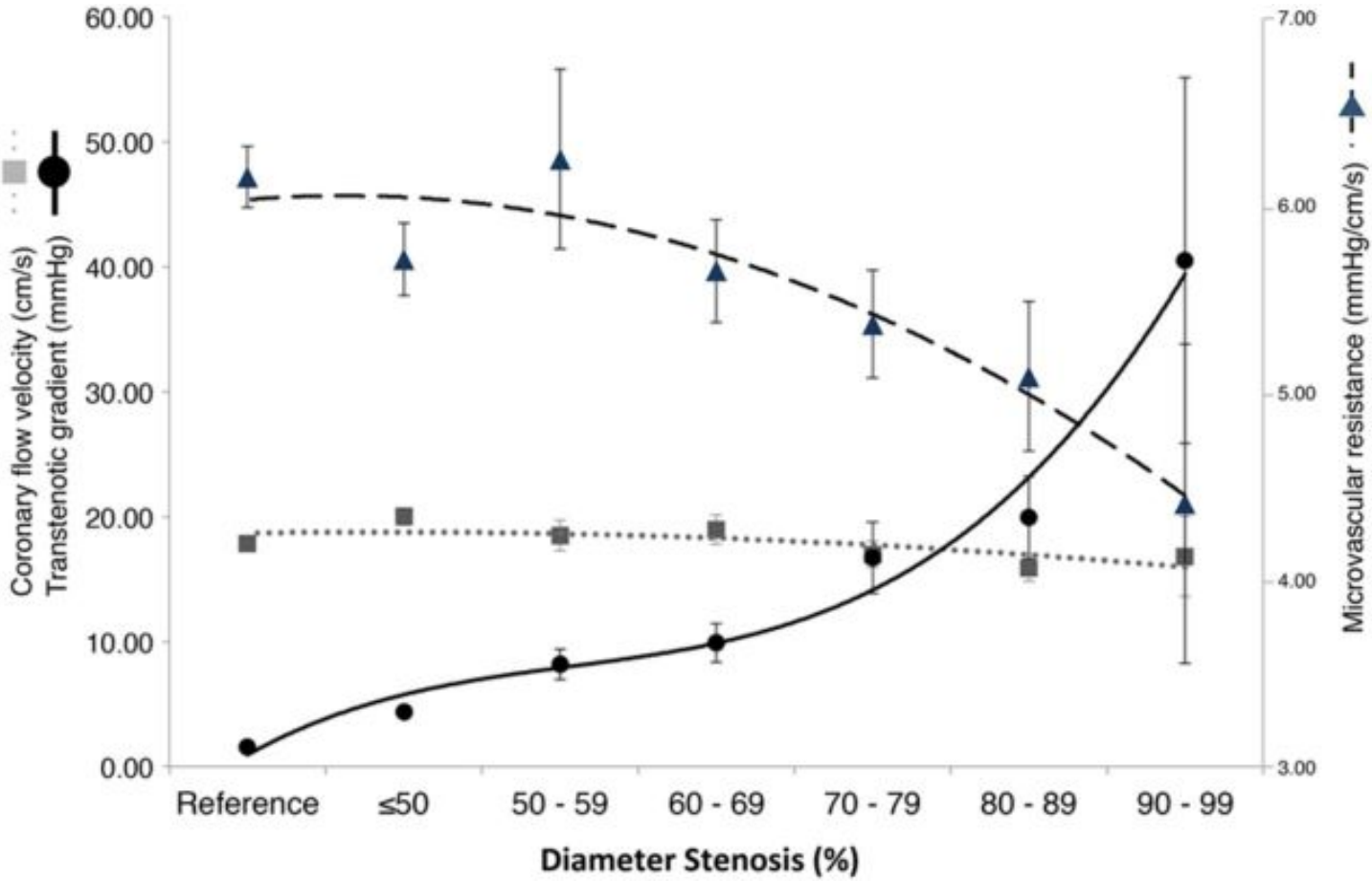


Figure 51 - Coronary Flow Versus Stenotic Gradient and Resistance. Flow is maintained even in the presence of worsening stenosis severity and gradient, at the expense of a gradually vasodilating microcirculation. From Nijjer et al., European Heart Journal, 2016. (Nijjer et al., 2016)

When hyperaemia is induced, flow augments based on the vasodilatory reserve left. In mild stenosis, the microcirculation is still not maximally vasodilated, so exogenous adenosine, produces a marked increase in flow. In severe stenoses, the microcirculation may be close to maximal vasodilatation, and hence the vasodilatory reserve is small. This leads to much smaller increase in flow, or possible no increase in flow at all, and potentially symptoms of angina on exertion.

In the study population, mean hyperaemic flow was approximately twice resting flow, i.e. a CFR of 2. Studies have previously demonstrated the prognostic value of CFR, with CFR values less than 2, being associated with worsening cardiovascular outcomes (Rigo et al., 2007), (van de Hoef et al., 2014). There are also instances where CFR and FFR are discordant. In such situations, some studies have found CFR to be a more reliable predictor of outcome than FFR, when the two are compared (van de Hoef et al., 2014). A recent has also demonstrated that iFR may correlate with CFR more closely with FFR (Cook et al., 2017), providing flow as an explanation for iFR/FFR discordance. It is unfortunate that doppler or flow-based systems have been largely replaced by pressure based invasive physiological system, largely due to ease of use.

A change of 5-10mmHg in the distal coronary vessel is therefore of no concern to coronary flow if the microcirculation autoregulates this change. If the microcirculation is unable to compensate (due to microvascular dysfunction or maximal vasodilatation), in theory hydrostatic pressure could alter coronary flow.

4.6.1 - Dysfunctional Microcirculation

Myocardial oxygen uptake is almost maximal even at rest, meaning any increase in oxygen demand must be delivered by increased coronary flow. Coronary flow augmentation, as previously described, is controlled by the microcirculation. The coronary microcirculation and microvascular dysfunction is a vast topic and beyond the scope of this thesis. In general, microcirculatory disease is known to be associated with heart failure, arrhythmias and adverse cardiovascular events (Taqueti and Di Carli, 2018). It has consistently been linked to certain risk factors such as hypertension, diabetes, renal impairment and epicardial coronary artery disease (Suzuki et al., 1994).

There is no literature on hydrostatic effect in the context of a dysfunctional microcirculation. However extrapolating from known principles, it is thought that below a coronary pressure of 40-60mmHg, the coronary vasculature is dependent on driving pressure upstream (Goodwill et al., 2017). Pressure is flow outside the autoregulatory window of approx 40-120mmHg. In this situation hydrostatic effect could have a direct effect on coronary blood flow. Especially relevant in patient's presenting acutely with ACS, in which the microcirculation may be compromised. The magnitude of effect is unknown, and would have to be assess in vivo for accurate estimates.

Interestingly, the right coronary artery appears to have less autoregulatory capacity than the left coronary system. Some studies have shown that blood flow can drop by 35% when reducing coronary pressure from 80 to 40mmHg, whereas flow in the left system remains constant (Canty and Smith, 1995). In turn, dysfunctional microcirculation in the right coronary artery could make hydrostatic effect more relevant.

4.7 - Potential Clinical Implications

4.7.1 - Pressure Based Measurements : A 'Level' Playing Field

In clinical cardiology, a treatment threshold exists for guiding clinical management in all coronary arteries based on the index used. There are no specified threshold based on the artery in question. Even in FAME (De Bruyne et al., 2014), FFR values were combined across all three coronary arteries. If analysed separately, one may find differing thresholds per artery for major cardiac events.

In almost all studies, the value for FFR is 0.75-0.80 (De Bruyne et al., 2012; Johnson et al., 2014), for iFR 0.89 and for Pd/Pa 0.92 (Hennigan et al., 2016). Resting indices are gaining scientific interest and popularity in recent months (Svanerud et al., 2018) for their ease of use, and ability to take measurements without the need for adenosine use. This increases the scope of relevance for hydrostatic pressure.

There is an assumption that each vessel's 'normal' reading will be 1.0 (distal and proximal pressure are equal). The data from this research suggests this is not the case, and the' playing field' is not level from the offset. Before the introduction of any stenosis, the value of 1.0 for a normal vessel has already been confounded. Whilst true that some lesions may be very proximal or ostial, where hydrostatic effect is less prominent, any vertical deviation from the ostial vessel will produce a hydrostatic effect, however small.

There exists therefore, separate levels of 'normality' where distal height varies from aortic height, and the Pd/Pa or FFR is not 1.0. Figure 52 plots all measurement points from CT coronary angiography data to represent this.

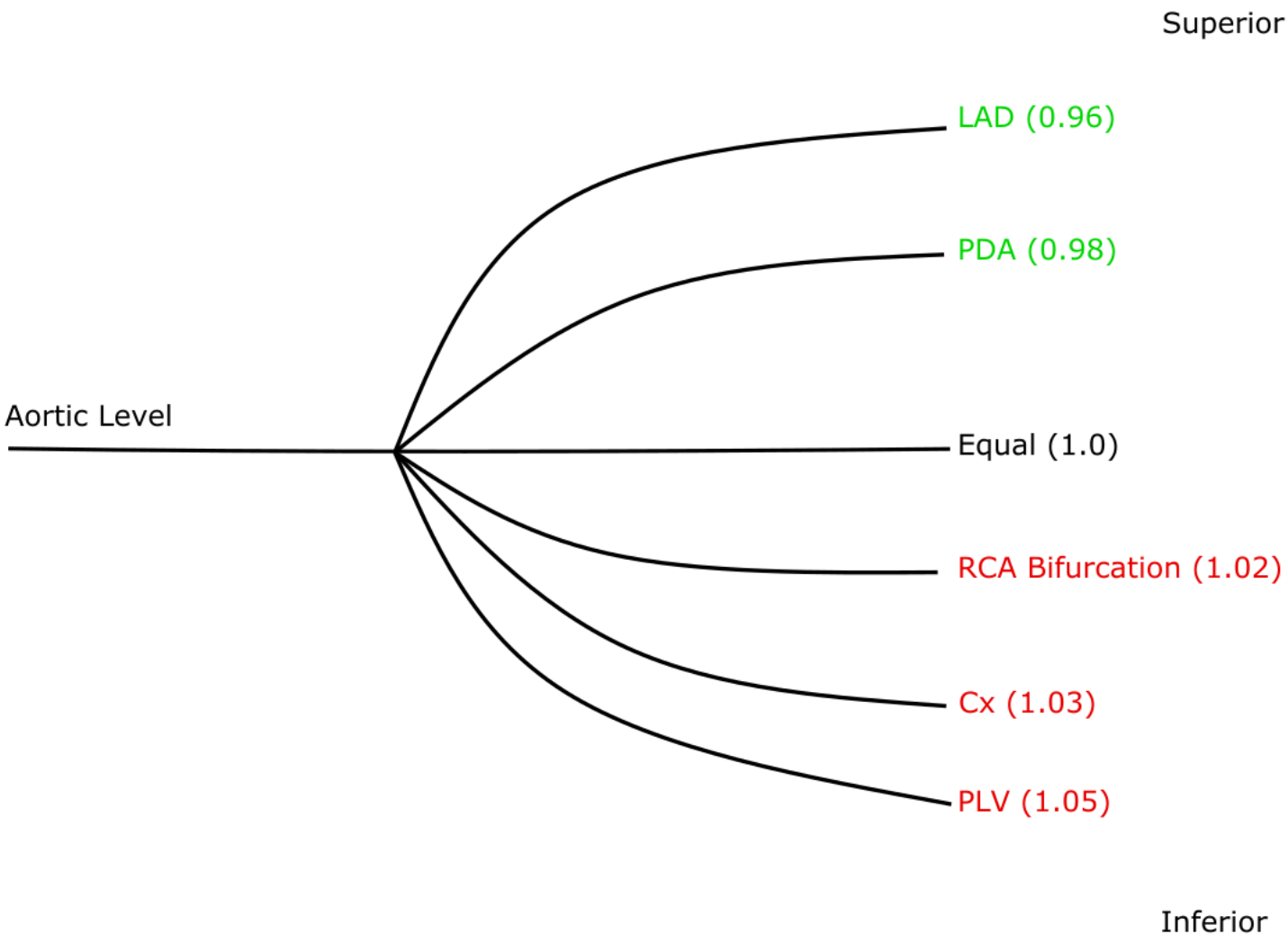


Figure 52- Hydrostatic Pressure Effect Per Artery. Diagrammatic representation of the 'level' playing field. In reality, multiple levels of height variation exist between the ostial and distal vessel. A standardised threshold for all vessels is therefore impossible. The resting Pd/Pa values at each level is shown in brackets.

In the LAD, with a wire positioned in the distal vessel, the value of 1.0 for normal is already abnormal at 0.96, in the absence of a stenosis. In turn, a lower transtenotic gradient is needed to reach the treatment threshold in the LAD. The LAD FFR must drop by 0.16 points to reach 0.8. Conversely, the PLV begins at a higher value (1.05), requiring 0.25 change to reach 0.8.

Extrapolating this further, a lesion which produces a transtenotic gradient of 20mmHg would be 'abnormal' in the LAD (FFR 0.76) but 'normal' in the circumflex artery (0.85). This leads to over-treatment of LAD lesions and under treatment of Cx lesions. In 214 coronary stenosis with equal severity, lesions in the circumflex and other inferiorly position arteries (also referred to as posterior) had significantly higher FFR values than superiorly positioned arteries (referred to as anterior) (Härle et al., 2017c).Unfortunately, this is overlooked in clinical medicine with a single oversimplified threshold for all vessels.

This has important clinical implications. Lesions may be mistreated, but it may also lead to learned behaviour in those who utilise coronary physiology. Lesions in the LAD were less severely stenosed than in any other vessel, but still referred for pressure wire assessment. This could be due to operator experience, learning that previous lesions in the LAD were significant, even if angiographically milder than other vessels.

Of the ten LAD cases where FFR measurements were taken, five were positive (i.e. FFR below 0.8) when the patient was in the standard supine position. However, when prone, only two of ten were considered positive. Moreover, the doppler flow in these arteries did not significantly change between positions. This means that FFR that is confounded by hydrostatic pressure and does not convey a true change in coronary physiology according to doppler flow.

The same is seen with circumflex artery measurements, but in reverse. In supine measurements, one lesion out of seven demonstrated an abnormal FFR, whereas three out of seven measurements were abnormal when prone. The circumflex artery has been positioned superiorly in an 'LAD position', when the patient is prone, in turn reducing FFR. Anecdotally, the phrase 'the circumflex is always negative!' is often heard amongst interventional cardiologists. This research may provide an explanation.

It is noted that the overall change is small (0.05 as a maximum) and that clinicians should use FFR as a diagnostic aid alongside clinical judgment. FFR alone should not be used to provide a binary decision on treatment strategy. Clinical judgement and decision making would be simplified however if FFR measurements across a given stenosis were as accurate as possible. Hydrostatic pressure is one of many potential confounding factors and eliminating these will provide the best clinical assessment possible.

4.7.2 - Clinical Measurement Point

The LAD clinical measurement point group was the only artery subgroup to have adequate numbers for statistical power. The results were statistically significant with a delta change of 0.06 between prone and supine measurements. Hydrostatic effects appear relevent even in more proximal portions of vessel. The clinical measurement data points in the LAD, all correlated correctly with the anticipated direction of change.

Guide to wire height at the clinical measurement point would have been a useful addition to the data set. Acquiring this during hyperaemic pullback would need ethical re-approval, given the time taken to acquire an acceptable left lateral image during adenosine infusion. This would also expose the patient to a larger infusion of adenosine. Realistically, the study protocol would require two pressure wire measurements per artery, per position (clinical and distal, prone and supine), meaning four pressure wire measurements per lesion. Ethically, this was not covered in the initial approval.

4.7.3 - Statistical Significance versus Clinical Significance

Despite a change of 0.05-0.06 in pressure-based indices being statistically significant, clinical significance and impact is harder to justify. A change of this magnitude is 25% and 50% of the required trans-stenotic gradient to class a lesion as significant using FFR and iFR respectively. A change of 0.06 re-classified 36% and 26% of lesions based on iFR and FFR respectively. Data from chapter II suggests that this number could be up to 46.5% in 'grey-zone' cases, i.e. those surrounding the threshold (0.75-0.85).

Härle recently a published a similar study with smaller changes to Pd/Pa, iFR and FFR, in a peer reviewed journal (Härle et al., 2018). This is excellent news for the field of hydrostatic pressure effect and encouraging to see colleagues value such data.

Recently, our institution showed that donor vessels to chronic total occlusions (CTO) increased FFR and iFR by 0.03 to 0.04 respectively after treatment of the CTO. This was accepted as significant by the scientific community and recently published (Mohdnazri et al., 2018). One hopes that the larger change in the current study in less complex lesions than CTO, will also be viewed as relevant in current clinical practice. The invasive data from this research is currently under review for publication.

4.7.4 - Wire Placement - PLV versus PDA

In chapter II section 2.6.5, a case report highlights the trivial decision of wire placement in a terminal branch of the right coronary artery. The right coronary artery has two terminal bifurcating branches, the PLV travelling inferiorly, and the PDA taking a superior course in a supine patient. The average difference in height between the distal PDA and PLV from CT data is 75.7mm. A lesion before this bifurcation can then be at risk of differing pressure results, depending on where the wire is placed.

Operators should remain mindful of wire position, especially if the lesion is close to or at the bifurcation of these vessels. PDA pressure indices are expected to be lower than in the PLV. As shown in the described case, the difference in FFR between each artery is 0.05, which is not clinically negligible. This may alter decision making or stenosis classification (as it did in the described case). Coronary doppler flow did not change significantly, demonstrating that hydrostatic effect is impacting the diagnostic tool of pressure-based measurement, rather than coronary physiology across the lesion.

4.7.5 - Diffuse Disease and Serial Stenosis

Regarding wire position, the initial FFR papers from Pijls and De Bruyne simply state the wire should be 'beyond the stenosis' (Pijls et al., 1996). In serial stenosis or diffuse coronary disease, the wire must be placed beyond the most distal stenosis (Pijls et al., 2000) meaning potentially a more distal wire position, and a greater hydrostatic pressure effect in such scenarios (Bruyne et al., 2000).

4.7.6 - Other Physiological Indices

Distal coronary pressure is also utilised in other physiological measurements within coronary arteries. The index of microvascular resistance (IMR) utilised distal coronary pressure in part of the equation for its calculation (Ng, Yeung and Fearon, 2006) as shown below.

IMR = Distal Artery Pressure x Mean Transmit Time

As distal pressure is affected by hydrostatic effects, there may also be an impact on IMR calculation. A vessel inferior to the aorta (such as the circumflex) with higher distal artery pressure will produce a higher IMR compared to the LAD for example.

4.7.8 - Accounting for Hydrostatic Pressure Effect

Some cardiologists may claim hydrostatic effect is another minor confounding factor, such as atrial pressure or the individual patient response to adenosine. A lettered response to Härle's CT

paper already summarises some of the communities' thoughts (Hydrostatic Forces: Don’t Let the Pressure Get to Your Head! - PubMed - NCBI, 2019). In summary, the response dampens the clinical importance of hydrostatic effect as just another minor confounding factor. The letter also highlights the wealth of data supporting pressure-based indices, and the fact that in reality, patients are standing upright in their daily lives, not lying prone or supine.

One cannot however deny the basic physical principles that underpin this concept. Patients are upright in daily life, but we have always assessed coronary physiology when supine. This study also does not aim to discredit the wealth of data for pressure-based indices, rather highlight a potential unknown variable. A single cut-off point is an oversimplification of pressure based physiological assessment. Vessels are not in the same vertical plane. In some cases, hydrostatic effects may be negligible, however there are some key concepts that have arisen from this study:

1. The more distal the wire is placed in the vessel, the larger the potential hydrostatic effect.

2. The same lesion in a superiorly positioned artery, will not yield the same FFR result if positioned in an inferiorly positioned artery (PLV vs. PDA).

3. There is potentially a greater effect in resting indices.

4. Re-classification of ischaemia is common around treatment thresholds when correcting for hydrostatic pressure effects.

The aim is to try and abolish or correct hydrostatic effect as a confounding variable. I feel there should be different treatment thresholds or cut-off points for each coronary artery. For example, the circumflex artery should have a raised FFR threshold (0.83-0.85) to account for the higher starting measurement, which is usually above 1.0 in mildly diseased or normal arteries. In turn the LAD should have a lowered threshold, to account for its lower starting point. Table 39 summarises the suggested values for FFR.

Vessel	Current FFR Threshold	Correction Factor	New FFR Threshold
LAD	0.80	-0.04	0.76
Cx	0.80	+0.03	0.83
PLV	0.80	+0.05	0.85
PDA	0.80	-0.02	0.78

Table 39 - Vessel Specific FFR

Vessel specific FFR, iFR and even Pd/Pa, could give the operator a more balanced assessment of a coronary stenosis. There are some limitations with such a suggestion however. Firstly, the vessel specific values given in table 39 are suggestions from the data set obtained during the study. More numerous data measurement points across the length of the artery are required to produce a robust and complete data set, the data from coronary CT for this study was in a selective group of patients (young female patients, low risk of ischaemic heart disease), and does not mirror the general population. Furthermore, height variations are affected by multiple factors, such as sex and body height, as demonstrated previously be Härle et al (Härle et al., 2017a).

Patients with certain disease processes such as cardiomyopathy or valvular heart disease, may have altered coronary anatomy. This means a single value given for all arteries, across all patient ages, sex and medical history, may not be absolute. Some patients also have anomalous coronary anatomy.

Secondly, the hydrostatic effect is not constant across the entire length of the vessel. A graded change in hydrostatic effect, where for example the proximal circumflex FFR is adjusted by 0.01, mid vessel by 0.02 and distal vessel by 0.03 would be more accurate (more describe under Vessel Mapping below).

In some situations, hydrostatic effect may not alter ischaemia classification. Using FFR as an example, the maximum hydrostatic effect in one position is thought to be 0.06 on average. If the FFR reading is below 0.74 or above 0.86, adjustment for hydrostatic effect is unlikely to change the clinical classification of the lesion from significant, to non-significant, and vice versa. If the FFR is between 0.74 and 0.86 however, the operator has several options. They may be mindful of the confounder of hydrostatic effect and make an informed decision. The operator may wish to correct for hydrostatic effect by using known correction factors. In the extreme, one could measure the guide to wire distance, in the catheter laboratory, using the left lateral position on the x-ray, and acquire the vertical distance between each. Using a correction factor of 0.8mmHg/cm, one could calculate the corrected FFR. This can then be combined with clinical judgment to decide on the most appropriate treatment strategy.

Each option has advantages and limitations, with the last adding extra radiation and time to the procedure, which operators would prefer to avoid. It would however provide a more accurate assessment of the lesion in question, especially in the FFR 'grey zone' of 0.75 to 0.85.

4.8 - Anatomical FFR and Hydrostatic Pressure

Anatomical measures such as CT FFR have been briefly discussed in Chapter I. CT FFR and similarly angiographic FFR are not confounded by hydrostatic pressure effects due to their very nature being non-invasive. There are other inherent flaws due to this, specifically the need for estimations of invasive haemodynamics required to produce an 'FFR value'. However, they may provide a more uniform assessment of ischaemia.

4.8.1 - CT FFR

CT coronary angiography has been used to provide a non-invasive version of FFR, known as CT FFR (Davies and Cook, 2017). CT images, a mathematical model, and several assumptions (cardiac output, aortic pressure and microvascular resistance) are combined to create a CT FFR value via several different mathematical models. CT FFR is shown to correlate with invasive FFR relatively well. The DISCOVER-FLOW (Koo et al., 2011) study and NXT trial (Nørgaard et al., 2014) reported diagnostic accuracies of 84.3 and 86% respectively. There is also evidence that CT FFR could reduce the number of referrals put forward for invasive angiography by up to half (Lu et al., 2017). As a diagnostic tool however, the assumptions inputted into the CT FFR mathematical model are not individual for each patient, meaning inevitable errors. This is shown in some studies having less favourable, moderate diagnostic accuracy (Gaur et al., 2017). Hydrostatic effect is not one of the factors in CT FFR calculation.

4.8.2 - Angio-FFR

Angiogram derived FFR was developed as an alternative to invasive FFR, as it can be done without an invasive wire insertion or a hyperaemic stimulus. The recent FAST-FFR (Fearon et al., 2019) trial demonstrated angiogram derived FFR has high sensitivity (94%) and specificity (91%) as well as diagnostic accuracy (92%) when compared to standard FFR. Diagnostic accuracy was maintained in 'grey zone' values of 0.75 to 0.85 at 87%.

Unlike CT FFR, invasive aortic pressure is available for angio FFR calculation. This combined with multiple angiographic images of the coronary tree and stenoses is factored into a mathematical algorithm which estimates resistances and flow, producing an FFR result. Studies have utilised slightly different methods with computational fluid dynamics, but all must use a set of boundary conditions to produce a result (Morris et al., 2017). Beneficially, 96% of cases in the FAST-FFR study were appropriate for analysis, compared to only 67% in the PROMISE trial, which used CT FFR (Lu et al., 2017)

4.8.3 - Hydrostatic Effect in Non-invasive FFR

As has been demonstrated, non-invasive FFR correlates well with invasive FFR (Koo et al., 2011) (Nørgaard et al., 2014). These studies did not individually compare each artery. This would have been useful to assess for any potential mismatch.

Lack of specific haemodynamic data is a notable flaw in non-invasive FFR calculation. However, the non-invasive nature of these measurements may also be beneficial, in that confounding factors which plague invasive FFR are irrelevant. Atrial pressure, LVEDP, response to hyperaemia and hydrostatic pressure are no longer a factor in angio or CT FFR. Anterior and posterior artery position should have negligible or no effect on measured FFR.

Interestingly, CT FFR data from the ADVANCE registry (Kitabata et al., 2018) showed a trend towards lower FFR values in LAD lesions compared to RCA lesions. The authors did not give an explanation for this or show any lesion specific data (e.g. lesion length). Boundary conditions which are required compute CT FFR are based on physical laws. Flow for example is calculated using myocardial wall volume extracted from CTA as a variable. This potentially has an impact on computed flow per vessel, as the LAD is known to supply the largest volume of myocardium.

No study has addressed hydrostatic effect in non-invasive measures of FFR and correlation with invasive FFR. No mathematical algorithm mentions hydrostatic pressure as an included variable in non-invasive FFR calculation. Many studies aim to show that CT FFR as diagnostically accurate as invasive FFR, where the wealth of data lies. However, with the assumptions and boundary limitations in non-invasive FFR, coupled against the confounding factors and patient specific issues in invasive FFR, discordance is likely to be forever present. It is still not clear which is truly the best measure of a significant stenosis.

4.9 - Arguments Against Hydrostatic Effect

Some experts stipulate the change in FFR along the length of a vessel, in the absence of a focal stenosis, is due to diffuse coronary artery disease (Bruyne et al., 2001) . This potentially explains why the FFR may be 0.97 in the distal LAD, in what appears to be a relatively disease-free vessel. Whilst this is certainly a valid physiological explanation, it does not explain why the FFR changes in the opposite direction during position change to prone. The diffuse atherosclerosis is still present, but the distal Pd/Pa is now seen to be above 1.0. This is exactly the situation for case 11, where supine Pd/Pa was 0.97 in the LAD, and prone Pd/Pa was 1.02.

Another interesting discussion point relates to the mass of myocardium supplied by a vessel. The suggested reason that the LAD has lower FFR values for the same stenosis severity than other vessels, relates to the mass of myocardium supplied. A larger myocardial mass means greater flow in the artery that supplies it, and in turn a larger gradient during maximal hyperaemia (Leone et al., 2013a). This does not detract from the change in FFR when a patient changes positions.

In the same lettered response to Härle et al., from Johnson et al (Hydrostatic Forces: Don’t Let the Pressure Get to Your Head! - PubMed - NCBI, 2019) the authors suggest that a change in 5mmHg for example, will have little effect on an FFR measurement which shows a 30mmHg transtenotic gradient. This is a valid response, however a significant proportion of stenoses have gradients closer to 20mmHg. A change of ± 5mmHg, is highly relevant.

Intra thoracic movement of organs is the basic principle in prone positioning in ARDS, as the weight of organs is lifted off dorsal structures (Scholten et al., 2017). One could argue the weight of the heart when changing position is responsible for the pressure change within the coronary arteries. Whilst this may contribute, it would not explain the variation in magnitude of change between the arteries themselves. One may expect all arteries to change by a set magnitude with minimal variation, which is not the case.

4.10 - Study Limitations

All patients were male. Male sex is a predictor for increased height from distal to proximal coronary artery (Härle et al., 2017a). Height is also a predictive factor for coronary height variations, and as on average, male patients are taller than females, the height calculations are potentially larger. This could lead to an overestimation of the hydrostatic effect.

The default wire position for all measurements was in the distal vessel. This may not be the point of measurement in every clinical case and exaggerate the hydrostatic effect.

The Pa pressure was lower on average when taking supine measurements. Prone measurements were first, followed by supine measurements. The reason for this was predominantly patient safety, in that starting supine, followed by prone, would mean positioning the patient back to supine if the artery needed treatment. To minimise the number of turns, and the risks associated with this, the study protocol was designed to take prone measurements first. Supine Pa was 5mmHg on average lower for Pd/Pa, and 6mmHg lower on average for FFR. The effect this has on delta change between positions is minimal, but noteworthy.

Guide to wire measurements were taken during angiography in the left lateral position. In some cases, the left lateral angle was not exactly 90 degrees. This may cause a minute amount of error in the guide to wire height measurement. Furthermore, a useful addition in retrospect would be to repeat guide to wire measurement in the supine position, not only the prone position. The combination of both measurements may lead to a more accurate correlation with delta change in Pd/Pa and FFR.

Stenosis assessment using QCA is has inaccuracies (Wunderlich et al., 1998). Calibration of the QCA system uses the size of a known calibre coronary catheter to measure distances on a still image. There is a potential for error in the measured distances, therefore.

Right atrial pressure was excluded in the assessment of FFR in the study demographic for safety reasons. However, recent studies demonstrate that right atrial pressure is negligible with regards to FFR measurement (Toth et al., 2016).

Lastly the correction factor of 0.8mmHg/cm to convert vertical height into hydrostatic pressure is the closest value available for use at the present time. Pressure simulator results from Härle et al., 2017a, show a conversion factor of 0.77mmHg/cm with 0.9% saline fluid instead of blood. Correcting for the density of blood, the value of 0.8mmHg/cm is more likely to represent the correct value. Further studies in vivo are needed to accurately define the conversion rate.

The possible weight of the heart affecting intracoronary pressure has already been discussed.

I designed, conducted and co-ordinated this study and performed all data collection and analysis. I was aware of the research hypothesis and was unblinded to the results. This may have introduced bias despite all precautions. I did have to guide placement of the physiology wire to keep positioning as constant as possible as well as ensure study protocol with regards to heparin and nitrates was adhered to. I did not have any intervention beyond this.

4.11 - Future Research

4.11.1 - Ideal Study Protocol

In an ideal scenario and protocol, a more comprehensive assessment of hydrostatic effect would measure the following:

1. Pd/Pa, iFR and FFR in all coronary arteries in every patient
2. Prone, supine, left and right lateral patient position.
3. Proximal, mid and distal measurement points in every artery
4. Measurement in arteries with no coronary stenosis

5. Doppler and thermodilution flow measurements

6. CTCA for all patients before invasive angiography to map their coronary circulation

7. LAO angiogram in every position.

This would of course be unethical and require extensive resources. It would however provide a robust and accurate data set however, to truly demonstrate the extent and magnitude of hydrostatic effect in vivo.

4.11.2 - STEMI

The initial research question still remains; does a change of patient position during an ST elevation myocardial infarction, alter flow to the affected heart muscle?

From the study results, it appears a change in patient position does not affect flow in mild to moderately diseased arteries. The study demographic did not have an occluded or sub occluded vessel as is usually the case in ST elevation myocardial infarction. The research team at the Essex Cardiothoracic Centre now have a better understanding of coronary physiology in non-emergency patients, and have the background knowledge to trial subsequent theories in STEMI.

Armed with the knowledge that flow does not change with position in a relatively normal artery, one can now attempt to ask the same question in acute myocardial infarction. In the acute setting of a myocardial infarction, the microcirculation is dysfunctional, and autoregulation is disturbed (Tamita et al., 2002). Changing pressure in this clinical context may therefore correlate into a change in flow if autoregulation cannot compensate.

It is unclear to what magnitude pressure would increase flow. We expect a change in coronary pressure of up to 10mm Hg. In animal models with impaired autoregulation this equates to a

change of approximately 10 to 20ml/min of coronary blood flow (Goodwill et al., 2017). How this translates into clinical outcomes is unknown, and would be the focus of future studies.

This next step would be to extend the current research into the acute group of patients. The current study has proved prone angiography is not only possible, but safe and with correct staff training and not overly time consuming. The risk of cardiac arrest in acute myocardial infarction is much higher than elective patients, and if the patient is prone, there will be added risk related to the time taken to manoeuvre back into the supine position to commence CPR. Figure 53 shows a provisional order of events in acute patients.

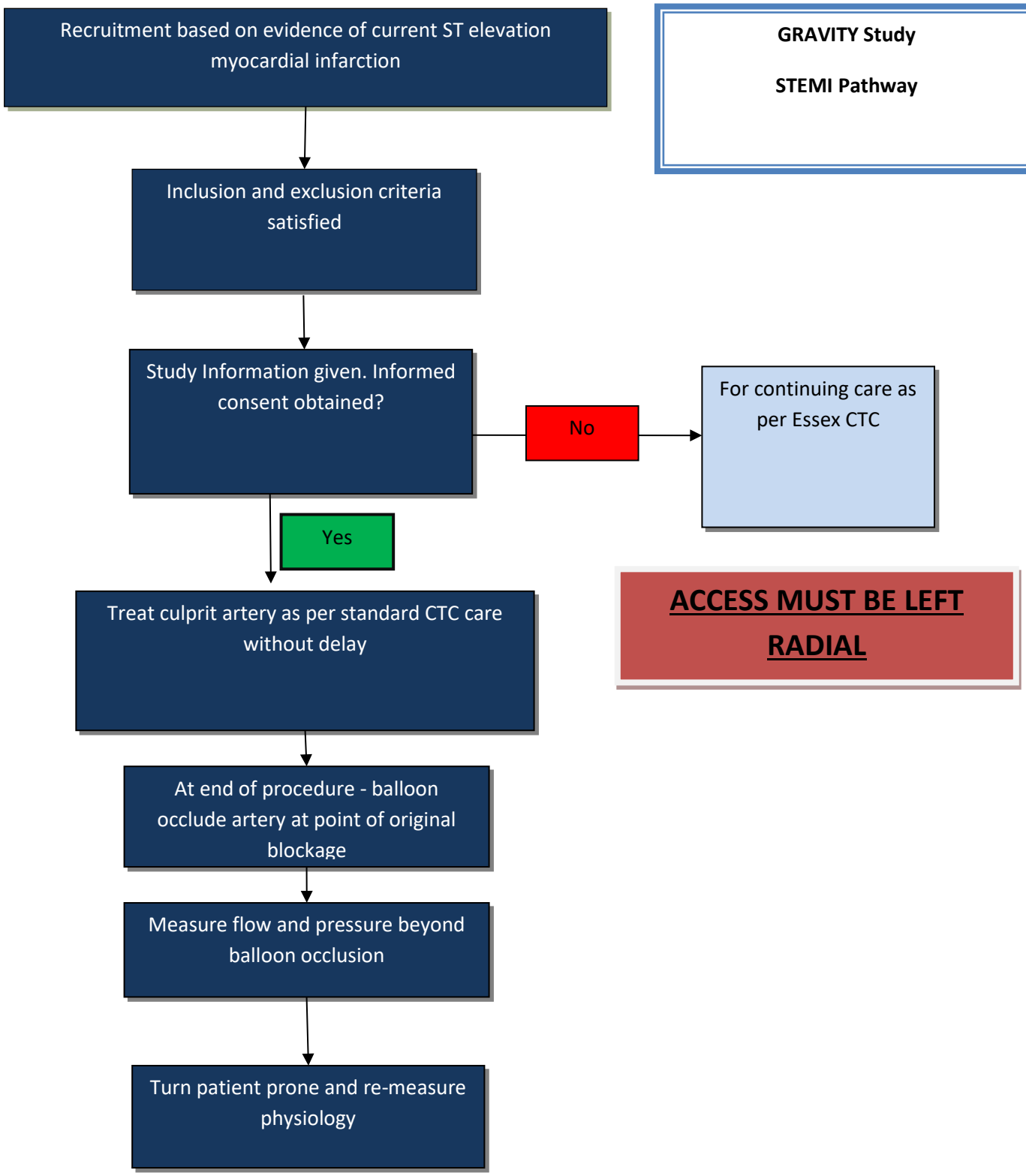


Figure 53 - Suggested STEMI Pathway. Possible chain of events in STEMI patients of future GRAVITY studies.

Measurements are taken from a physiology wire beyond a balloon which is occluding the vessel. This mimics occlusion of the vessel. Myocardial blood flow beyond this blockage is supplied by coronary collaterals as there is no antegrade flow. The pressure and flow measurements obtained will therefore be collateral flow and collateral pressure. The centre has experience in obtaining these measurements from previous studies (Mohdnazri et al., 2018). If flow can be increased with changes in position, ambulance or emergency staff could position patient prone for certain infarcts during transfer to a PCI centre, saving myocardium and reducing infarct size. Infarct size is a clear determinant of outcomes for patients suffering acute myocardial infarction (Stone et al., 2016a).

A prospective randomised trial of prone versus supine positioning versus control (standard care), and the assessment of infarct size (CMRI) and adverse cardiac events at 30 days and 1 year.

4.11.3 - Chronic Total Occlusion

Before studying acute myocardial infarction, and acute blockages of a coronary artery, the intermediate step may be to study patients with a chronic occlusion of an artery. In chronic total occlusion, the microcirculation is thought to be dysfunctional (Ladwiniec et al., 2016). Ethical approval for this has already been obtained, recruitment could commence at any time. The counter argument is that if the final target group is STEMI patients, one should not involve a separate group of patients who are subjected to the small, but potential risks of the study protocol and instead go straight to acute infarct patients.

4.11.4 - Vessel Mapping

The current research suggests single thresholds for all coronary arteries is an oversimplification. However, a single adjustment factor per artery would also be only partially correct.

A more elegant solution would be specific correction factors for each segment of each artery. The vessel is 'mapped' to assess hydrostatic pressure effect at each point. In clinical practice, this may mean separate adjustments for proximal, mid and distal vessel.

The most accurate way to do this, would be to study normal coronary arteries in live patients, with pressure-based measurements at multiple points in each artery. With enough data, one could create a hydrostatic map for each coronary artery. Studying non culprit arteries as part of the protocol was explored during the study period. Unfortunately, an ethical amendment was rejected by the local ethics committee. It was deemed that five extra pressure wire measurements instead of one was excessive for study purposes. Physiology measurements in unobstructed coronary arteries would be unethical.

CT coronary angiography may provide an alternative solution. From an anatomical perspective, CTCA could still be useful in mapping hydrostatic effect via vertical height. This could be gathered from retrospective CT coronary angiograms, to build a database of height measurement for each coronary artery at multiple points. This translates into hydrostatic effect, and would map effect per portion of artery. Being non invasive, this bypasses many ethical issues, and having a full database of scans at the Essex Cardiothoracic Centre means this could be done locally and rapidly.

CT scans would map multiple points in the coronary tree, and provide a correction factor for proximal, mid and distal vessel in all coronary arteries (Figure 54). The correction factor could either be applied directly to pressure wire software, or be available to angioplasty operators during stenosis assessment.

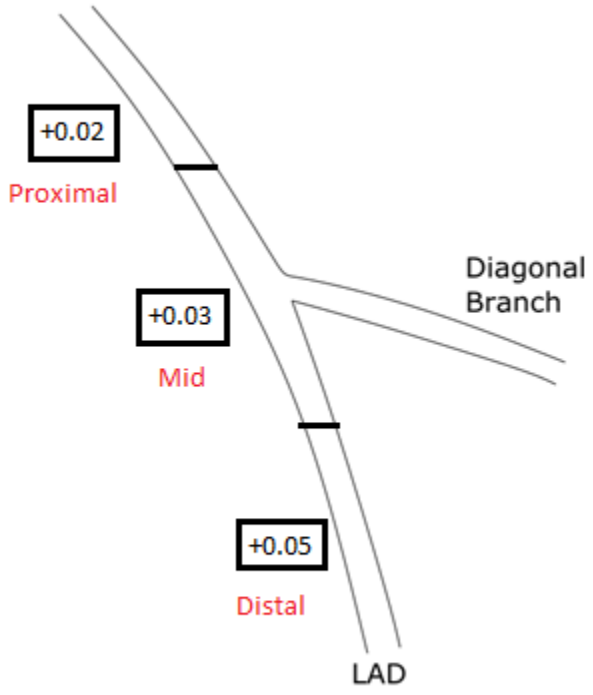


Figure 54 - Graduated Hydrostatic Correction - demonstration of LAD with proximal, mid and distal LAD correction factors

4.12 - Novel Pressure Wires Immune to Hydrostatic Effect

The concept of hydrostatic effect has impressed upon medical equipment developers. In the final few months of research, a medical devices company approached the institution with interest surrounding our CT coronary angiogram data.

There appears to be a way in vivo to abolish hydrostatic effect by using a specific kind of physiology wire, which is undergoing preliminary trials. The concept involves measuring pressure distal to the stenosis using a physiology wire with a saline filled centre. The pressure is projected through the saline central lumen to an external pressure sensor sitting at aortic level

outside of the patient. This abolishes hydrostatic pressure, by ensuring the distal sensor is always at the same vertical level. The pressure in the distal vessel is now not compounded by hydrostatic effect. Figure 55 demonstrates this.

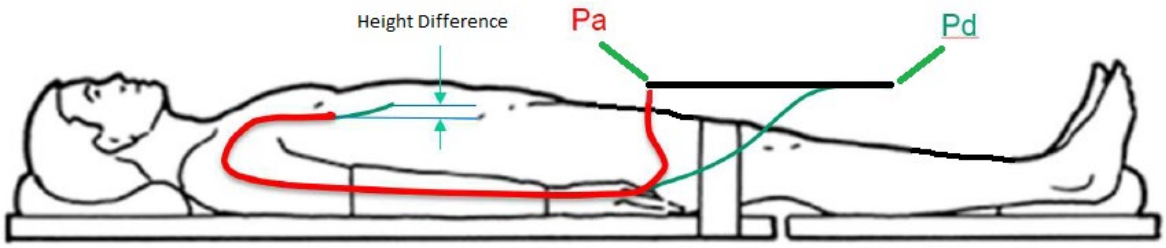


Figure 55 - Hydrostatic Effect Immune Wires - Pd pressure is transferred through a saline centred wire and measured externally through a transducer at the same level as Pa. The height difference is therefore abolished

This wire, if fully produced, could negate all hydrostatic effect, and give a pure stenosis pressure signal. This would make vessel mapping obsolete if incorporated into angiography laboratory set-up.

It is hugely re-assuring to know that a concept which has considered largely irrelevant, is being investigated by other academics in the field, partly due to the literature this study has produced. There may indeed be future collaborations between industry and our institution, in developing novel, and clinically relevant medical equipment.

4.13 - Final Thoughts

The aim of this study was not to change clinical practice, or specifically alter the use of pressure-based indices. It would be impossible to invalidate over twenty-five years of data with a

relatively small data set. The hope is to emphasise the importance of widely neglected phenomenon to clinicians who use pressure-based indices as a daily diagnostic tool.

The study has certainly changed the way operators at the Essex Cardiothoracic Centre approach pressure wire studies. If this ethos could spread to the wider community, it should only aid the continuous learning process in delivering the best patient care.

In my personal practice, I am mindful of the position of the physiology wire and the vessel I am assessing. I believe in a multi-faceted approach in the assessment of the patient and their coronary anatomy. Pressure based indices are a single piece of the whole, and whilst FFR is an excellent diagnostic aid, like any clinical tool, it has limitations. This research has certainly enlightened my clinical practice, and I hope it will for similarly for my colleagues.

References

Adjedj, J., Xaplanteris, P., Toth, G., Ferrara, A., Pellicano, M., Ciccarelli, G., Floré, V., Barbato, E. and De Bruyne, B., 2017. Visual and Quantitative Assessment of Coronary Stenoses at Angiography Versus Fractional Flow Reserve: The Impact of Risk Factors. *Circulation. Cardiovascular Imaging*, 10(7).

Ahn, J.-M., Park, D.-W., Shin, E.-S., Koo, B.-K., Nam, C.-W., Doh, J.-H., Kim, J.H., Chae, I.-H., Yoon, J.-H., Her, S.-H., Seung, K.-B., Chung, W.-Y., Yoo, S.-Y., Lee, J.B., Choi, S.W., Park, K., Hong, T.J., Lee, S.Y., Han, M., Lee, P.H., Kang, S.-J., Lee, S.-W., Kim, Y.-H., Lee, C.W., Park, S.-W., Park, S.-J. and IRIS-FFR Investigators†, 2017. Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation*, 135(23), pp.2241–2251.

Al-Janabi, F., Karamasis, G., Cook, C.M., Kabir, A.M., Jagathesan, R.O., Robinson, N.M., Sayer, J.W., Aggarwal, R.K., Clesham, G.J., Kelly, P.R., Gamma, R.A., Tang, K.H., Keeble, T.R. and Davies, J.R., 2019. Coronary artery height differences and their effect on fractional flow reserve. *Cardiology Journal*.

Al-Lamee, R., Davies, J. and Malik, I.S., 2016. What is the role of coronary angioplasty and stenting in stable angina? *BMJ*, 352, p.i205.

Al-Lamee, R., Thompson, D., Dehbi, H.-M., Sen, S., Tang, K., Davies, J., Keeble, T., Mielewczik, M., Kaprielian, R., Malik, I.S., Nijjer, S.S., Petraco, R., Cook, C., Ahmad, Y., Howard, J., Baker, C., Sharp, A., Gerber, R., Talwar, S., Assomull, R., Mayet, J., Wensel, R., Collier, D., Shun-Shin, M., Thom, S.A., Davies, J.E., Francis, D.P. and ORBITA investigators, 2018. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet (London, England)*, 391(10115), pp.31–40.

Al-Mukhaini, M., Panduranga, P., Sulaiman, K., Riyami, A.A., Deeb, M. and Riyami, M.B., 2011. Coronary perforation and covered stents: an update and review. *Heart Views: The Official Journal of the Gulf Heart Association*, 12(2), pp.63–70.

Andersen, H.R., Nielsen, T.T., Rasmussen, K., Thuesen, L., Kelbaek, H., Thayssen, P., Abildgaard, U., Pedersen, F., Madsen, J.K., Grande, P., Villadsen, A.B., Krusell, L.R., Haghfelt, T., Lomholt, P., Husted, S.E., Vigholt, E., Kjaergard, H.K., Mortensen, L.S. and DANAMI-2 Investigators, 2003. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *The New England Journal of Medicine*, 349(8), pp.733–742.

Anderson, H.V., Shaw, R.E., Brindis, R.G., McKay, C.R., Klein, L.W., Krone, R.J., Ho, K.K.L., Rumsfeld, J.S., Smith, S.C. and Weintraub, W.S., 2007. Risk-adjusted mortality analysis of percutaneous coronary interventions by American College of Cardiology/American Heart Association guidelines recommendations. *The American Journal of Cardiology*, 99(2), pp.189–196.

Anon 1994. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet (London, England)*, 343(8893), pp.311–322.

Anon 2018. *Avoidable mortality in England and Wales - Office for National Statistics*. [online] Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/avoidablemortalityinenglandandwales/2015> [Accessed 16 Apr. 2018].

Anon 2018. *Chest pain of recent onset: assessment and diagnosis | Guidance and guidelines | NICE*. [online] Available at: <https://www.nice.org.uk/guidance/cg95/chapter/Recommendations#people-presenting-with-stable-chest-pain> [Accessed 21 Jun. 2018].

Anon 2018. *Heart statistics*. [online] Available at: <https://www.bhf.org.uk/research/heart-statistics> [Accessed 24 Apr. 2018].

Anon 2018. *Stable angina: management | Guidance and guidelines | NICE*. [online] Available at: <https://www.nice.org.uk/guidance/CG126> [Accessed 1 May 2018].

Anon 2019. *Hydrostatic Forces: Don't Let the Pressure Get to Your Head! - PubMed - NCBI*. [online] Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28797436> [Accessed 29 Oct. 2019].

Anon 2020. *ESC Guidelines on Chronic Coronary Syndromes (Previously titled Stable Coronary Artery Disease)*. [online] Available at: <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes, https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes> [Accessed 14 May 2020].

Anon 2020. *PCR Abstract book*. [online] Available at: <https://abstractbook.pcronline.com/index/slide/abstract/100377/search/hydro> [Accessed 17 Jul. 2020].

Antithrombotic Trialists' Collaboration, 2002. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ (Clinical research ed.)*, 324(7329), pp.71–86.

Authors/Task Force members, Windecker, S., Kolh, P., Alfonso, F., Collet, J.-P., Cremer, J., Falk, V., Filippatos, G., Hamm, C., Head, S.J., Jüni, P., Kappetein, A.P., Kastrati, A., Knuuti, J., Landmesser, U., Laufer, G., Neumann, F.-J., Richter, D.J., Schauerte, P., Sousa Uva, M., Stefanini, G.G., Taggart, D.P., Torracca, L., Valgimigli, M., Wijns, W. and Witkowski, A., 2014. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *European Heart Journal*, 35(37), pp.2541–2619.

Axel, D.I., Kunert, W., Göggelmann, C., Oberhoff, M., Herdeg, C., Küttner, A., Wild, D.H., Brehm, B.R., Riessen, R., Köveker, G. and Karsch, K.R., 1997. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation*, 96(2), pp.636–645.

Baigent, C., Collins, R., Appleby, P., Parish, S., Sleight, P. and Peto, R., 1998. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *BMJ (Clinical research ed.)*, 316(7141), pp.1337–1343.

Bangalore, S., Kumar, S., Fusaro, M., Amoroso, N., Kirtane, A.J., Byrne, R.A., Williams, D.O., Slater, J., Cutlip, D.E. and Feit, F., 2012. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ (Clinical research ed.)*, 345, p.e5170.

BARI 2D Study Group, Frye, R.L., August, P., Brooks, M.M., Hardison, R.M., Kelsey, S.F., MacGregor, J.M., Orchard, T.J., Chaitman, B.R., Genuth, S.M., Goldberg, S.H., Hlatky, M.A., Jones, T.L.Z., Molitch, M.E., Nesto, R.W., Sako, E.Y. and Sobel, B.E., 2009. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *The New England Journal of Medicine*, 360(24), pp.2503–2515.

Barrett, B.J. and Carlisle, E.J., 1993. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology*, 188(1), pp.171–178.

Bauters, C., Meurice, T., Hamon, M., McFadden, E., Lablanche, J.M. and Bertrand, M.E., 1996. Mechanisms and prevention of restenosis: from experimental models to clinical practice. *Cardiovascular Research*, 31(6), pp.835–846.

Bech, G.J., De Bruyne, B., Pijls, N.H., de Muinck, E.D., Hoorntje, J.C., Escaned, J., Stella, P.R., Boersma, E., Bartunek, J., Koolen, J.J. and Wijns, W., 2001. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*, 103(24), pp.2928–2934.

Berry, C., van ’t Veer, M., Witt, N., Kala, P., Bocek, O., Pyxaras, S.A., McClure, J.D., Fearon, W.F., Barbato, E., Tonino, P.A.L., De Bruyne, B., Pijls, N.H.J. and Oldroyd, K.G., 2013. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. *Journal of the American College of Cardiology*, 61(13), pp.1421–1427.

Biondi-Zoccai, G.G.L., Agostoni, P., Sangiorgi, G.M., Airoldi, F., Cosgrave, J., Chieffo, A., Barbagallo, R., Tamburino, C., Vittori, G., Falchetti, E., Margheri, M., Briguori, C., Remigi, E., Iakovou, I. and Colombo, A., 2006. Incidence, predictors, and outcomes of coronary dissections left untreated after drug-eluting stent implantation. *European Heart Journal*, 27(5), pp.540–546.

Blows, L.J. and Redwood, S.R., 2007. The pressure wire in practice. *Heart*, 93(4), pp.419–422.

Boden, W.E., O'Rourke, R.A., Teo, K.K., Hartigan, P.M., Maron, D.J., Kostuk, W.J., Knudtson, M., Dada, M., Casperson, P., Harris, C.L., Chaitman, B.R., Shaw, L., Gosselin, G., Nawaz, S., Title, L.M., Gau, G., Blaustein, A.S., Booth, D.C., Bates, E.R., Spertus, J.A., Berman, D.S., Mancini, G.B.J., Weintraub, W.S. and COURAGE Trial Research Group, 2007. Optimal medical therapy with or without PCI for stable coronary disease. *The New England Journal of Medicine*, 356(15), pp.1503–1516.

Borden, W.B., Spertus, J.A., Mushlin, A.I., Roe, M.T., McCoy, L.A. and Redberg, R.F., 2013. Antianginal Therapy Before Percutaneous Coronary Intervention. *Circulation: Cardiovascular Interventions*, 6(4), pp.436–443.

BrJCardiol, 2018. *Chronic stable angina guidelines – is there an emerging international consensus?* [online] The British Journal of Cardiology. Available at: <https://bjcardio.co.uk/2012/08/chronic-stable-angina-guidelines-is-there-an-emerging-international-consensus/> [Accessed 2 Jul. 2018].

Brodie, B.R., Stuckey, T.D., Wall, T.C., Kissling, G., Hansen, C.J., Muncy, D.B., Weintraub, R.A. and Kelly, T.A., 1998. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *Journal of the American College of Cardiology*, 32(5), pp.1312–1319.

de Bruyne, B., Bartunek, J., Sys, S.U., Pijls, N.H., Heyndrickx, G.R. and Wijns, W., 1996. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation*, 94(8), pp.1842–1849.

Bruyne, B.D., Hersbach, F., Pijls, N.H.J., Bartunek, J., Bech, J.-W., Heyndrickx, G.R., Gould, K.L. and Wijns, W., 2001. Abnormal Epicardial Coronary Resistance in Patients With Diffuse Atherosclerosis but "Normal" Coronary Angiography. *Circulation*, 104(20), pp.2401–2406.

Bruyne, B.D., Pijls, N.H.J., Heyndrickx, G.R., Hodeige, D., Kirkeeide, R. and Gould, K.L., 2000. Pressure-Derived Fractional Flow Reserve to Assess Serial Epicardial Stenoses: Theoretical Basis and Animal Validation. *Circulation*, 101(15), pp.1840–1847.

Budoff, M.J., Dowe, D., Jollis, J.G., Gitter, M., Sutherland, J., Halamert, E., Scherer, M., Bellinger, R., Martin, A., Benton, R., Delago, A. and Min, J.K., 2008. Diagnostic Performance of 64-Multidetector Row Coronary Computed Tomographic Angiography for Evaluation of Coronary Artery Stenosis in Individuals Without Known Coronary Artery Disease: Results From the Prospective Multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) Trial. *Journal of the American College of Cardiology*, 52(21), pp.1724–1732.

Budoff, M.J., Nakazato, R., Mancini, G.B.J., Gransar, H., Leipsic, J., Berman, D.S. and Min, J.K., 2016. CT Angiography for the Prediction of Hemodynamic Significance in Intermediate and Severe Lesions: Head-to-Head Comparison With Quantitative Coronary Angiography Using Fractional Flow Reserve as the Reference Standard. *JACC. Cardiovascular imaging*, 9(5), pp.559–564.

Busk, M., Maeng, M., Rasmussen, K., Kelbaek, H., Thayssen, P., Abildgaard, U., Vigholt, E., Mortensen, L.S., Thuesen, L., Kristensen, S.D., Nielsen, T.T., Andersen, H.R. and DANAMI-2 Investigators, 2008. The Danish multicentre randomized study of fibrinolytic therapy vs. primary angioplasty in acute myocardial infarction (the DANAMI-2 trial): outcome after 3 years follow-up. *European Heart Journal*, 29(10), pp.1259–1266.

Cannon, C.P., Weintraub, W.S., Demopoulos, L.A., Vicari, R., Frey, M.J., Lakkis, N., Neumann, F.J., Robertson, D.H., DeLucca, P.T., DiBattiste, P.M., Gibson, C.M., Braunwald, E. and TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)--Thrombolysis in Myocardial Infarction 18 Investigators, 2001. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *The New England Journal of Medicine*, 344(25), pp.1879–1887.

Canty, J.M. and Smith, T.P., 1995. Modulation of coronary autoregulatory responses by endothelium-derived nitric oxide. *International Journal of Cardiology*, 50(3), pp.207–215.

Castellano, I.A., Nicol, E.D., Bull, R.K., Roobottom, C.A., Williams, M.C. and Harden, S.P., 2017. A prospective national survey of coronary CT angiography radiation doses in the United Kingdom. *Journal of Cardiovascular Computed Tomography*, 11(4), pp.268–273.

Chin, C.T., L'Allier, P., Neumann, F.-J., Engstrøm, T., Jüni, P. and Olivecrona, G.K., 2017. The Compare-Acute trial of fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*, 13(5), pp.e613–e616.

Cho, H.-O., Nam, C.-W., Cho, Y.-K., Yoon, H.-J., Park, H.-S., Kim, H., Chung, I.-S., Doh, J.-H., Koo, B.-K., Hyun, D.-W., Hur, S.-H., Kim, Y.-N. and Kim, K.-B., 2014. Characteristics of function-anatomy mismatch in patients with coronary artery disease. *Korean Circulation Journal*, 44(6), pp.394–399.

Choi, J.W., Gibson, C.M., Murphy, S.A., Davidson, C.J., Kim, R.J. and Ricciardi, M.J., 2004. Myonecrosis following stent placement: Association between impaired TIMI myocardial perfusion grade and MRI visualization of microinfarction. *Catheterization and Cardiovascular Interventions*, 61(4), pp.472–476.

Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent, C., Blackwell, L., Emberson, J., Holland, L.E., Reith, C., Bhala, N., Peto, R., Barnes, E.H., Keech, A., Simes, J. and Collins, R., 2010. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet (London, England)*, 376(9753), pp.1670–1681.

Claessen, B.E., Henriques, J.P.S., Jaffer, F.A., Mehran, R., Piek, J.J. and Dangas, G.D., 2014. Stent Thrombosis: A Clinical Perspective. *JACC: Cardiovascular Interventions*, 7(10), pp.1081–1092.

Claeys, M.J., Bosmans, J.M., Hendrix, J. and Vrints, C.J., 2001. Reliability of fractional flow reserve measurements in patients with associated microvascular dysfunction: Importance of flow

on translesional pressure gradient. *Catheterization and Cardiovascular Interventions*, 54(4), pp.427–434.

Clayton, B., Roobottom, C. and Morgan-Hughes, G., 2015. CT coronary angiography in atrial fibrillation: a comparison of radiation dose and diagnostic confidence with retrospective gating vs prospective gating with systolic acquisition. *The British Journal of Radiology*, 88(1055), p.20150533.

Cook, C.M., Jeremias, A., Petraco, R., Sen, S., Nijjer, S., Shun-Shin, M.J., Ahmad, Y., de Waard, G., van de Hoef, T., Echavarria-Pinto, M., van Lavieren, M., Al Lamee, R., Kikuta, Y., Shiono, Y., Buch, A., Meuwissen, M., Danad, I., Knaapen, P., Maehara, A., Koo, B.-K., Mintz, G.S., Escaned, J., Stone, G.W., Francis, D.P., Mayet, J., Piek, J.J., van Royen, N. and Davies, J.E., 2017. Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance in Angiographically Intermediate Coronary Stenoses: An Analysis Using Doppler-Derived Coronary Flow Measurements. *JACC. Cardiovascular interventions*, 10(24), pp.2514–2524.

Cutlip, D.E., Windecker, S., Mehran, R., Boam, A., Cohen, D.J., Es, G.-A. van, Steg, P.G., Morel, M., Mauri, L., Vranckx, P., McFadden, E., Lansky, A., Hamon, M., Krucoff, M.W. and Serruys, P.W., 2007. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. *Circulation*, 115(17), pp.2344–2351.

Davidson, C., Stacul, F., McCullough, P.A., Tumlin, J., Adam, A., Lameire, N. and Becker, C.R., 2006. Contrast Medium Use. *American Journal of Cardiology*, 98(6), pp.42–58.

Davies, J.E. and Cook, C.M., 2017. Is FFRCT Ready to Assume the Crown Jewels of Invasive FFR?∗. *JACC: Cardiovascular Imaging*, 10(4), pp.434–436.

Davies, J.E., Sen, S., Dehbi, H.-M., Al-Lamee, R., Petraco, R., Nijjer, S.S., Bhindi, R., Lehman, S.J., Walters, D., Sapontis, J., Janssens, L., Vrints, C.J., Khashaba, A., Laine, M., Van Belle, E., Krackhardt, F., Bojara, W., Going, O., Härle, T., Indolfi, C., Niccoli, G., Ribichini, F., Tanaka, N., Yokoi, H., Takashima, H., Kikuta, Y., Erglis, A., Vinhas, H., Canas Silva, P., Baptista, S.B., Alghamdi, A., Hellig, F., Koo, B.-K., Nam, C.-W., Shin, E.-S., Doh, J.-H., Brugaletta, S., Alegria-Barrero, E., Meuwissen, M., Piek, J.J., van Royen, N., Sezer, M., Di Mario, C., Gerber, R.T., Malik, I.S., Sharp, A.S.P., Talwar, S., Tang, K., Samady, H., Altman, J., Seto, A.H., Singh, J., Jeremias, A., Matsuo, H., Kharbanda, R.K., Patel, M.R., Serruys, P. and Escaned, J., 2017. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *The New England Journal of Medicine*, 376(19), pp.1824–1834.

Davies, J.E., Whinnett, Z.I., Francis, D.P., Manisty, C.H., Aguado-Sierra, J., Willson, K., Foale, R.A., Malik, I.S., Hughes, A.D., Parker, K.H. and Mayet, J., 2006. Evidence of a dominant backward-propagating 'suction' wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*, 113(14), pp.1768–1778.

Davies, M.J., Woolf, N., Rowles, P.M. and Pepper, J., 1988. Morphology of the endothelium over atherosclerotic plaques in human coronary arteries. *British Heart Journal*, 60(6), pp.459–464.

Dawber, T.R., Kannel, W.B., Revotskie, N., Stokes, J., Kagan, A. and Gordon, T., 1959. Some factors associated with the development of coronary heart disease: six years' follow-up experience in the Framingham study. *American Journal of Public Health and the Nation's Health*, 49, pp.1349–1356.

De Bruyne, B., Baudhuin, T., Melin, J.A., Pijls, N.H., Sys, S.U., Bol, A., Paulus, W.J., Heyndrickx, G.R. and Wijns, W., 1994. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation*, 89(3), pp.1013–1022.

De Bruyne, B., Fearon, W.F., Pijls, N.H.J., Barbato, E., Tonino, P., Piroth, Z., Jagic, N., Mobius-Winckler, S., Rioufol, G., Witt, N., Kala, P., MacCarthy, P., Engström, T., Oldroyd, K., Mavromatis, K., Manoharan, G., Verlee, P., Frobert, O., Curzen, N., Johnson, J.B., Limacher, A., Nüesch, E. and Jüni, P., 2014. Fractional Flow Reserve–Guided PCI for Stable Coronary Artery Disease. *New England Journal of Medicine*, 371(13), pp.1208–1217.

De Bruyne, B., Pijls, N.H.J., Kalesan, B., Barbato, E., Tonino, P.A.L., Piroth, Z., Jagic, N., Möbius-Winkler, S., Mobius-Winckler, S., Rioufol, G., Witt, N., Kala, P., MacCarthy, P., Engström, T., Oldroyd, K.G., Mavromatis, K., Manoharan, G., Verlee, P., Frobert, O., Curzen, N., Johnson, J.B., Jüni, P., Fearon, W.F. and FAME 2 Trial Investigators, 2012. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *The New England Journal of Medicine*, 367(11), pp.991–1001.

Demirel, F., Rasoul, S., Elvan, A., Ottervanger, J.P., Dambrink, J.-H.E., Gosselink, A.T.M., Hoorntje, J.C.A., Ramdat Misier, A.R. and van 't Hof, A.W.J., 2015. Impact of out-of-hospital cardiac arrest due to ventricular fibrillation in patients with ST-elevation myocardial infarction admitted for primary percutaneous coronary intervention: Impact of ventricular fibrillation in STEMI patients. *European Heart Journal. Acute Cardiovascular Care*, 4(1), pp.16–23.

DeWood, M.A., Spores, J., Notske, R., Mouser, L.T., Burroughs, R., Golden, M.S. and Lang, H.T., 1980. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *The New England Journal of Medicine*, 303(16), pp.897–902.

Donnelly, P.M., Higginson, J.D.S. and Hanley, P.D., 2005. Multidetector CT coronary angiography: have we found the holy grail of non-invasive coronary imaging? *Heart*, 91(11), pp.1385–1388.

Dukkipati, S., O'Neill, W.W., Harjai, K.J., Sanders, W.P., Deo, D., Boura, J.A., Bartholomew, B.A., Yerkey, M.W., Sadeghi, H.M. and Kahn, J.K., 2004. Characteristics of cerebrovascular accidents after percutaneous coronary interventions. *Journal of the American College of Cardiology*, 43(7), pp.1161–1167.

Einstein, A.J., Moser, K.W., Thompson, R.C., Cerqueira, M.D. and Henzlova, M.J., 2007. Radiation Dose to Patients From Cardiac Diagnostic Imaging. *Circulation*, 116(11), pp.1290–1305.

Engstrøm, T., Kelbæk, H., Helqvist, S., Høfsten, D.E., Kløvgaard, L., Holmvang, L., Jørgensen, E., Pedersen, F., Saunamäki, K., Clemmensen, P., De Backer, O., Ravkilde, J., Tilsted, H.-H.,

Villadsen, A.B., Aarøe, J., Jensen, S.E., Raungaard, B., Køber, L. and DANAMI-3—PRIMULTI Investigators, 2015. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet (London, England)*, 386(9994), pp.665–671.

Eshtehardi, P., Adorjan, P., Togni, M., Tevaearai, H., Vogel, R., Seiler, C., Meier, B., Windecker, S., Carrel, T., Wenaweser, P. and Cook, S., 2010. Iatrogenic left main coronary artery dissection: incidence, classification, management, and long-term follow-up. *American Heart Journal*, 159(6), pp.1147–1153.

Farkouh, M.E., Boden, W.E., Bittner, V., Muratov, V., Hartigan, P., Ogdie, M., Bertolet, M., Mathewkutty, S., Teo, K., Maron, D.J., Sethi, S.S., Domanski, M., Frye, R.L. and Fuster, V., 2013. Risk factor control for coronary artery disease secondary prevention in large randomized trials. *Journal of the American College of Cardiology*, 61(15), pp.1607–1615.

Faul, F., Erdfelder, E., Lang, A.-G. and Buchner, A., 2007. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), pp.175–191.

Faxon, D.P., Fuster, V., Libby, P., Beckman, J.A., Hiatt, W.R., Thompson, R.W., Topper, J.N., Annex, B.H., Rundback, J.H., Fabunmi, R.P., Robertson, R.M., Loscalzo, J. and American Heart Association, 2004. Atherosclerotic Vascular Disease Conference: Writing Group III: pathophysiology. *Circulation*, 109(21), pp.2617–2625.

Fearon, W.F., 2015. Invasive Coronary Physiology for Assessing Intermediate Lesions. *Circulation: Cardiovascular Interventions*, 8(2), p.e001942.

Fearon, W.F., Achenbach, S., Engstrom, T., Assali, A., Shlofmitz, R., Jeremias, A., Fournier, S., Kirtane, A.J., Kornowski, R., Greenberg, G., Jubeh, R., Kolansky, D.M., McAndrew, T., Dressler, O., Maehara, A., Matsumura, M., Leon, M.B., De Bruyne, B. and FAST-FFR Study Investigators, 2019. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. *Circulation*, 139(4), pp.477–484.

de Feyter, P.J., de Jaegere, P.P. and Serruys, P.W., 1994. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. *American Heart Journal*, 127(3), pp.643–651.

Fischman, D.L., Leon, M.B., Baim, D.S., Schatz, R.A., Savage, M.P., Penn, I., Detre, K., Veltri, L., Ricci, D. and Nobuyoshi, M., 1994. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *The New England Journal of Medicine*, 331(8), pp.496–501.

Ford, E.S., Ajani, U.A., Croft, J.B., Critchley, J.A., Labarthe, D.R., Kottke, T.E., Giles, W.H. and Capewell, S., 2007. Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000. *New England Journal of Medicine*, 356(23), pp.2388–2398.

Fox, K. a. A., Poole-Wilson, P., Clayton, T.C., Henderson, R.A., Shaw, T.R.D., Wheatley, D.J., Knight, R. and Pocock, S.J., 2005. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet (London, England)*, 366(9489), pp.914–920.

Fox, K. a. A., Poole-Wilson, P.A., Henderson, R.A., Clayton, T.C., Chamberlain, D.A., Shaw, T.R.D., Wheatley, D.J., Pocock, S.J. and Randomized Intervention Trial of unstable Angina Investigators, 2002. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet (London, England)*, 360(9335), pp.743–751.

Fuchs, S., Gruberg, L., Singh, S., Stabile, E., Duncan, C., Wu, H., Waksman, R., Satler, L.F., Pichard, A.D., Kent, K.M. and Kornowski, R., 2001. Prognostic value of cardiac troponin I re-elevation following percutaneous coronary intervention in high-risk patients with acute coronary syndromes. *American Journal of Cardiology*, 88(2), pp.129–133.

Gandjour, A. and Lauterbach, K.W., 1999. Review of quality-of-life evaluations in patients with angina pectoris. *PharmacoEconomics*, 16(2), pp.141–152.

Garg, P., Normand, S.-L.T., Silbaugh, T.S., Wolf, R.E., Zelevinsky, K., Lovett, A., Varma, M.R., Zhou, Z. and Mauri, L., 2008. Drug-eluting or bare-metal stenting in patients with diabetes mellitus: results from the Massachusetts Data Analysis Center Registry. *Circulation*, 118(22), pp.2277–2285, 7p following 2285.

Gaur, S., Taylor, C.A., Jensen, J.M., Bøtker, H.E., Christiansen, E.H., Kaltoft, A.K., Holm, N.R., Leipsic, J., Zarins, C.K., Achenbach, S., Khem, S., Wilk, A., Bezerra, H.G., Lassen, J.F. and Nørgaard, B.L., 2017. FFR Derived From Coronary CT Angiography in Nonculprit Lesions of Patients With Recent STEMI. *JACC: Cardiovascular Imaging*, 10(4), pp.424–433.

Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators, 1997. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *The New England Journal of Medicine*, 336(23), pp.1621–1628.

Goodwill, A.G., Dick, G.M., Kiel, A.M. and Tune, J.D., 2017. Regulation of Coronary Blood Flow. *Comprehensive Physiology*, 7(2), pp.321–382.

Gould, K.L., Kirkeeide, R.L. and Buchi, M., 1990. Coronary flow reserve as a physiologic measure of stenosis severity. *Journal of the American College of Cardiology*, 15(2), pp.459–474.

Gould, K.L. and Lipscomb, K., 1974. Effects of coronary stenoses on coronary flow reserve and resistance. *The American Journal of Cardiology*, 34(1), pp.48–55.

Grech, E.D., 2003. Percutaneous coronary intervention. I: History and development. *BMJ : British Medical Journal*, 326(7398), pp.1080–1082.

Grines, C.L., Browne, K.F., Marco, J., Rothbaum, D., Stone, G.W., O'Keefe, J., Overlie, P., Donohue, B., Chelliah, N. and Timmis, G.C., 1993. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *The New England Journal of Medicine*, 328(10), pp.673–679.

Grüntzig, A.R., Senning, Å. and Siegenthaler, W.E., 1979. Nonoperative Dilatation of Coronary-Artery Stenosis. *New England Journal of Medicine*, 301(2), pp.61–68.

Hammal, F., Ezekowitz, J.A., Norris, C.M., Wild, T.C. and Finegan, B.A., 2014. Smoking status and survival: impact on mortality of continuing to smoke one year after the angiographic diagnosis of coronary artery disease, a prospective cohort study. *BMC Cardiovascular Disorders*, [online] 14. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4190449/> [Accessed 24 Apr. 2018].

Härle, T., Luz, M., Meyer, S., Kronberg, K., Nickau, B., Escaned, J., Davies, J. and Elsässer, A., 2017a. Effect of Coronary Anatomy and Hydrostatic Pressure on Intracoronary Indices of Stenosis Severity. *JACC. Cardiovascular interventions*, 10(8), pp.764–773.

Härle, T., Luz, M., Meyer, S., Kronberg, K., Nickau, B., Escaned, J., Davies, J. and Elsässer, A., 2017b. Effect of Coronary Anatomy and Hydrostatic Pressure on Intracoronary Indices of Stenosis Severity. *JACC. Cardiovascular interventions*, 10(8), pp.764–773.

Härle, T., Luz, M., Meyer, S., Vahldiek, F., van der Harst, P., van Dijk, R., Ties, D., Escaned, J., Davies, J. and Elsässer, A., 2018. Influence of hydrostatic pressure on intracoronary indices of stenosis severity in vivo. *Clinical Research in Cardiology: Official Journal of the German Cardiac Society*, 107(3), pp.222–232.

Härle, T., Meyer, S., Bojara, W., Vahldiek, F. and Elsässer, A., 2017c. Intracoronary pressure measurement differences between anterior and posterior coronary territories. *Herz*, 42(4), pp.395–402.

Härle, T., Meyer, S., Bojara, W., Vahldiek, F. and Elsässer, A., 2017d. Intracoronary pressure measurement differences between anterior and posterior coronary territories. *Herz*, 42(4), pp.395–402.

Head, S.J., Kieser, T.M., Falk, V., Huysmans, H.A. and Kappetein, A.P., 2013. Coronary artery bypass grafting: Part 1—the evolution over the first 50 years. *European Heart Journal*, 34(37), pp.2862–2872.

Hennigan, B., Oldroyd, K.G., Berry, C., Johnson, N., McClure, J., McCartney, P., McEntegart, M.B., Eteiba, H., Petrie, M.C., Rocchiccioli, P., Good, R., Lindsay, M.M., Hood, S. and Watkins, S., 2016. Discordance Between Resting and Hyperemic Indices of Coronary Stenosis Severity: The VERIFY 2 Study (A Comparative Study of Resting Coronary Pressure Gradient, Instantaneous Wave-Free Ratio and Fractional Flow Reserve in an Unselected Population Referred for Invasive Angiography). *Circulation. Cardiovascular Interventions*, 9(11).

Herrmann, J., 2005. Peri-procedural myocardial injury: 2005 update. *European Heart Journal*, 26(23), pp.2493–2519.

van de Hoef, T.P., van Lavieren, M.A., Damman, P., Delewi, R., Piek, M.A., Chamuleau, S.A.J., Voskuil, M., Henriques, J.P.S., Koch, K.T., de Winter, R.J., Spaan, J.A.E., Siebes, M., Tijssen, J.G.P., Meuwissen, M. and Piek, J.J., 2014. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circulation. Cardiovascular Interventions*, 7(3), pp.301–311.

van de Hoef, T.P., Meuwissen, M., Escaned, J., Davies, J.E., Siebes, M., Spaan, J.A.E. and Piek, J.J., 2013. Fractional flow reserve as a surrogate for inducible myocardial ischaemia. *Nature Reviews. Cardiology*, 10(8), pp.439–452.

Hoenig, M.R., Doust, J.A., Aroney, C.N. and Scott, I.A., 2006. Early invasive versus conservative strategies for unstable angina & non-ST-elevation myocardial infarction in the stent era. *The Cochrane Database of Systematic Reviews*, (3), p.CD004815.

Hoffmann, U., Truong, Q.A., Schoenfeld, D.A., Chou, E.T., Woodard, P.K., Nagurney, J.T., Pope, J.H., Hauser, T.H., White, C.S., Weiner, S.G., Kalanjian, S., Mullins, M.E., Mikati, I., Peacock, W.F., Zakroysky, P., Hayden, D., Goehler, A., Lee, H., Gazelle, G.S., Wiviott, S.D., Fleg, J.L. and Udelson, J.E., 2012. Coronary CT Angiography versus Standard Evaluation in Acute Chest Pain. *New England Journal of Medicine*, 367(4), pp.299–308.

Hueb, W., Lopes, N., Gersh, B.J., Soares, P.R., Ribeiro, E.E., Pereira, A.C., Favarato, D., Rocha, A.S.C., Hueb, A.C. and Ramires, J.A.F., 2010. Ten-Year Follow-Up Survival of the Medicine, Angioplasty, or Surgery Study (MASS II): A Randomized Controlled Clinical Trial of 3 Therapeutic Strategies for Multivessel Coronary Artery Disease. *Circulation*, 122(10), pp.949–957.

Insull, W., 2009. The Pathology of Atherosclerosis: Plaque Development and Plaque Responses to Medical Treatment. *The American Journal of Medicine*, 122(1), pp.S3–S14.

Iqbal, J., Gunn, J. and Serruys, P.W., 2013. Coronary stents: historical development, current status and future directions. *British Medical Bulletin*, 106(1), pp.193–211.

ISCHEMIA Trial Research Group, Maron, D.J., Hochman, J.S., O'Brien, S.M., Reynolds, H.R., Boden, W.E., Stone, G.W., Bangalore, S., Spertus, J.A., Mark, D.B., Alexander, K.P., Shaw, L., Berger, J.S., Ferguson, T.B., Williams, D.O., Harrington, R.A. and Rosenberg, Y., 2018. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: Rationale and design. *American Heart Journal*, 201, pp.124–135.

James, M.T., Samuel, S.M., Manning, M.A., Tonelli, M., Ghali, W.A., Faris, P., Knudtson, M.L., Pannu, N. and Hemmelgarn, B.R., 2013. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. *Circulation. Cardiovascular Interventions*, 6(1), pp.37–43.

Jeremias, A., Maehara, A., Généreux, P., Asrress, K.N., Berry, C., De Bruyne, B., Davies, J.E., Escaned, J., Fearon, W.F., Gould, K.L., Johnson, N.P., Kirtane, A.J., Koo, B.-K., Marques, K.M., Nijjer, S., Oldroyd, K.G., Petraco, R., Piek, J.J., Pijls, N.H., Redwood, S., Siebes, M., Spaan, J.A.E., van 't Veer, M., Mintz, G.S. and Stone, G.W., 2014. Multicenter core laboratory

comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *Journal of the American College of Cardiology*, 63(13), pp.1253–1261.

Johnson, N.P., Johnson, D.T., Kirkeeide, R.L., Berry, C., De Bruyne, B., Fearon, W.F., Oldroyd, K.G., Pijls, N.H.J. and Gould, K.L., 2015. Repeatability of Fractional Flow Reserve Despite Variations in Systemic and Coronary Hemodynamics. *JACC: Cardiovascular Interventions*, 8(8), pp.1018–1027.

Johnson, N.P., Kirkeeide, R.L. and Gould, K.L., 2015. History and Development of Coronary Flow Reserve and Fractional Flow Reserve for Clinical Applications. *Interventional Cardiology Clinics*, 4(4), pp.397–410.

Johnson, N.P., Tóth, G.G., Lai, D., Zhu, H., Açar, G., Agostoni, P., Appelman, Y., Arslan, F., Barbato, E., Chen, S.-L., Di Serafino, L., Domínguez-Franco, A.J., Dupouy, P., Esen, A.M., Esen, O.B., Hamilos, M., Iwasaki, K., Jensen, L.O., Jiménez-Navarro, M.F., Katritsis, D.G., Kocaman, S.A., Koo, B.-K., López-Palop, R., Lorin, J.D., Miller, L.H., Muller, O., Nam, C.-W., Oud, N., Puymirat, E., Rieber, J., Rioufol, G., Rodés-Cabau, J., Sedlis, S.P., Takeishi, Y., Tonino, P.A.L., Van Belle, E., Verna, E., Werner, G.S., Fearon, W.F., Pijls, N.H.J., De Bruyne, B. and Gould, K.L., 2014. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *Journal of the American College of Cardiology*, 64(16), pp.1641–1654.

Kallet, R.H., 2015. A Comprehensive Review of Prone Position in ARDS. *Respiratory Care*, 60(11), pp.1660–1687.

Kanaganayagam, G.S., Ngo, A.T., Alsafi, A., Kamanahalli, R., Sutaria, N., Mittal, T. and Ariff, B., 2014. CT coronary angiography in the investigation of chest pain — Beyond coronary artery atherosclerosis; A pictorial review. *International Journal of Cardiology*, 176(3), pp.618–629.

Kannel, W.B., Dawber, T.R., Kagan, A., Revotskie, N. and Stokes, J., 1961. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. *Annals of Internal Medicine*, 55, pp.33–50.

Karamasis, G.V., Kalogeropoulos, A.S., Mohdnazri, S.H., Al-Janabi, F., Jagathesan, R., Clesham, G.J., Tang, K.H., Kelly, P.A., Davies, J.R. and Keeble, T.R., 2018. Impact of right atrial pressure on fractional flow reserve calculation in the presence of a chronic total occlusion. *Cardiovascular Revascularization Medicine: Including Molecular Interventions*.

Kawaguchi, Y., Ito, K., Kin, H., Shirai, Y., Okazaki, A., Miyajima, K., Watanabe, T., Tatsuguchi, M., Wakabayashi, Y. and Maekawa, Y., 2019. Impact of Hydrostatic Pressure Variations Caused by Height Differences in Supine and Prone Positions on Fractional Flow Reserve Values in the Coronary Circulation. *Journal of Interventional Cardiology*, 2019.

Kedhi, E., Joesoef, K.S., McFadden, E., Wassing, J., van Mieghem, C., Goedhart, D. and Smits, P.C., 2010. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *The Lancet*, 375(9710), pp.201–209.

Keeley, E.C., Boura, J.A. and Grines, C.L., 2003. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet*, 361(9351), pp.13–20.

Kiernan, T.J., Yan, B.P., Ruggiero, N., Eisenberg, J.D., Bernal, J., Cubeddu, R.J., Witzke, C., Don, C., Cruz-Gonzalez, I., Rosenfield, K., Pomersantev, E. and Palacios, I., 2009. Coronary artery perforations in the contemporary interventional era. *Journal of Interventional Cardiology*, 22(4), pp.350–353.

Kim, H.-S., Tonino, P.A.L., De Bruyne, B., Yong, A.S.C., Tremmel, J.A., Pijls, N.H.J., Fearon, W.F. and FAME Study Investigators, 2012. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. *JACC. Cardiovascular interventions*, 5(10), pp.1037–1042.

Kim, H.Y., Lim, H.-S., Doh, J.-H., Nam, C.-W., Shin, E.-S., Koo, B.-K., Yoon, M.-H., Tahk, S.-J., Kang, D.K., Song, Y.B., Hahn, J.-Y., Choi, S.H., Gwon, H.-C., Lee, S.-H., Kim, E.-K., Kim, S.M., Choe, Y. and Choi, J.-H., 2016. Physiological Severity of Coronary Artery Stenosis Depends on the Amount of Myocardial Mass Subtended by the Coronary Artery. *JACC. Cardiovascular interventions*, 9(15), pp.1548–1560.

Kitabata, H., Leipsic, J., Patel, M.R., Nieman, K., De Bruyne, B., Rogers, C., Pontone, G., Nørgaard, B.L., Bax, J.J., Raff, G., Chinnaiyan, K.M., Rabbat, M., Rønnow Sand, N.P., Blanke, P., Fairbairn, T.A., Matsuo, H., Amano, T., Kawasaki, T., Morino, Y. and Akasaka, T., 2018. Incidence and predictors of lesion-specific ischemia by FFRCT: Learnings from the international ADVANCE registry. *Journal of Cardiovascular Computed Tomography*, 12(2), pp.95–100.

Knickelbine, T., Lesser, J.R., Haas, T.S., Brandenburg, E.R., Gleason-Han, B.K., Flygenring, B., Longe, T.F., Schwartz, R.S. and Maron, B.J., 2009. Identification of Unexpected Nonatherosclerotic Cardiovascular Disease With Coronary CT Angiography. *JACC: Cardiovascular Imaging*, 2(9), pp.1085–1092.

Kobayashi, N., Maehara, A., Brener, S.J., Généreux, P., Witzenbichler, B., Guagliumi, G., Peruga, J.Z., Mehran, R., Mintz, G.S. and Stone, G.W., 2015a. Usefulness of the Left Anterior Descending Coronary Artery Wrapping Around the Left Ventricular Apex to Predict Adverse Clinical Outcomes in Patients With Anterior Wall ST-Segment Elevation Myocardial Infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial). *American Journal of Cardiology*, 116(11), pp.1658–1665.

Kobayashi, N., Maehara, A., Brener, S.J., Généreux, P., Witzenbichler, B., Guagliumi, G., Peruga, J.Z., Mehran, R., Mintz, G.S. and Stone, G.W., 2015b. Usefulness of the Left Anterior Descending Coronary Artery Wrapping Around the Left Ventricular Apex to Predict Adverse Clinical Outcomes in Patients With Anterior Wall ST-Segment Elevation Myocardial Infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial). *The American Journal of Cardiology*, 116(11), pp.1658–1665.

Koo, B.-K., Erglis, A., Doh, J.-H., Daniels, D.V., Jegere, S., Kim, H.-S., Dunning, A., DeFrance, T., Lansky, A. and Leipsic, J., 2011. Diagnosis of ischemia-causing coronary stenoses by

noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *Journal of the American College of Cardiology*, 58(19), pp.1989–1997.

Kumar, A. and Cannon, C.P., 2009. Acute Coronary Syndromes: Diagnosis and Management, Part I. *Mayo Clinic Proceedings*, 84(10), pp.917–938.

Kvakkestad, K.M., Sandvik, L., Andersen, G.Ø., Sunde, K. and Halvorsen, S., 2018. Long-term survival in patients with acute myocardial infarction and out-of-hospital cardiac arrest: A prospective cohort study. *Resuscitation*, 122, pp.41–47.

Kwon, S.W., Cha, J.-J. and Rhee, J.-H., 2012. Prone position coronary angiography due to intractable back pain: another merit of transradial approach compared to transfemoral approach. *The Journal of Invasive Cardiology*, 24(11), pp.605–607.

Ladwiniec, A., Cunnington, M.S., Rossington, J., Mather, A.N., Alahmar, A., Oliver, R.M., Nijjer, S.S., Davies, J.E., Thackray, S., Alamgir, F. and Hoye, A., 2015. Collateral donor artery physiology and the influence of a chronic total occlusion on fractional flow reserve. *Circulation. Cardiovascular Interventions*, 8(4).

Ladwiniec, A., Cunnington, M.S., Rossington, J., Thackray, S., Alamgir, F. and Hoye, A., 2016. Microvascular dysfunction in the immediate aftermath of chronic total coronary occlusion recanalization. *Catheterization and Cardiovascular Interventions*, 87(6), pp.1071–1079.

Landau, C., Lange, R.A., Glamann, D.B., Willard, J.E. and Hillis, L.D., 1994. Vasovagal reactions in the cardiac catheterization laboratory. *The American Journal of Cardiology*, 73(1), pp.95–97.

Le May, M.R., Labinaz, M., Davies, R.F., Marquis, J.F., Laramée, L.A., O'Brien, E.R., Williams, W.L., Beanlands, R.S., Nichol, G. and Higginson, L.A., 2001. Stenting versus thrombolysis in acute myocardial infarction trial (STAT). *Journal of the American College of Cardiology*, 37(4), pp.985–991.

Leone, A.M., Caterina, A.R.D., Basile, E., Gardi, A., Laezza, D., Mazzari, M.A., Mongiardo, R., Kharbanda, R., Cuculi, F., Porto, I., Niccoli, G., Burzotta, F., Trani, C., Banning, A.P., Rebuzzi, A.G. and Crea, F., 2013a. Influence of the Amount of Myocardium Subtended by a Stenosis on Fractional Flow Reserve. *Circulation: Cardiovascular Interventions*, 6(1), pp.29–36.

Leone, A.M., De Caterina, A.R., Basile, E., Gardi, A., Laezza, D., Mazzari, M.A., Mongiardo, R., Kharbanda, R., Cuculi, F., Porto, I., Niccoli, G., Burzotta, F., Trani, C., Banning, A.P., Rebuzzi, A.G. and Crea, F., 2013b. Influence of the amount of myocardium subtended by a stenosis on fractional flow reserve. *Circulation. Cardiovascular Interventions*, 6(1), pp.29–36.

Li, J., Elrashidi, M.Y., Flammer, A.J., Lennon, R.J., Bell, M.R., Holmes, D.R., Bresnahan, J.F., Rihal, C.S., Lerman, L.O. and Lerman, A., 2013. Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice. *European Heart Journal*, 34(18), pp.1375–1383.

Libby, P., Ridker, P.M. and Hansson, G.K., 2011. Progress and challenges in translating the biology of atherosclerosis. *Nature*, 473(7347), pp.317–325.

López-Palop, R., Carrillo, P., Cordero, A., Frutos, A., Mateo, I., Mashlab, S. and Roldán, J., 2013. Effect of lesion length on functional significance of intermediate long coronary lesions. *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions*, 81(4), pp.E186-194.

Lu, M.T., Ferencik, M., Roberts, R.S., Lee, K.L., Ivanov, A., Adami, E., Mark, D.B., Jaffer, F.A., Leipsic, J.A., Douglas, P.S. and Hoffmann, U., 2017. Noninvasive FFR Derived From Coronary CT Angiography: Management and Outcomes in the PROMISE Trial. *JACC. Cardiovascular imaging*, 10(11), pp.1350–1358.

Madhavan, M.V., Tarigopula, M., Mintz, G.S., Maehara, A., Stone, G.W. and Généreux, P., 2014. Coronary artery calcification: pathogenesis and prognostic implications. *Journal of the American College of Cardiology*, 63(17), pp.1703–1714.

Malbouisson, L.M., Busch, C.J., Puybasset, L., Lu, Q., Cluzel, P. and Rouby, J.J., 2000. Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. *American Journal of Respiratory and Critical Care Medicine*, 161(6), pp.2005–2012.

Mario, C.D., Gil, R. and Serruys, P.W., 1995. Long-term reproducibility of coronary flow velocity measurements in patients with coronary artery disease. *American Journal of Cardiology*, 75(16), pp.1177–1180.

Mauri, L., Hsieh, W., Massaro, J.M., Ho, K.K.L., D'Agostino, R. and Cutlip, D.E., 2009. *Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents*. [research-article] http://dx.doi.org/10.1056/NEJMoa067731. Available at: <https://www.nejm.org/doi/10.1056/NEJMoa067731> [Accessed 2 May 2018].

McCullough, P.A., Bertrand, M.E., Brinker, J.A. and Stacul, F., 2006. A Meta-Analysis of the Renal Safety of Isosmolar Iodixanol Compared With Low-Osmolar Contrast Media. *Journal of the American College of Cardiology*, 48(4), pp.692–699.

Meijboom, W.B., Meijs, M.F.L., Schuijf, J.D., Cramer, M.J., Mollet, N.R., van Mieghem, C.A.G., Nieman, K., van Werkhoven, J.M., Pundziute, G., Weustink, A.C., de Vos, A.M., Pugliese, F., Rensing, B., Jukema, J.W., Bax, J.J., Prokop, M., Doevendans, P.A., Hunink, M.G.M., Krestin, G.P. and de Feyter, P.J., 2008. Diagnostic Accuracy of 64-Slice Computed Tomography Coronary Angiography: A Prospective, Multicenter, Multivendor Study. *Journal of the American College of Cardiology*, 52(25), pp.2135–2144.

Meyer, J.A., 1990. Werner Forssmann and catheterization of the heart, 1929. *The Annals of Thoracic Surgery*, 49(3), pp.497–499.

Mohdnazri, S.R., Karamasis, G.V., Al-Janabi, F., Cook, C.M., Hampton-Till, J., Zhang, J., Al-Lamee, R., Dungu, J.N., Gedela, S., Tang, K.H., Kelly, P.A., Davies, J.E., Davies, J.R. and Keeble, T.R., 2018. The impact of coronary chronic total occlusion percutaneous coronary

intervention upon donor vessel fractional flow reserve and instantaneous wave-free ratio: Implications for physiology-guided PCI in patients with CTO. *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions*.

Montalescot, G., Sechtem, U., Achenbach, S., Andreotti, F., Arden, C., Budaj, A., Bugiardini, R., Crea, F., Cuisset, T., Di Mario, C., Ferreira, J.R., Gersh, B.J., Gitt, A.K., Hulot, J.-S., Marx, N., Opie, L.H., Pfisterer, M., Prescott, E., Ruschitzka, F., Sabaté, M., Senior, R., Taggart, D.P., Wall, V.D., E, E., Vrints, C.J.M., Zamorano, J.L., Achenbach, S., Baumgartner, H., Bax, J.J., Bueno, H., Dean, V., Deaton, C., Erol, C., Fagard, R., Ferrari, R., Hasdai, D., Hoes, A.W., Kirchhof, P., Knuuti, J., Kolh, P., Lancellotti, P., Linhart, A., Nihoyannopoulos, P., Piepoli, M.F., Ponikowski, P., Sirnes, P.A., Tamargo, J.L., Tendera, M., Torbicki, A., Wijns, W., Windecker, S., Knuuti, J., Valgimigli, M., Bueno, H., Claeys, M.J., Donner-Banzhoff, N., Erol, C., Frank, H., Funck-Brentano, C., Gaemperli, O., Gonzalez-Juanatey, J.R., Hamilos, M., Hasdai, D., Husted, S., James, S.K., Kervinen, K., Kolh, P., Kristensen, S.D., Lancellotti, P., Maggioni, A.P., Piepoli, M.F., Pries, A.R., Romeo, F., Rydén, L., Simoons, M.L., Sirnes, P.A., Steg, P.G., Timmis, A., Wijns, W., Windecker, S., Yildirir, A. and Zamorano, J.L., 2013. 2013 ESC guidelines on the management of stable coronary artery diseaseThe Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European Heart Journal*, 34(38), pp.2949–3003.

Morice, M.-C., Serruys, P.W., Sousa, J.E., Fajadet, J., Ban Hayashi, E., Perin, M., Colombo, A., Schuler, G., Barragan, P., Guagliumi, G., Molnàr, F., Falotico, R. and RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions, 2002. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *The New England Journal of Medicine*, 346(23), pp.1773–1780.

Morris, P.D., Silva Soto, D.A., Feher, J.F.A., Rafiroiu, D., Lungu, A., Varma, S., Lawford, P.V., Hose, D.R. and Gunn, J.P., 2017. Fast Virtual Fractional Flow Reserve Based Upon Steady-State Computational Fluid Dynamics Analysis. *JACC: Basic to Translational Science*, 2(4), pp.434–446.

Moses, J.W., Leon, M.B., Popma, J.J., Fitzgerald, P.J., Holmes, D.R., O'Shaughnessy, C., Caputo, R.P., Kereiakes, D.J., Williams, D.O., Teirstein, P.S., Jaeger, J.L., Kuntz, R.E. and SIRIUS Investigators, 2003. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *The New England Journal of Medicine*, 349(14), pp.1315–1323.

Muller, O., Mangiacapra, F., Ntalianis, A., Verhamme, K.M.C., Trana, C., Hamilos, M., Bartunek, J., Vanderheyden, M., Wyffels, E., Heyndrickx, G.R., van Rooij, F.J.A., Witteman, J.C.M., Hofman, A., Wijns, W., Barbato, E. and De Bruyne, B., 2011. Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior descending coronary artery stenosis. *JACC. Cardiovascular interventions*, 4(11), pp.1175–1182.

Murthy, V.L. and Eagle, K.A., 2018. ISCHEMIA: A Search for clarity and why we may not find it. *American heart journal*, 203, pp.82–84.

Nair, P. and Roguin, A., 2006. Coronary perforations. *EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*, 2(3), pp.363–370.

Nakamura, M., Yamagishi, M., Ueno, T., Hara, K., Ishiwata, S., Itoh, T., Hamanaka, I., Wakatsuki, T., Sugano, T., Kawai, K., Akasaka, T., Tanaka, N. and Kimura, T., 2014. Prevalence of visual-functional mismatch regarding coronary artery stenosis in the CVIT-DEFER registry. *Cardiovascular Intervention and Therapeutics*, 29(4), pp.300–308.

Nash, K., Hafeez, A. and Hou, S., 2002. Hospital-acquired renal insufficiency. *American Journal of Kidney Diseases*, 39(5), pp.930–936.

Newby, D.E. and Fox, K.A.A., 2002. Invasive assessment of the coronary circulation: intravascular ultrasound and Doppler. *British Journal of Clinical Pharmacology*, 53(6), pp.561–575.

Ng, M.K.C., Yeung, A.C. and Fearon, W.F., 2006. Invasive Assessment of the Coronary Microcirculation: Superior Reproducibility and Less Hemodynamic Dependence of Index of Microcirculatory Resistance Compared With Coronary Flow Reserve. *Circulation*, 113(17), pp.2054–2061.

Nichol, G., Thomas, E., Callaway, C.W., Hedges, J., Powell, J.L., Aufderheide, T.P., Rea, T., Lowe, R., Brown, T., Dreyer, J., Davis, D., Idris, A., Stiell, I. and Resuscitation Outcomes Consortium Investigators, 2008. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*, 300(12), pp.1423–1431.

Nieminen, M.S., Dickstein, K., Fonseca, C., Serrano, J.M., Parissis, J., Fedele, F., Wikström, G., Agostoni, P., Atar, S., Baholli, L., Brito, D., Colet, J.C., Édes, I., Mesa, J.E.G., Gorjup, V., Garza, E.H., Juanatey, J.R.G., Karanovic, N., Karavidas, A., Katsytadze, I., Kivikko, M., Matskeplishvili, S., Merkely, B., Morandi, F., Novoa, A., Oliva, F., Ostadal, P., Pereira-Barretto, A., Pollesello, P., Rudiger, A., Schwinger, R.H.G., Wieser, M., Yavelov, I. and Zymliński, R., 2015. The patient perspective: Quality of life in advanced heart failure with frequent hospitalisations. *International Journal of Cardiology*, 191, pp.256–264.

Nijjer, S.S., de Waard, G.A., Sen, S., van de Hoef, T.P., Petraco, R., Echavarría-Pinto, M., van Lavieren, M.A., Meuwissen, M., Danad, I., Knaapen, P., Escaned, J., Piek, J.J., Davies, J.E. and van Royen, N., 2016. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. *European Heart Journal*, 37(26), pp.2069–2080.

Nørgaard, B.L., Leipsic, J., Gaur, S., Seneviratne, S., Ko, B.S., Ito, H., Jensen, J.M., Mauri, L., De Bruyne, B. and Bezerra, H., 2014. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *Journal of the American College of Cardiology*, 63(12), pp.1145–1155.

Ohman, E.M., 2016. Chronic Stable Angina. *New England Journal of Medicine*, 374(12), pp.1167–1176.

Park, K.W., Kang, S.-H., Velders, M.A., Shin, D.-H., Hahn, S., Lim, W.-H., Yang, H.-M., Lee, H.-Y., Van Boven, A.J., Hofma, S.H., Kang, H.-J., Koo, B.-K., Oh, B.-H., Park, Y.-B., Kandzari, D.E. and Kim, H.-S., 2013. Safety and efficacy of everolimus- versus sirolimus-eluting stents: a systematic review and meta-analysis of 11 randomized trials. *American Heart Journal*, 165(2), pp.241-250.e4.

Patel, M.R., Calhoon, J.H., Dehmer, G.J., Grantham, J.A., Maddox, T.M., Maron, D.J. and Smith, P.K., 2017. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology*, 69(17), pp.2212–2241.

Pedersen, T.R., Kjekshus, J., Berg, K., Haghfelt, T., Faergeman, O., Faergeman, G., Pyörälä, K., Miettinen, T., Wilhelmsen, L., Olsson, A.G., Wedel, H. and Scandinavian Simvastatin Survival Study Group, 2004. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. *Atherosclerosis. Supplements*, 5(3), pp.81–87.

Perkins, G.D. and Cooke, M.W., 2012. Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators. *Emerg Med J*, 29(1), pp.3–5.

Petraco, R., Escaned, J., Sen, S., Nijjer, S., Asrress, K.N., Echavarria-Pinto, M., Lockie, T., Khawaja, M.Z., Cuevas, C., Foin, N., Broyd, C., Foale, R.A., Hadjiloizou, N., Malik, I.S., Mikhail, G.W., Sethi, A., Kaprielian, R., Baker, C.S., Lefroy, D., Bellamy, M., Al-Bustami, M., Khan, M.A., Hughes, A.D., Francis, D.P., Mayet, J., Di Mario, C., Redwood, S. and Davies, J.E., 2013. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. *EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*, 9(1), pp.91–101.

Pijls, N.H., De Bruyne, B., Bech, G.J., Liistro, F., Heyndrickx, G.R., Bonnier, H.J. and Koolen, J.J., 2000. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation*, 102(19), pp.2371–2377.

Pijls, N.H., van Son, J.A., Kirkeeide, R.L., De Bruyne, B. and Gould, K.L., 1993. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*, 87(4), pp.1354–1367.

Pijls, N.H.J., de Bruyne, B., Peels, K., van der Voort, P.H., Bonnier, H.J.R.M., Bartunek, J. and Koolen, J.J., 1996. Measurement of Fractional Flow Reserve to Assess the Functional Severity of Coronary-Artery Stenoses. *New England Journal of Medicine*, 334(26), pp.1703–1708.

Pijls, N.H.J., Fearon, W.F., Tonino, P.A.L., Siebert, U., Ikeno, F., Bornschein, B., van't Veer, M., Klauss, V., Manoharan, G., Engstrøm, T., Oldroyd, K.G., Ver Lee, P.N., MacCarthy, P.A., De Bruyne, B. and FAME Study Investigators, 2010. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *Journal of the American College of Cardiology*, 56(3), pp.177–184.

Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators, 1998. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *The New England Journal of Medicine*, 338(21), pp.1488–1497.

Poon, M., Marx, S.O., Gallo, R., Badimon, J.J., Taubman, M.B. and Marks, A.R., 1996. Rapamycin inhibits vascular smooth muscle cell migration. *The Journal of Clinical Investigation*, 98(10), pp.2277–2283.

Pursnani, S., Korley, F., Gopaul, R., Kanade, P., Chandra, N., Shaw, R.E. and Bangalore, S., 2012. Percutaneous Coronary Intervention Versus Optimal Medical Therapy in Stable Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Circulation: Cardiovascular Interventions*, p.CIRCINTERVENTIONS.112.970954.

Qian, J., Ge, J., Baumgart, D., Oldenburg, O., Haude, M., Sack, S. and Erbel, R., 2000. Safety of intracoronary Doppler flow measurement. *American Heart Journal*, 140(3), pp.502–510.

Quadros, A.S., Cambruzzi, E., Sebben, J., David, R.B., Abelin, A., Welter, D., Sarmento-Leite, R., Mehta, R.H., Gottschall, C.A. and Lopes, R.D., 2012. Red versus white thrombi in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: clinical and angiographic outcomes. *American Heart Journal*, 164(4), pp.553–560.

Ramanathan, T. and Skinner, H., 2005. Coronary blood flow. *Continuing Education in Anaesthesia Critical Care & Pain*, 5(2), pp.61–64.

Reynolds Harmony R., Picard Michael H. and Hochman Judith S., 2015. Does Ischemia Burden in Stable Coronary Artery Disease Effectively Identify Revascularization Candidates? *Circulation: Cardiovascular Imaging*, 8(5), p.e000362.

Rigo, F., Sicari, R., Gherardi, S., Djordjevic-Dikic, A., Cortigiani, L. and Picano, E., 2007. Prognostic value of coronary flow reserve in medically treated patients with left anterior descending coronary disease with stenosis 51% to 75% in diameter. *The American Journal of Cardiology*, 100(10), pp.1527–1531.

Rihal, C.S., Textor, S.C., Grill, D.E., Berger, P.B., Ting, H.H., Best, P.J., Singh, M., Bell, M.R., Barsness, G.W., Mathew, V., Garratt, K.N. and Holmes, D.R., 2002. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*, 105(19), pp.2259–2264.

Rubin, G.D., 2014. Computed Tomography: Revolutionizing the Practice of Medicine for 40 Years. *Radiology*, 273(2S), pp.S45–S74.

Ryan, T.J., 2002. The coronary angiogram and its seminal contributions to cardiovascular medicine over five decades. *Transactions of the American Clinical and Climatological Association*, 113, pp.261–271.

Sajobi, T.T., Wang, M., Awosoga, O., Santana, M., Southern, D., Liang, Z., Galbraith, D., Wilton, S.B., Quan, H., Graham, M.M., James, M.T., Ghali, W.A., Knudtson, M.L., Norris, C. and APPROACH Investigators, 2018. Trajectories of Health-Related Quality of Life in Coronary Artery Disease. *Circulation. Cardiovascular Quality and Outcomes*, 11(3), p.e003661.

Sartini, C., Tresoldi, M., Scarpellini, P., Tettamanti, A., Carcò, F., Landoni, G. and Zangrillo, A., 2020. Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit. *JAMA*, 323(22), pp.2338–2340.

Scholten, E.L., Beitler, J.R., Prisk, G.K. and Malhotra, A., 2017. Treatment of ARDS With Prone Positioning. *Chest*, 151(1), pp.215–224.

Schömig, A., Kastrati, A., Dirschinger, J., Mehilli, J., Schricke, U., Pache, J., Martinoff, S., Neumann, F.J. and Schwaiger, M., 2000. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. *The New England Journal of Medicine*, 343(6), pp.385–391.

Serruys, P.W., de Jaegere, P., Kiemeneij, F., Macaya, C., Rutsch, W., Heyndrickx, G., Emanuelsson, H., Marco, J., Legrand, V. and Materne, P., 1994. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *The New England Journal of Medicine*, 331(8), pp.489–495.

Serruys, P.W., Kutryk, M.J.B. and Ong, A.T.L., 2006. Coronary-Artery Stents. *New England Journal of Medicine*, 354(5), pp.483–495.

Serruys, P.W., di Mario, C., Piek, J., Schroeder, E., Vrints, C., Probst, P., de Bruyne, B., Hanet, C., Fleck, E., Haude, M., Verna, E., Voudris, V., Geschwind, H., Emanuelsson, H., Mühlberger, V., Danzi, G., Peels, H.O., Ford, A.J. and Boersma, E., 1997. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty: the DEBATE Study (Doppler Endpoints Balloon Angioplasty Trial Europe). *Circulation*, 96(10), pp.3369–3377.

Serruys, P.W., Silber, S., Garg, S., van Geuns, R.J., Richardt, G., Buszman, P.E., Kelbaek, H., van Boven, A.J., Hofma, S.H., Linke, A., Klauss, V., Wijns, W., Macaya, C., Garot, P., DiMario, C., Manoharan, G., Kornowski, R., Ischinger, T., Bartorelli, A., Ronden, J., Bressers, M., Gobbens, P., Negoita, M., van Leeuwen, F. and Windecker, S., 2010. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *The New England Journal of Medicine*, 363(2), pp.136–146.

Serruys, P.W., Strauss, B.H., Beatt, K.J., Bertrand, M.E., Puel, J., Rickards, A.F., Meier, B., Goy, J.-J., Vogt, P., Kappenberger, L. and Sigwart, U., 1991. Angiographic Follow-up after Placement of a Self-Expanding Coronary-Artery Stent. *New England Journal of Medicine*, 324(1), pp.13–17.

Sieljacks, P., Knudsen, L., Wernbom, M. and Vissing, K., 2018. Body position influences arterial occlusion pressure: implications for the standardization of pressure during blood flow restricted exercise. *European Journal of Applied Physiology*, 118(2), pp.303–312.

Siudak, Z., Birkemeyer, R., Dziewierz, A., Rakowski, T., Zmudka, K., Dubiel, J.S. and Dudek, D., 2012. Out-of-hospital cardiac arrest in patients treated with primary PCI for STEMI. Long-term follow up data from EUROTRANSFER registry. *Resuscitation*, 83(3), pp.303–306.

Smulders, M.W., Jaarsma, C., Nelemans, P.J., Bekkers, S.C.A.M., Bucerius, J., Leiner, T., Crijns, H.J.G.M., Wildberger, J.E. and Schalla, S., 2017. Comparison of the prognostic value of negative non-invasive cardiac investigations in patients with suspected or known coronary artery disease-a meta-analysis. *European Heart Journal Cardiovascular Imaging*, 18(9), pp.980–987.

Snowden, C.B., McNamara, P.M., Garrison, R.J., Feinleib, M., Kannel, W.B. and Epstein, F.H., 1982. Predicting coronary heart disease in siblings--a multivariate assessment: the Framingham Heart Study. *American Journal of Epidemiology*, 115(2), pp.217–222.

Sobel, B.E., Bresnahan, G.F., Shell, W.E. and Yoder, R.D., 1972. Estimation of infarct size in man and its relation to prognosis. *Circulation*, 46(4), pp.640–648.

Spaan, J.A.E., Piek, J.J., Hoffman, J.I.E. and Siebes, M., 2006. Physiological basis of clinically used coronary hemodynamic indices. *Circulation*, 113(3), pp.446–455.

Steg, P.G. and Ducrocq, G., 2016. Future of the Prevention and Treatment of Coronary Artery Disease. *Circulation Journal: Official Journal of the Japanese Circulation Society*, 80(5), pp.1067–1072.

Stergiopoulos, K., Boden, W.E., Hartigan, P., Möbius-Winkler, S., Hambrecht, R., Hueb, W., Hardison, R.M., Abbott, J.D. and Brown, D.L., 2014. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA internal medicine*, 174(2), pp.232–240.

Stone, G.W., Ellis, S.G., Cox, D.A., Hermiller, J., O'Shaughnessy, C., Mann, J.T., Turco, M., Caputo, R., Bergin, P., Greenberg, J., Popma, J.J., Russell, M.E. and TAXUS-IV Investigators, 2004. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *The New England Journal of Medicine*, 350(3), pp.221–231.

Stone, G.W., Selker, H.P., Thiele, H., Patel, M.R., Udelson, J.E., Ohman, E.M., Maehara, A., Eitel, I., Granger, C.B., Jenkins, P.L., Nichols, M. and Ben-Yehuda, O., 2016a. Relationship Between Infarct Size and Outcomes Following Primary PCI: Patient-Level Analysis From 10 Randomized Trials. *Journal of the American College of Cardiology*, 67(14), pp.1674–1683.

Stone, G.W., Selker, H.P., Thiele, H., Patel, M.R., Udelson, J.E., Ohman, E.M., Maehara, A., Eitel, I., Granger, C.B., Jenkins, P.L., Nichols, M. and Ben-Yehuda, O., 2016b. Relationship Between Infarct Size and Outcomes Following Primary PCI: Patient-Level Analysis From 10 Randomized Trials. *Journal of the American College of Cardiology*, 67(14), pp.1674–1683.

Strong, J.P., Malcom, G.T., McMahan, C.A., Tracy, R.E., Newman, W.P., Herderick, E.E. and Cornhill, J.F., 1999. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA*, 281(8), pp.727–735.

Sun, Z., Choo, G.H. and Ng, K.H., 2012. Coronary CT angiography: current status and continuing challenges. *The British Journal of Radiology*, 85(1013), pp.495–510.

Sun, Z. and Xu, L., 2014. Coronary CT angiography in the quantitative assessment of coronary plaques. *BioMed Research International*, 2014, p.346380.

Suzuki, H., Takeyama, Y., Koba, S., Suwa, Y. and Katagiri, T., 1994. Small vessel pathology and coronary hemodynamics in patients with microvascular angina. *International Journal of Cardiology*, 43(2), pp.139–150.

Svanerud, J., Ahn, J.-M., Jeremias, A., van 't Veer, M., Gore, A., Maehara, A., Crowley, A., Pijls, N.H.J., De Bruyne, B., Johnson, N.P., Hennigan, B., Watkins, S., Berry, C., Oldroyd, K.G., Park, S.-J. and Ali, Z.A., 2018. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. *EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*.

Tamita, K., Akasaka, T., Takagi, T., Yamamuro, A., Yamabe, K., Katayama, M., Morioka, S. and Yoshida, K., 2002. Effects of microvascular dysfunction on myocardial fractional flow reserve after percutaneous coronary intervention in patients with acute myocardial infarction. *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions*, 57(4), pp.452–459.

Taqueti, V.R. and Di Carli, M.F., 2018. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*, 72(21), pp.2625–2641.

Taylor, C.A., Fonte, T.A. and Min, J.K., 2013. Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve: Scientific Basis. *Journal of the American College of Cardiology*, 61(22), pp.2233–2241.

Tebaldi, M., Biscaglia, S., Fineschi, M., Manari, A., Menozzi, M., Secco, G.G., Di Lorenzo, E., D'Ascenzo, F., Fabbian, F., Tumscitz, C., Ferrari, R. and Campo, G., 2016. Fractional Flow Reserve Evaluation and Chronic Kidney Disease: Analysis From a Multicenter Italian Registry (the FREAK Study). *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions*, 88(4), pp.555–562.

Tebaldi, M., Biscaglia, S., Fineschi, M., Musumeci, G., Marchese, A., Leone, A.M., Rossi, M.L., Stefanini, G., Maione, A., Menozzi, A., Tarantino, F., Lodolini, V., Gallo, F., Barbato, E., Tarantini, G. and Campo, G., 2018. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. *JACC. Cardiovascular interventions*, 11(15), pp.1482–1491.

Tonino, P.A.L., De Bruyne, B., Pijls, N.H.J., Siebert, U., Ikeno, F., van `t Veer, M., Klauss, V., Manoharan, G., Engstrøm, T., Oldroyd, K.G., Ver Lee, P.N., MacCarthy, P.A. and Fearon, W.F., 2009. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *New England Journal of Medicine*, 360(3), pp.213–224.

Toth, G.G., De Bruyne, B., Rusinaru, D., Di Gioia, G., Bartunek, J., Pellicano, M., Vanderheyden, M., Adjedj, J., Wijns, W., Pijls, N.H.J. and Barbato, E., 2016. Impact of Right Atrial Pressure on Fractional Flow Reserve Measurements: Comparison of Fractional Flow Reserve and Myocardial Fractional Flow Reserve in 1,600 Coronary Stenoses. *JACC. Cardiovascular interventions*, 9(5), pp.453–459.

Virmani, R., Kolodgie, F.D., Burke, A.P., Farb, A. and Schwartz, S.M., 2000a. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 20(5), pp.1262–1275.

Virmani, R., Kolodgie, F.D., Burke, A.P., Farb, A. and Schwartz, S.M., 2000b. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 20(5), pp.1262–1275.

Waard, G.A. de, Fahrni, G., Wit, D. de, Kitabata, H., Williams, R., Patel, N., Teunissen, P.F., Ven, P.M. van de, Umman, S., Knaapen, P., Perera, D., Akasaka, T., Sezer, M., Kharbanda, R.K. and Royen, N. van, 2018. Hyperaemic microvascular resistance predicts clinical outcome and microvascular injury after myocardial infarction. *Heart*, 104(2), pp.127–134.

Wagner, L., 2007. Radiation injury is a potentially serious complication to fluoroscopically-guided complex interventions. *Biomedical Imaging and Intervention Journal*, [online] 3(2). Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097662/> [Accessed 25 Apr. 2018].

Wallentin, L., Lindhagen, L., Ärnström, E., Husted, S., Janzon, M., Johnsen, S.P., Kontny, F., Kempf, T., Levin, L.-Å., Lindahl, B., Stridsberg, M., Ståhle, E., Venge, P., Wollert, K.C., Swahn, E., Lagerqvist, B. and FRISC-II study group, 2016. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. *Lancet (London, England)*, 388(10054), pp.1903–1911.

Wi, J., Ko, Y.-G., Kim, J.-S., Kim, B.-K., Choi, D., Ha, J.-W., Hong, M.-K. and Jang, Y., 2011. Impact of contrast-induced acute kidney injury with transient or persistent renal dysfunction on long-term outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Heart (British Cardiac Society)*, 97(21), pp.1753–1757.

Wijns, W., Serruys, P.W., Reiber, J.H., van den Brand, M., Simoons, M.L., Kooijman, C.J., Balakumaran, K. and Hugenholtz, P.G., 1985. Quantitative angiography of the left anterior descending coronary artery: correlations with pressure gradient and results of exercise thallium scintigraphy. *Circulation*, 71(2), pp.273–279.

Wilson, R.F., Wyche, K., Christensen, B.V., Zimmer, S. and Laxson, D.D., 1990. Effects of adenosine on human coronary arterial circulation. *Circulation*, 82(5), pp.1595–1606.

Windecker, S., Latib, A., Kedhi, E., Kirtane, A.J., Kandzari, D.E., Mehran, R., Price, M.J., Abizaid, A., Simon, D.I., Worthley, S.G., Zaman, A., Hudec, M., Poliacikova, P., Abdul Ghapar, A.K. bin, Selvaraj, K., Petrov, I., Mylotte, D., Pinar, E., Moreno, R., Fabbiocchi, F., Pasupati, S., Kim, H.-S., Aminian, A., Tie, C., Wlodarczak, A., Hur, S.-H., Marx, S.O., Jankovic, I., Brar, S., Bousquette, L., Liu, M. and Stone, G.W., 2020. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. *New England Journal of Medicine*, 382(13), pp.1208–1218.

Wong, P.C.Y., Li, Z., Guo, J. and Zhang, A., 2012. Pathophysiology of contrast-induced nephropathy. *International Journal of Cardiology*, 158(2), pp.186–192.

Wunderlich, W., Roehrig, B., Fischer, F., Arntz, H.-R., Agrawal, R., Morguet, A., Schultheiss, H.-P. and Horstkotte, D., 1998. The impact of vessel and catheter position on the measurement accuracy in catheter-based quantitative coronary angiography. *The International Journal of Cardiac Imaging*, 14(4), pp.217–227.

Xaplanteris, P., Fournier, S., Pijls, N.H.J., Fearon, W.F., Barbato, E., Tonino, P.A.L., Engstrøm, T., Kääb, S., Dambrink, J.-H., Rioufol, G., Toth, G.G., Piroth, Z., Witt, N., Fröbert, O., Kala, P., Linke, A., Jagic, N., Mates, M., Mavromatis, K., Samady, H., Irimpen, A., Oldroyd, K., Campo, G., Rothenbühler, M., Jüni, P. and De Bruyne, B., 2018a. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *New England Journal of Medicine*, 379(3), pp.250–259.

Xaplanteris, P., Fournier, S., Pijls, N.H.J., Fearon, W.F., Barbato, E., Tonino, P.A.L., Engstrøm, T., Kääb, S., Dambrink, J.-H., Rioufol, G., Toth, G.G., Piroth, Z., Witt, N., Fröbert, O., Kala, P., Linke, A., Jagic, N., Mates, M., Mavromatis, K., Samady, H., Irimpen, A., Oldroyd, K., Campo, G., Rothenbühler, M., Jüni, P., De Bruyne, B. and FAME 2 Investigators, 2018b. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *The New England Journal of Medicine*.

Yonetsu, T., Murai, T., Kanaji, Y., Lee, T., Matsuda, J., Usui, E., Hoshino, M., Araki, M., Niida, T., Hada, M., Ichijo, S., Hamaya, R., Kanno, Y. and Kakuta, T., 2017. Significance of Microvascular Function in Visual—Functional Mismatch Between Invasive Coronary Angiography and Fractional Flow Reserve. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, [online] 6(6). Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5669189/> [Accessed 30 Jun. 2020].

Zijlstra, F., de Boer, M.J., Hoorntje, J.C., Reiffers, S., Reiber, J.H. and Suryapranata, H., 1993. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *The New England Journal of Medicine*, 328(10), pp.680–684.

Zimmermann, F.M., Ferrara, A., Johnson, N.P., van Nunen, L.X., Escaned, J., Albertsson, P., Erbel, R., Legrand, V., Gwon, H.-C., Remkes, W.S., Stella, P.R., van Schaardenburgh, P., Bech,

G.J.W., De Bruyne, B. and Pijls, N.H.J., 2015a. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *European Heart Journal*, 36(45), pp.3182–3188.

Zimmermann, F.M., Ferrara, A., Johnson, N.P., van Nunen, L.X., Escaned, J., Albertsson, P., Erbel, R., Legrand, V., Gwon, H.-C., Remkes, W.S., Stella, P.R., van Schaardenburgh, P., Bech, G.J.W., De Bruyne, B. and Pijls, N.H.J., 2015b. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *European Heart Journal*, 36(45), pp.3182–3188.

Appendix A - General Introduction to Coronary Artery Disease

Pathology

Coronary artery disease is the second largest cause of premature death in the UK (Avoidable mortality in England and Wales - Office for National Statistics, 2018). By definition, it is a disease process which leads to a restriction or obstruction of blood flow to the myocardium. For the purpose of this thesis, this will be synonymous with atherosclerosis. Atherosclerosis is a pathological process involving coronary, cerebral, peripheral arteries and the aorta (Faxon et al., 2004; Libby, Ridker and Hansson, 2011). The process can be divided into stages which lead to progressive deposition of cholesterol and fibrous tissue in the wall of the coronary arteries (Figure X).The stages are summarised below:

1. *Fatty streak* - This process starts when low density lipoprotein (LDL) enters the vessel intima. This triggers an inflammatory process and leads to lipid-laden macrophages accumulation. Smooth muscle cell proliferation and extracellular matrix deposition leads to focal intimal thickening. Progressive smooth muscle cell proliferation expands the streak. Some of these smooth muscles cells undergo apoptosis, leading to further macrophage infiltration and progression to an atherosclerotic plaque (Davies et al., 1988)

2. *Atheroma and Fibroatheroma* - Increased accumulation of macrophages, inflammatory cells and smooth muscle cells lead to continuing vessel thickening. Increasing amounts of lipid are bound within the atheroma, and an on-going cycle of cell death leads to necrotic debris and further inflammation (Insull, 2009).

   On-going inflammation and necrosis causes loss of the normal intimal structure, which is replaced by lipid rich necrotic cores. The plaque continues to grow into the adjacent media and adventitia of the vessel, causing distortion in vessel layers and occupying up to 50% of the vessel wall. To compensate for threatened lumen reduction, the arterial wall may enlarge its diameter. Finally fibrous tissue forms above the core, just under the endothelium

at the blood interface. This is known as a thin fibrous cap, and is susceptible to rupture, causing myocardial infarction and even sudden cardiac death (Virmani et al., 2000).

3. *Complex lesion formation* - Many ruptures of thin fibrous caps are silent and re-heal by further fibrous tissue formation (Virmani et al., 2000). This can happen multiple times per lesion. Calcium deposition is seen at this stage, in a cumulative fashion as the disease progresses. The mass of the plaque alone may become enough to trigger symptoms in the patient (Insull, 2009).

As can be seen, luminal area is progressively lost during disease progression, with symptoms rarely present until 80% vessel stenosis (Fearon, 2015). Even in the first decade of life, the initial stages of disease can be seen in the aorta. A post-mortem study of 2,876 men and women aged 15 to 34 found fatty aortic streaks in all studied individuals (Strong et al., 1999).

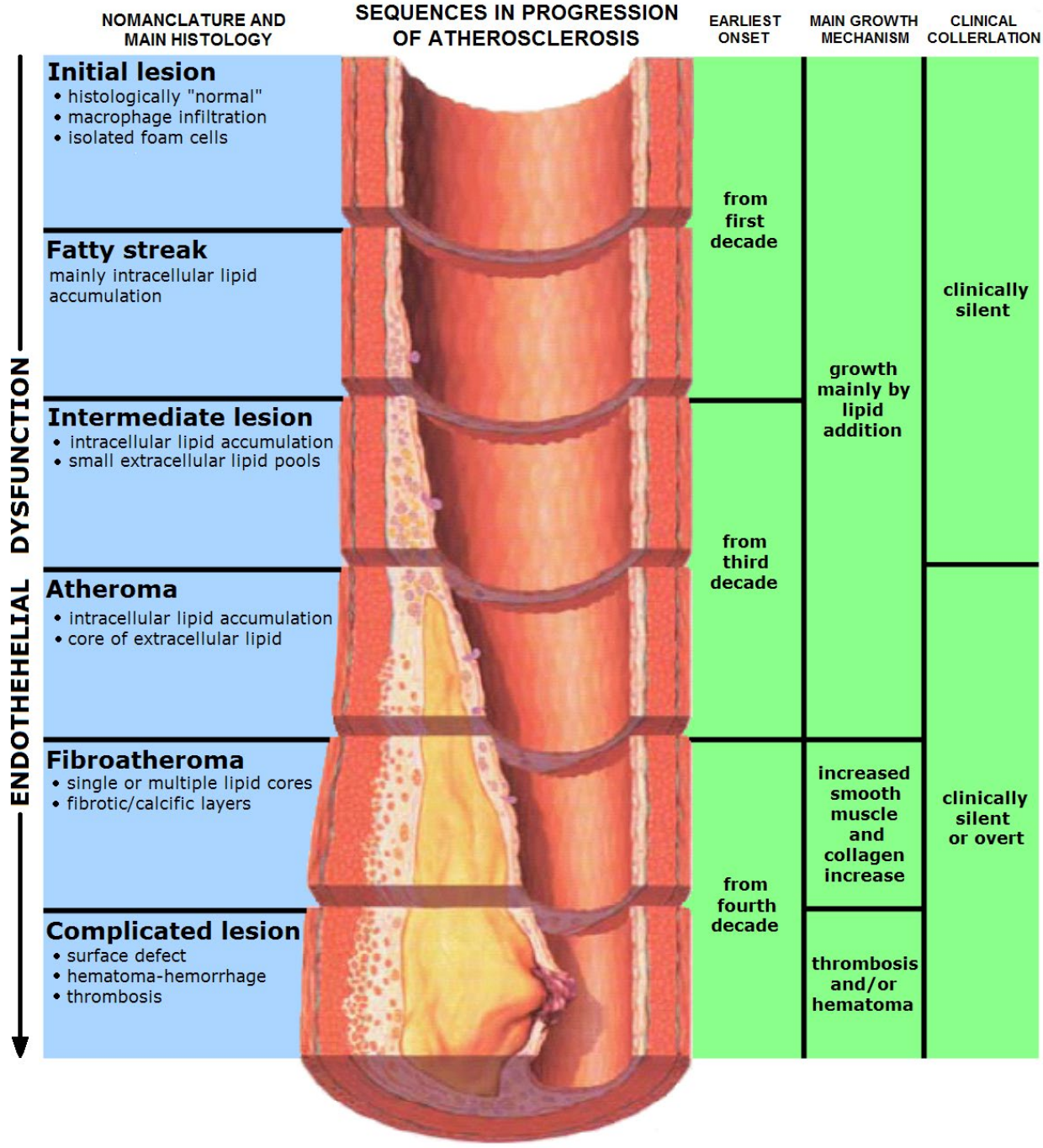


Figure X, stages of atherosclerosis.
(Stages of endothelial dysfunction in atherosclerosis, (https://commons.wikimedia.org/wiki/File:Endo_dysfunction_Athero.PNG), Endo dysfunction Athero, https://creativecommons.org/licenses/by-sa/3.0/legalcode)

Risk Factors

Data exists to predict certain 'risk factors' in the development of atherosclerosis. The earliest study to identify such factors was the Framingham Heart Study published initially in 1957. The study enrolled 5,209 men and women aged 30-59 in the town of Framingham, Massachusetts, USA, and collected various demographic data, including blood samples, blood pressure, heart rate, electrocardiograms, and medical histories. The Framingham heart study outlined the main risk factors for coronary artery disease we still follow to this day, namely hypertension, hypercholesterolaemia, diabetes, smoking and family history (Dawber et al., 1959; Kannel et al., 1961; Snowden et al., 1982). The disease process does not follow risk factors strictly, as those with none may still develop aggressive atherosclerosis, and vice versa.

Additionally, patients who modify and control their risk factors after a diagnosis of coronary artery disease, have better prognosis and outcomes from treatment (Ford et al., 2007; Farkouh et al., 2013; Hammal et al., 2014).

Implications of Coronary Artery Disease

Coronary artery disease is only superseded by cancer as the largest cause of premature death in the UK (Avoidable mortality in England and Wales - Office for National Statistics, 2018). The footprint of mortality is therefore enormous.

The effect on morbidity is equally large. With the potential development of heart failure, persistent anginal symptoms, recurrent cardiovascular events and the need for bypass surgery or other invasive treatment (Madhavan et al., 2014).

At a patient level, a quarter of patients report a significant decline in their quality of life after diagnosis (Sajobi et al., 2018). This could be attributable to anginal symptoms related to their coronary artery disease (Gandjour and Lauterbach, 1999) or heart failure (Nieminen et al., 2015).

It is more likely however, due to the complex physical, emotional and social interactions which constitute quality of life. Truly identifying the cause is problematic.

Heart Disease in Today's World

The impact of heart disease in the current health climate is huge. Statistics from the British Heart Foundation show that 26% of all deaths in the UK are due to heart disease (Heart statistics, 2018) with 2.3 million current sufferers of coronary artery disease. One hospital visit every three minutes is due to a myocardial infarction, leading to 180 deaths per day.

Coronary artery disease is estimated to cost the National Health Service (NHS) just over seven billion pounds annually. Death rates have fallen over the past 5 decades, but an aging and growing population is putting further stress on our healthcare system.

Primary Prevention

Identifying and modifying the risk factors identified from the Framingham heart study is the cornerstone of preventing morbidity and mortality from coronary artery disease. Anti-hypertensive and lipid lowering agents are widely used, but advances in coronary prevention are still on-going. Newer lipid lowering drugs (PCSK9 Inhibitors) are expected to further lower the incidence of coronary artery disease (Steg and Ducrocq, 2016). Furthermore, genetic testing could provide an individually personalised plan for coronary prevention in the near future (Steg and Ducrocq, 2016).

Secondary Prevention and Long Term Treatment

Management of cardiovascular risk factors in patients with established atherosclerosis has been shown to improve outcomes (Ford et al., 2007; Farkouh et al., 2013; Hammal et al., 2014). Patients

who have suffered a cardiovascular event, and therefore require secondary prevention derive benefit when taking aspirin and statin therapy compared to those who do not. For aspirin, this was first demonstrated in the ISIS-2 trial published in 1998 (Baigent et al., 1998). Further meta-analyses further contributed to this stance, showing low dose aspirin (75mg once daily) also has protective effects against further events (Antithrombotic Trialists' Collaboration, 2002). Statin therapy also has compelling evidence regarding secondary prevention, with the first trial published in 1994 of over 4000 patients showing mortality reduction with statin therapy compared to placebo (Pedersen et al., 2004). Further meta-analyses showed reduction in mortality and further ischaemic events (Cholesterol Treatment Trialists' (CTT) Collaboration et al., 2010).

Appendix B - Risks of Percutaneous Coronary Intervention

Death

The rate of death is higher than basic angiography alone, and also dependent on the clinical context. From large volume United States registry data sets, elective PCI mortality was 0.65% compared to 4.81% in STEMI patients. Overall mortality was 1.27% (Anderson et al., 2007). Of course advances in technology over time may have reduced this number in today's clinical practice.

Myocardial Infarction

The reported rates of peri-procedural myocardial infarction are highly variable. They are linked with multiple factors including age, burden of atherosclerosis, lesion and procedure complexity and procedural complications such as dissection and vessel closure. Depending on the diagnostic criteria used, rates of peri-procedural myocardial infarction are on average 25%, but can range from 0-70% (Herrmann, 2005). Presentation is often clinically silent, but some studies have linked peri-procedural myocardial infarction with increased long term risks of cardiac mortality (Fuchs et al., 2001). There appears to be two major type of infarction, namely proximal (type I) distal (type II). In proximal type infarctions, local occlusion of a side branch causes infarction at that local site, whereas type II infarction is caused by distal embolisation of thrombus, which can be seen on subsequent cardiac magnetic resonance imaging (MRI) (Choi et al., 2004).

Stroke / Cerebrovascular Event

Due to the nature of coronary intervention, the rate of stroke is higher when compared to diagnostic angiography. A large study of over twenty thousand patients demonstrated an incidence of 0.3% for cerebrovascular events (Dukkipati et al., 2004). Patients were also more likely to suffer an event if they suffered from diabetes, hypertension or previous strokes. The cause of ischaemic stroke during catheterisation is thought to be due to micro-embolism propagating into the cerebral circulation.

Coronary Dissection and Perforation

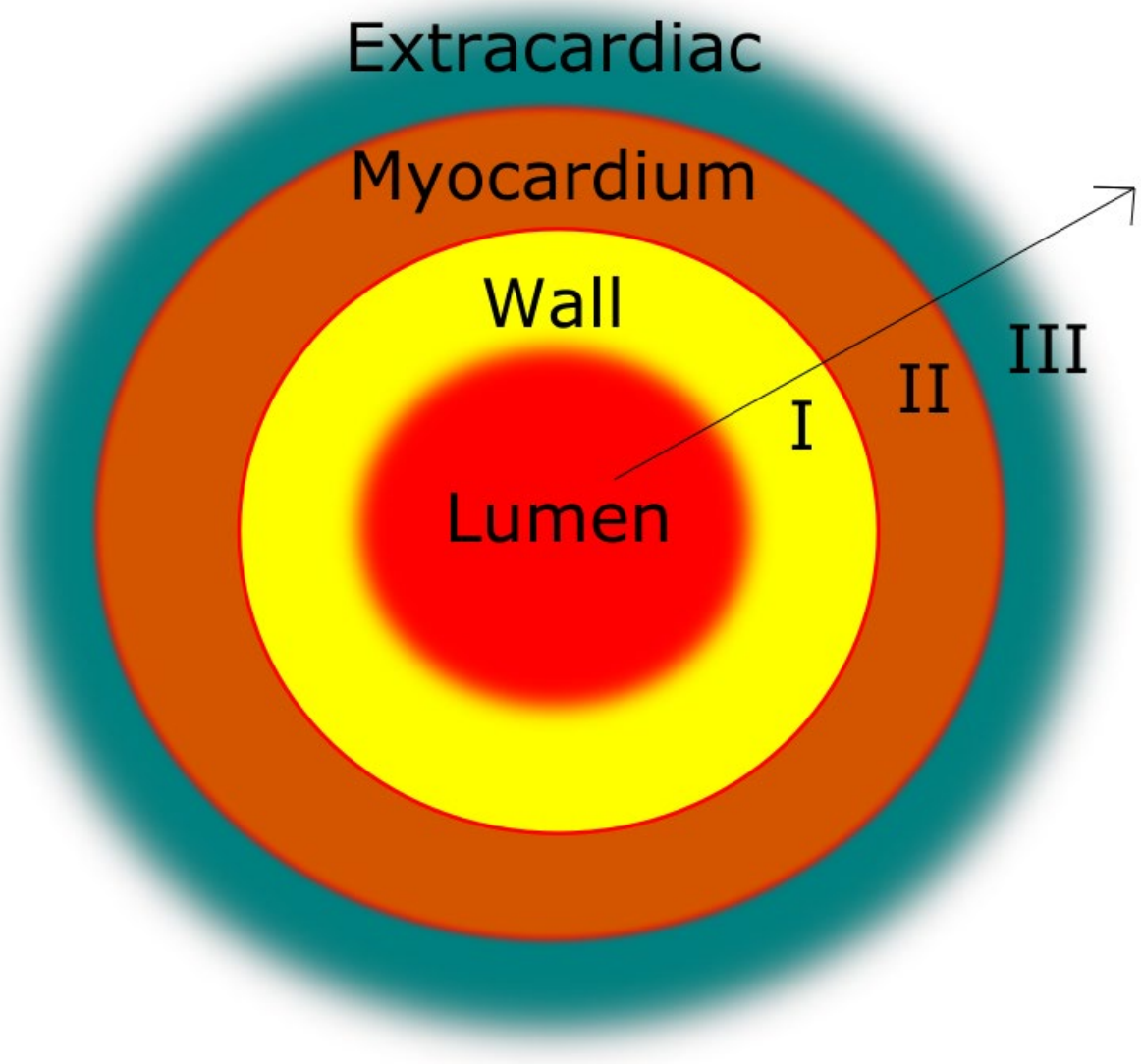
Coronary damage is rarely seen in diagnostic procedures, and is often caused by aggressive guide catheter selection or intubation. In PCI, this is still a possibility, but coronary dissection and perforation are more often due to instrumentation of the artery in question, either with coronary guidewires, or dilatations balloons and stents themselves. The reported incidence is around 2% after stent implantation (Biondi-Zoccai et al., 2006). Left untreated, they were associated with higher in hospital and 1 month rates of major adverse cardiac events (MACE-mortality, myocardial infarction or coronary revascularisation).

Coronary artery perforation is a more serious complication, and often caused by guidewire perforation. Incidence in most studies is <1% but can range up to 3% (Nair and Roguin, 2006). The use of advanced guidewires, especially in treatment of chronic total occlusions (CTO), may lead to an increase in incidence. Studies have not shown an increase in the current interventional era (Kiernan et al., 2009). Treatment varies from conservative observation, to stenting of the area of perforation to seal the leak, and in extreme cases CABG. The chance of needing CABG following coronary perforation is approximately 0.3% (Nair and Roguin, 2006). Cardiac tamponade may ensue in minutes with large perforation, necessitating pericardiocentesis.

Perforation is divided into three types (Al-Mukhaini et al., 2011);

- **Type 1** - Extra luminal perforation without extravasation into surrounding tissue
- **Type 2** - Perforation into pericardium or myocardium

- **Type 3** - Extravasation through a frank perforation, sometimes into an adjacent coronary cavity



Coronary perforation and types. Type I - into the wall of the artery, type II - into surrounding myocardium or pericardium, and type III - frank extravasation or into an adjacent cardiac cavity

Stent Thrombosis

Balloon angioplasty was plagued by acute vessel closure, leading to the implementation of stent technology. The early bare metal stents were then found to have a high rate of restenosis (Serruys et al., 1994; Fischman et al., 1994), leading to the implementation of drug eluting stents, which inhibited smooth muscle cell proliferation, and growth of the intima over the stent. Delayed endothelialisation led to concern regarding increased rates of stent thrombosis. Definite stent thrombosis is defined as angiographic or pathological confirmation of partial or total thrombotic occlusion within the peri-stent region (Cutlip et al., 2007). Timing is also divided into;

1. Acute - within 24 hours.
2. Subacute - between 24 hours and 30 days.
3. Late - 31 days to 1 year.
4. Very late - over 1 year.

Early studies using bare metal stents and different anticoagulation regimes often quoted stent thrombosis rates of around 20% (Serruys et al., 1991; Claessen et al., 2014). Thanks to dual antiplatelet therapy (DAPT) and adequate expansion of stents with high pressure balloons, rates of stent thrombosis up to 1 year range from 0.5 - 3% (Kedhi et al., 2010). The incidence does not differ between bare metal and drug eluting stents (Mauri et al., 2009). Early stent thrombosis is linked to suboptimal procedural results, whereas late stent thrombosis is linked to delayed endothelial coverage and on-going vessel inflammation (Claessen et al., 2014). Mortality after stent thrombosis ranges from 11-42% across multiple trials (Claessen et al., 2014).

Appendix C - Standard Angiography and Laboratory Set-up

Standard angiography uses the supine position and commonly access is gained through the right radial artery or right femoral artery. Left sided arteries are also used but less commonly. A guide catheter is placed into the coronary artery ostium and iodinated contrast media injected to outline the coronary artery of interest under fluoroscopy. To take physiological measurements, a physiology wire is advanced into the required position, and measurements taken. Infusion of adenosine is required to produce a hyperaemic steady state. Routinely, pressure measurements are used to assess coronary artery stenoses and guide clinical treatment, due to ease of use. Velocity or 'flow' measurements, are used in clinical practice less routinely, but have important uses in research studies. Velocity measurements take longer to obtain and results can be operator dependent. Pressure studies are more robust and reliable, hence their more common clinical use.

A standard angiography laboratory or 'lab' in the UK has several standard components. Firstly, there are core members of staff enlisted to ensure safety and efficiency of the procedure for the patients and all others involved. These are outlined below;

1. Scrub Nurse - This nurse will assist the operator by donning surgical gowns and gloves. They will assist in preparing equipment, such as coronary catheters, coronary wires, medications, arterial access equipment, contrast injection equipment and maintaining all of this on a sterile trolley. They are trained in intra-arterial contrast injection, and will aid the operator when they are busy manipulating the catheter. Their role is vital, as although a single operator coronary angiogram is standard practice in other countries, it can add time and unneeded complexity to the procedure, as well as compromising safety.

2. Runner Nurse - This nurse is not in sterile surgical vestments and will aid the scrub nurse and operator with obtaining needed equipment. They will hand equipment from its outer packing in a sterile way to the operator and scrub nurse. Medication preparation and administration through intravenous cannulae is part of their role. Any needs the patient has (such as oxygen, oral care and comfort issues) will also be tended to by the running nurse. If emergency medication needs to be administered (such as for hypotension or an

allergic reaction), they will need to be swift and on hand to dispense this. They are also a key part the resuscitation team in the event of a cardiac arrest and are advanced life support (ALS) trained.

3. Radiographer - The radiographers principle role is to manipulate the x-ray tube and table in order for the operator to acquire adequate pictures of the coronary artery. They will angulate the x-ray equipment and table based on prompts from the operator to achieve satisfactory acquisitions of the coronary vasculature. The radiographer is also in control of contrast medium use, and is bound to remind the operator if use is excessive, potentially risking renal injury in a patient. Furthermore, they are the advocate for radiation protection for the entire team and patient, trying to minimise radiation exposure. They must ensure radiation shielding equipment, from the lead skirt sitting underneath the table, to radiation glasses are being properly utilised. If a procedure exceeds preset radiation limits, they must document and report this.

4. Cardiac Physiologist - the role of the physiologist is to monitor haemodynamics and electrocardiogram outputs continuously from the patient. They must alert the operator of any significant changes in blood pressure and heart rate, as well as the onset of any arrhythmias. They log the procedure electronically on the relevant lab system. They are also responsible for using software required by physiology equipment, such as pressure wires, to obtain further information, useful to the operator. This again applies to intravascular imaging, such as intravascular ultrasound and optical coherence tomography. If needed urgently, the cardiac physiologist is often called on to provide an urgent echocardiogram whilst the patient is still on the table. In similar fashion, in cases where an intra-aortic balloon pump is needed, the cardiac physiologist is responsible for setting up and using this hardware initially (perfusionists are on-site who have further expertise should there be any problems).

5. Cardiologist - The cardiologist is the primary operator for the procedure. They are responsible for gaining arterial access and passing catheters towards the coronary artery origins. They must manipulate the catheter to engage into the coronary ostium and

acquire diagnostic pictures. In coronary intervention or physiology measurements, the appropriate wire must be passed into the coronary artery and 'steered' into the correct position. They are responsible for the overall safety of the patient, and responsible for dealing with complications should they arise. The cardiologist should lead the team and prompt necessary actions. The first operator is normally a cardiology consultant or senior cardiac registrar, with adequate previous experience (minimum of 300 previous cases). Decisions on treatment, medication administration and continuing care are made by the cardiologist.

6. Research Fellow / Registrar - My role in the procedure was to brief the whole team on how study protocol differed from routine practice and potentially train or introduce new techniques. Whilst the cardiologist still led the case, I had to guide the procedure to ensure not only the safety of all involved, but also the collection of scientifically adequate, robust and quality data. The use of a specific research physiology wire meant that I operated the required equipment (see below) rather than the cardiac physiologist. I also was the patients advocate, and ensured their safety and comfort during the procedure.

Appendix D - Turning Checklist and Description

Illustration of order of events / checklist when turning a patient prone during angiography.

Order of Events / Checklist	Responsible Person
Only sheath left in situ	Cardiologist
X-ray tube moved aside	Radiographer
Disconnect cannula	Nurse
Two slide sheets on correct side	Nurse / Radiographer / Physiologist
Two members of staff on each side of the table	Nurse / Radiographer /Physiologist / Researcher
Turn prone (pull slide sheets) and keep patient central on fluoroscopy table	Nurse / Radiographer /Physiologist / Researcher
Reconnect cannula	Nurse

Adjust ECG stickers if needed	Physiologist
Re-drape / resterilise	Nurse/Cardiologist
Continue with procedure	Cardiologist

The physical movement of a supine patient to prone and vice versa was something the institution had experience of in the intensive care unit. The expertise from the intensive care unit was passed down to the catheter laboratory staff and incorporated into the study. Patients were not sedated as on intensive care, the arterial sheath used during angiography is larger and less malleable than an arterial line, and the fluoroscopy table is also significantly narrower than a standard ICU bed. ECG monitoring and intravenous lines were another potential issue which we had to take into consideration. On turning, sterile drapes would need to be replaced.

To prepare for the real situation, multiple 'dry runs' using volunteer members of staff were conducted, mimicking the turning procedure. On simulation of turning during these dry runs, arterial sheaths and venous cannulae were taped onto the skin, and ECG stickers attached as on a real patient. Two members of staff from each catheter laboratory discipline were invited (two nurses, two physiologists, two radiographers and two cardiologists) as well a senior ICU nurse. The patient was treated as a 'sedated' patient and prompted not to assist or move the left arm (holding the radial sheath). Two slide sheets are inserted under the patient and pulled in the correct direction to assist proning. Two members of staff are situated on each side of the table to ensure the patient cannot fall off the table and a central position is maintained.

In real situations, patients would start prone and would be turned supine. Before turning, all coronary catheters, physiology wires were removed from the patient. Cannulae were disconnected and reconnected once the manoeuvre had finished. ECG leads were not removed but could be adjusted if displaced during repositioning. The only invasive device left in situ, was the radial sheath itself. This was covered with an inflatable band or clear dressing, to help keep it

in position during the turn. Displacement of the sheath was a possibility during turning, and the team had to be observant regarding this issue.

Once two members of staff were on each side of the patient, the slide sheets were pulled to turn the patient over. The patient was positioned centrally on the table after turning. ECG stickers were checked to ensure adequate contact. Cannulae were reconnected and the procedure continued as in a normal supine patient via the left radial artery with the catheter and wire re-inserted.

It became clear after the first two patients, that most were able to turn themselves, with assistance and instructions regarding the arterial sheath. Slide sheets were no longer required, and often patients turned independently, without using the left arm to maintain the radial sheath and avoid damaging the radial artery.

Appendix E - Image Acquisition During Angiography

Difference in viewing angles to achieve the same visualisation when comparing supine to prone imaging. AP - Anterioposterior, LAO - Left anterior oblique, RAO - right anterior oblique

Vessel Imaged	Supine X-ray view	Prone X-ray view
LAD	AP Cranial	AP Caudal
LAD	LAO Cranial	RAO Caudal
Cx	AP Caudal	AP Cranial
Cx	LAO Caudal	RAO Cranial
RCA	LAO	RAO

Appendix F - Published CT Coronary Paper (Original Manuscript)

Al-Janabi F, Karamasis G, Cook CM, et al. Coronary artery height differences and their effect on fractional flow reserve [published online ahead of print, 2019 Mar 26]. *Cardiol J*. 2019;10.5603/CJ.a2019.0031. doi:10.5603/CJ.a2019.0031

Coronary artery height differences and their effect on fractional flow reserve

Running Title: Hydrostatic pressure and FFR

Firas Al-Janabi[1,2], Grigoris Karamasis[1,2], Christopher Cook[3], Alamgir Kabir[1], Rohan Jagathesan[1], Nicholas Robinson[1], Jeremy Sayer[1], Rajesh Aggarwal[1], Gerald Clesham[1,2], Paul Kelly[1], Reto Gamma[1], Kare Tang[1], Thomas Keeble[1,2], John Davies[1,2].

1. Essex Cardiothoracic Centre, Nethermayne, Basildon, Essex, United Kingdom, SS16 5NL.

2. Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, United Kingdom, CM1 1SQ

3. National Heart and Lung Institute, Dovehouse Street, London, United Kingdom, SW3 6LR.

Corresponding Author:

Firas Al-Janabi
firas.aljanabi@btuh.nhs.uk
Phone: +00441268 394155

Word Count: 2672

Abstract

Background: Fractional flow reserve (FFR) uses pressure-based measurements to assess the severity of a coronary stenosis. Distal pressure (Pd) is often at a different vertical height to that of the proximal pressure (Pa). The difference in pressure between Pd and Pa due to hydrostatic pressure, may impact FFR calculation.

Methods: One hundred CT coronary angiographies were used to measure height differences between the coronary ostia and points in the coronary tree. Mean heights were used to calculate the hydrostatic pressure effect in each artery, using a correction factor of 0.8mmHg/cm. This was tested in a simulation of intermediate coronary stenosis to give the "corrected FFR" (cFFR) and percentage of values, which crossed a threshold of 0.8.

Results: The mean height from coronary ostium to distal LAD was +5.26cm, distal Cx -3.35cm, distal RCA-PLV -5.74cm and distal RCA-PDA +1.83cm.For the LAD, correction resulted in a mean change in FFR of +0.042, -0.027 in the Cx, -0.046 in the PLV and +0.015 in the PDA. Using 200 random FFR values between 0.75 and 0.85, the resulting cFFR crossed the clinical treatment threshold of 0.8 in 43% of LAD, 27% of Cx, 47% of PLV and 15% of PDA cases.

Conclusions: There are significant vertical height differences between the distal artery (Pd) and its point of normalisation (Pa). This is likely to have a modest effect on FFR calculation and the results in values crossing the treatment threshold. Operators should be mindful of this phenomenon when interpreting FFR values.

Keywords: Hydrostatic Pressure, CT Coronary Angiography, Coronary Stenosis

Introduction

Fractional flow reserve (FFR) is the gold standard for invasive assessment of flow limitation caused by a coronary stenosis and it has been shown to improve clinical outcomes in randomised clinical trials [1, 2, 3]. In practice, FFR is calculated as the ratio of the distal trans-stenotic pressure to the proximal coronary or aortic pressure during pharmacological hyperaemia. The hydrostatic consequences of the wire position are one of the recognised pitfalls when FFR measurements are performed. Coronary arteries lie in different vertical planes and height variations are part of normal anatomy. Thus, the pressure wire sensor measuring distal pressure (Pd) is seldom at the same level with the coronary ostium where aortic pressure (Pa) is measured and where the Pd and Pa were previously equalised. This effect is present in any pressure based measurement, including the resting indices such as instantaneous wave free ratio (iFR) (Davies et al., 2017). Despite strong evidence for its use, FFR remains underutilised (Tebaldi et al., 2018). Avoiding confounding factors when using pressure based indices is crucial in accurate stenosis assessment.

In clinical practice hydrostatic effect produces FFR values higher than 1.00 in a non-diseased vessels, most commonly positioned posteriorly (Nijjer et al., 2016). A recent study documented coronary ostia and distal vessels height differences in an elderly patient cohort with aortic stenosis (Härle et al., 2017b). Furthermore, the investigators used an *in vitro* model to calculate the impact of their observed height difference in pressure derived physiological indices. The observed changes were small meaning that it is unlikely to cause a significant change of FFR value in clinical practice. However, when using a binary cut-off for flow limitation for a given coronary stenosis, even a change of 0.02 can change the classification of FFR from ischaemic to non-ischaemic (FFR form 0.79 to 0.81).

In this study, we aimed to quantify the height differences between the distal coronary vessels and the corresponding coronary ostia in a supine position in a real life cohort of patients undergoing investigations for coronary artery disease. Based on these measurements, we tried to quantify the effect of coronary anatomical variations on FFR values around the ischaemic cut-off point of 0.80.

Methods

We conducted a retrospective analysis of 100 patients undergoing CT coronary angiograms from August 2016 to April 2017 for new onset chest pain suspected to be angina. Vertical coronary height measurements were recorded in all coronary arteries and then used to calculate the potential hydrostatic effect on that specific point in the artery. The effect of the calculated pressure difference and hence effect on FFR was applied to a model of two hundred randomly generated FFR values. FFR was compared pre- and post-correction for hydrostatic force.

Inclusion and Exclusion Criteria

All patients were elective outpatients under investigation for angina. Patients with previous bypass grafting or valve surgery were excluded. Scans, which did not show the upper rim of the CT table could not be analysed (as this was the reference point for measurement). Coronary visualisations with poor contrast penetration, or significant artefact were excluded. Finally, left dominant coronary circulations were not included in analysis.

CT Coronary Angiogram

CT coronary angiography was performed as per local criteria at our institution using a 64-slice CT scanner. A resting heart rate of less than 80 beats per minute was required. Intravenous metoprolol was administered for heart rate reduction if necessary.

Coronary Height Analysis

Using an electronic radiology reporting program (Agfa IMPAX™) and a measuring calliper, distance from the upper rim of the CT table to multiple points in the coronary tree were obtained. Arterial measurement points included;

1. Left coronary ostium
2. Right coronary ostium
3. Ostial left anterior descending (LAD)
4. Distal LAD - at its highest point
5. Distal circumflex (Cx) - at its lowest point
6. Right coronary artery bifurcation
7. Distal posterior descending artery (PDA) - at its highest point
8. Distal posterior left ventricular artery (PLV) - at its lowest point

Measurements were in millimetres and taken at the furthest point of contrast penetration visible in the vessel.

FFR Impact Analysis

The difference in height between the coronary ostium and the measurement point in the artery is the calculated height difference. This was multiplied by 0.8 (according to Pascal's Law and adjusting for blood density) to give a positive or negative change in pressure - in mmHg. This is the theoretical effect on Pd. The denominator (Pa) is assumed to be 100 in the following calculation model. The resulting value was factored into 200 random computer generated FFR values between 0.75 and 0.85 to give a corrected FFR (cFFR) using Microsoft Excel™. Corrected FFR was compared with baseline FFR and the percentage of values that crossed the threshold of 0.8 (from positive to negative or vice versa) was calculated.

Statistical Analysis

Continuous variables are expressed as mean values plus or minus standard deviation. Categorical variables are described as numbers and percentages. Statistical significance of coronary height variations were calculated using the Student *t-test*.

Results

Study Population

Patient demographics are summarised in table 1.

All patients had a resting heart rate below 80 beats per minute before scanning.

Coronary Height Data

Figure 1 shows an example of coronary height measurement. The measuring calliper in green calculates height from the upper rim of the CT table to the corresponding point in the coronary artery. In this particular example the calliper is measuring from ostial left main stem.

Results are displayed below of all measurement points within the coronary tree (Table 2, Figure 2). Height measurement is taken from the upper rim of the CT table.

Table 3 summarises data points from each coronary artery with regard to their respective coronary ostia. The height difference between the coronary specific coronary ostium (Pa) and the vessel containing the height measurement point (Pd), is the value used to calculate effect on FFR and hence, the cFFR.

Hydrostatic effect and cFFR

The corresponding hydrostatic effect of distal LAD, distal Cx, distal PDA and distal PLV were factored into the FFR equation to give the cFFR (Table 3). For anterior vessels, the FFR increased, for posterior vessels, it fell. Out of the 200randomly generated FFR values, 45.5% were below 0.8 and 55.5% above. After correction and calculation of cFFR, these percentages changed substantially. Those that crossed from positive to negative, or vice versa were calculated. Table 4 summarises the results.

Clinical Case Example

An *in vivo* example demonstrating the effect of wire position is presented of a 73-year old male with a lesion in the mid right coronary artery (RCA) (figure 3). The patient presented with typical stable angina. There is a background history of inflammatory bowel disease, but no typical cardiac risk factors. Ejection fraction was normal. A combined pressure and velocity wire (Combowire,

Volcano Corporation™, San Diego, California, USA) is passed through a 6F guiding catheter. The wire is passed beyond the lesion and FFR is measured firstly in the PDA (as distal as a clear velocity tracing allowed), followed by the PLV (distally as per PDA) and lastly placed 3 vessel diameters beyond the stenosis in the main mid RCA. 400 micrograms of intra-arterial nitrates were administered before FFR measurement. Intravenous adenosine at 140mcg/kg was used to induce a steady state of hyperaemia. There was no drift with any of the acquired measurements. Invasive measurements are presented in Table 5.

For the same lesion, placement of the wire in the PDA or PLV altered FFR by 0.05. Placing the wire 3 vessel diameters beyond the stenosis, gives an FFR of 0.79. The small flow variations measured on each occasion are not significantly different, and within normal variations expected during doppler measurements (Davies et al., 2006).

Discussion

In summary, our findings show that coronary anatomy results in statistically significant height variations between proximal (Pa) and distal vessel (Pd). There is a potential change in FFR of 0.02-0.05, causing a number of 'grey-zone' FFR results to cross a binary cut-off point.

In our cohort, the most superior points in a supine patient were the distal LAD, followed by distal PDA. The most inferior points were the distal Cx and distal PLV. All measurements were statistically significant when compared to the respective ostium, apart from the ostial LAD. Even though the mean height of PLV and Cx were identical with reference to the CT table, when compared to their respective ostium (Pa), the PLV had a larger height difference, owing to the more superior position of the RCA ostium. In turn, the hydrostatic pressure effect was more

pronounced in the PLV. More proximal points in a vessel, e.g ostial LAD or RCA bifurcation had a smaller height variation when compared to their respective coronary artery ostium. In general there is a gradual change in height from proximal to distal vessel. Note however, that the most distal point in the vessel does not always have the greatest height variation. An example of this is in a 'wrap around' LAD, where the vessel height falls after reaching the apex. This occurs in over half of patients in one study (Kobayashi et al., 2015b).

CT coronary angiography can accurately map the course of coronary vessels and their vertical heights. Subsequently, the height of the distal vessel (i.e the position of the pressure wire, or Pd) may be higher, or lower than its origin (Pa), depending on the course it takes. This may explain observed changes in groups of patients with 'moderate' coronary stenoses in which posterior vessels (those vertically lower when supine - Circumflex, Posterior left ventricular) have higher mean FFR values than anterior vessels (those that are vertically higher - left anterior descending, posterior descending) (Härle et al., 2017d). Resting Pd/Pa can also often be seen above 1.0. Studies have identified this phenomenon (Nijjer et al., 2016) and it is caused by the distal pressure sensor sitting vertically lower than the aortic pressure sensor (and original point of normalisation). For a resting index to be above one, disease in the vessel is usually mild. While often attributed to drift, physical principles can predict this concept. It is useful to note this phenomenon rather than assume the physiology wire is at fault.

A recent study assessing coronary artery height variations using CT coronary angiograms has been conducted recently in a group composed predominantly of transcutaneous aortic valve implantation (TAVI) patients [5]. Hydrostatic pressure effects were then confirmed using an *in vitro* model. The anatomy of these patients with severe aortic stenosis may slightly alter the anatomy of the coronary arteries themselves due to changes in the aortic root. Our assessment of

coronary height variations in a more heterogeneous group of patients presenting with stable cardiac chest pain was thought to be a useful addition to current knowledge. In general, our patients were younger females in keeping with the low to intermediate risk group initially assessed with CT coronary angiography at the time. There were some differences in height measurements from CT scans between our study and Härle et al. Measurements from ostial left coronary artery to LAD and Cx were similar (5.3cm vs. 4.9 and 3.4 vs. 3.9 respectively). There were however more pronounced differences in the measurement of PLV and PDA from the right coronary ostium (5.7 vs. 2.6 and 1.8 vs. 3.8). There are potential explanations. Observer variation between two studies may account for some of the change. Contrast penetration into the distal vessel can significantly alter the measurement point within the artery, leading to error in measurements in both studies. Finally, the patient cohort varies between the studies. One anticipates that coronary height measurements may vary between a predominantly older population with aortic stenosis, and a younger cohort without.

Pressure based invasive physiology such as FFR, has been well validated over many years. However, pressure-based measurements are subject to the potential effects of hydrostatic pressure. If hydrostatic forces alter distal pressure recordings FFR will in turn change. The change may be small (0.02 - 0.05) but useful to know in FFR values circling the cut-off point (0.75-0.85) (Petraco et al., 2013). In theory, the addition of adenosine should not alter the physical hydrostatic pressure effect in a coronary vessel *in vivo*, as height, fluid density and gravitational effect have not changed. An important consideration is the hypotensive effect and hence reduction in Pa during adenosine infusion. Pa pressure may fall below 100mmHg during hyperaemia, meaning alterations in Pd have a larger effect on overall Pd/Pa. Hydrostatic effect is constant across resting and hyperaemic states. A change in Pd of 5mmHg is therefore of greater

relative importance in resting indices (where a transtenotic gradient of 10mmHg is considered abnormal) compared to hyperaemic indices (where 20mmHg is considered abnormal)

Whilst the effect of hydrostatic pressure upon FFR is described, we believe that this novel data demonstrates that depending on the coronary artery in question and its anatomical course the physiological significance of a coronary stenosis can be both over or under-estimated. Treatment of intermediate coronary stenoses therefore must not be a binary decision, and the operator must exert clinical judgment when faced with grey zone physiology values.

The exact position of the pressure sensor of the physiology wire is often not considered. Hydrostatic effect becomes more pronounced as the pressure sensor is positioned more distally. Avoiding an unnecessarily distal wire position will minimise the hydrostatic effect on obtained measurements by reducing the guide to pressure sensor distance.

By changing patient position during angiography, (i.e turning onto one side), and leaving the wire in exactly the same position in the artery, FFR values have been shown to change (Härle et al., 2018). Correcting for the presumed hydrostatic effect due to this position change (by using measured height difference between guide and wire), abolished the difference between the two FFR recordings, seemingly explaining the difference.

Another important observation is the pressure change along the longitudinal length of a coronary artery, which has been attributed to diffuse atherosclerosis (Bruyne et al., 2001). The additive effect of hydrostatic pressure however cannot be excluded, as vertical height also gradually changes along the length of an artery. This along with other confounding factors, such chronic kidney disease (Tebaldi et al., 2016) may also impact stenosis assessment. Finally, hydrostatic

pressure effects may also contribute to measurements that use mean distal pressure, such as the index of microvascular resistance (IMR) measured using thremodilution.

In our clinical case example, wire placement altered FFR by 0.05 (PDA vs. PLV placement). Flow within the artery does not change in our case study as coronary autoregulation maintains flow over a wide pressure range when these mechanisms are intact (Ramanathan and Skinner, 2005) . Using our coronary CT data, the mean height difference between the PLV and PDA was 7.57cm, equating into a potential distal pressure difference (Pd) of 6.06mmHg. Therefore a change in FFR of up to 0.06 is possible on average. Of course this is a mean change, and patient factors such as height, play a role in individual FFR measurements (Härle et al., 2017b). Although clinical decision-making takes into account multiple factors and is not a binary process revolving around a cut-off point, one should recognise the potential effects of wire position and hydrostatic pressure.

Study Limitations

The study group consisted of low to intermediate risk patients, meaning the majority were younger females. This is not in keeping with a typical demographics of patients who require invasive treatment for coronary artery disease.

The visualisation of the coronary artery in question was limited by contrast penetration into the distal vessel. Some vessels were not completely opacified, meaning a potential underestimation of height measurements. This seemed especially prominent in the PDA where contrast did not penetrate to the distal vessel in 15% of cases. Measurements for these patients were excluded.

Height was measured at distal sections in the coronary artery, as this was the point of maximal height variation. In clinical practice the wire is often not positioned as far distal as these measurements were taken, meaning a potential overestimation of the hydrostatic effect.

With regards to the 200 random FFR results generated, it can be seen that 54.5% of FFR values generated were over 0.8. This was obviously a chance occurrence, but the lack of a more linear 50/50 split of values will effect subsequent analysis.

The hydrostatic effect on FFR in this study takes into account a Pa pressure of 100mmHg.Further data on alterations in Pa and the subsequent impact on FFR may have been a useful addition.

The calculated hydrostatic effect is theoretical, and needs further investigation *in vivo*. Recent trials have upheld anticipated changes in pressure based measurements due to hydrostatic forces (Härle et al., 2018).

Conclusion

The anatomical path of coronary arteries results in a significant vertical height difference between the distal artery (Pd) and its point of normalisation (Pa). According to our hydrostatic pressure model, this is likely to have a modest effect on FFR calculation, which in turn could result in values crossing the treatment threshold. Operators should be mindful of this phenomenon when interpreting FFR values, particularly in the LAD and RCA-PLV.

Acknowledgements

We thank the authors for their contribution in production of this manuscript.

Statement of Competing Interests

The authors report no competing interests

List of Abbreviations

FFR - Fractional Flow Reserve

Pd - Distal Pressure

Pa - Proximal Pressure

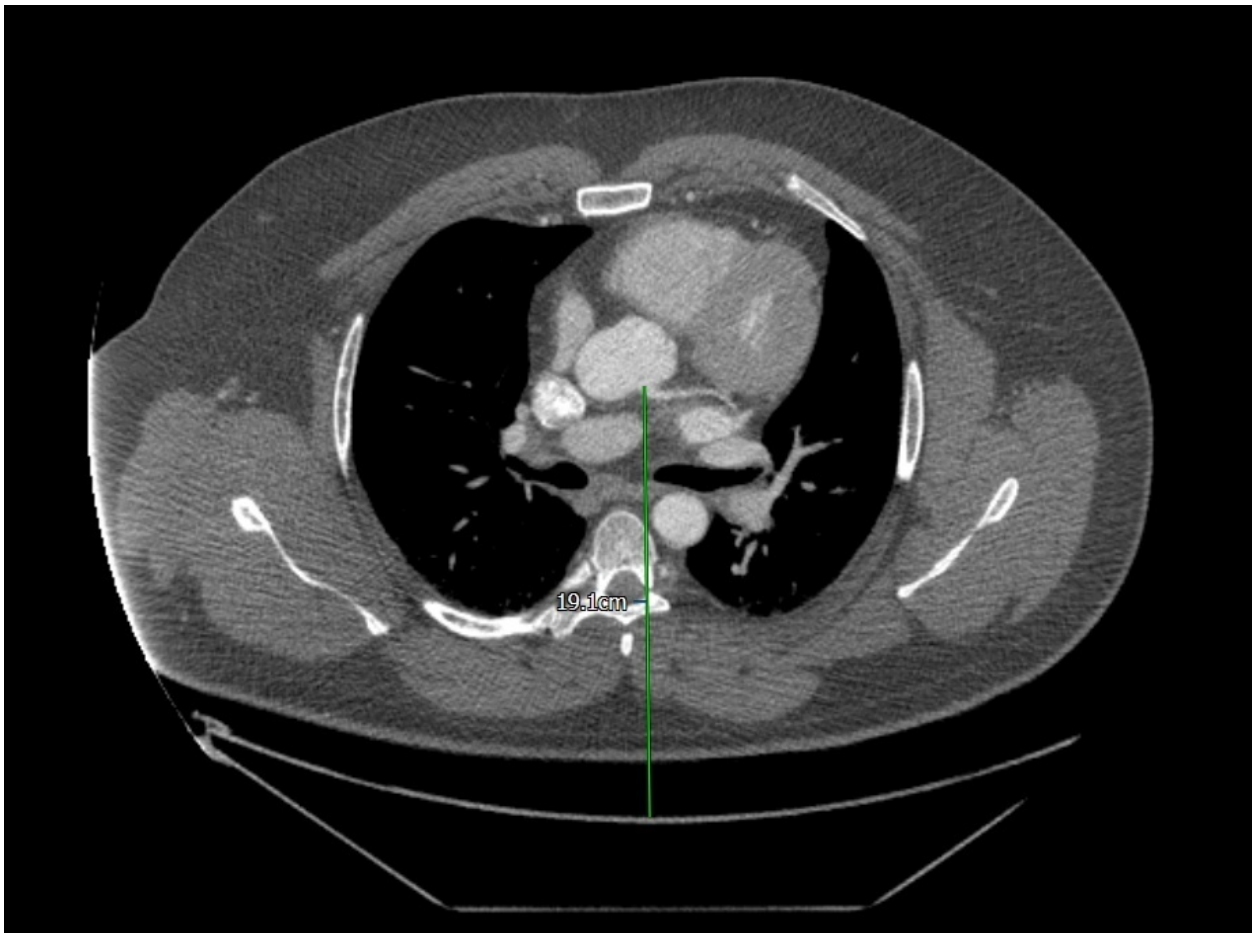
cFFR - corrected FFR

iFR - instantaneous wave free ratio

TAVI - transcutaneous aortic valve implantation

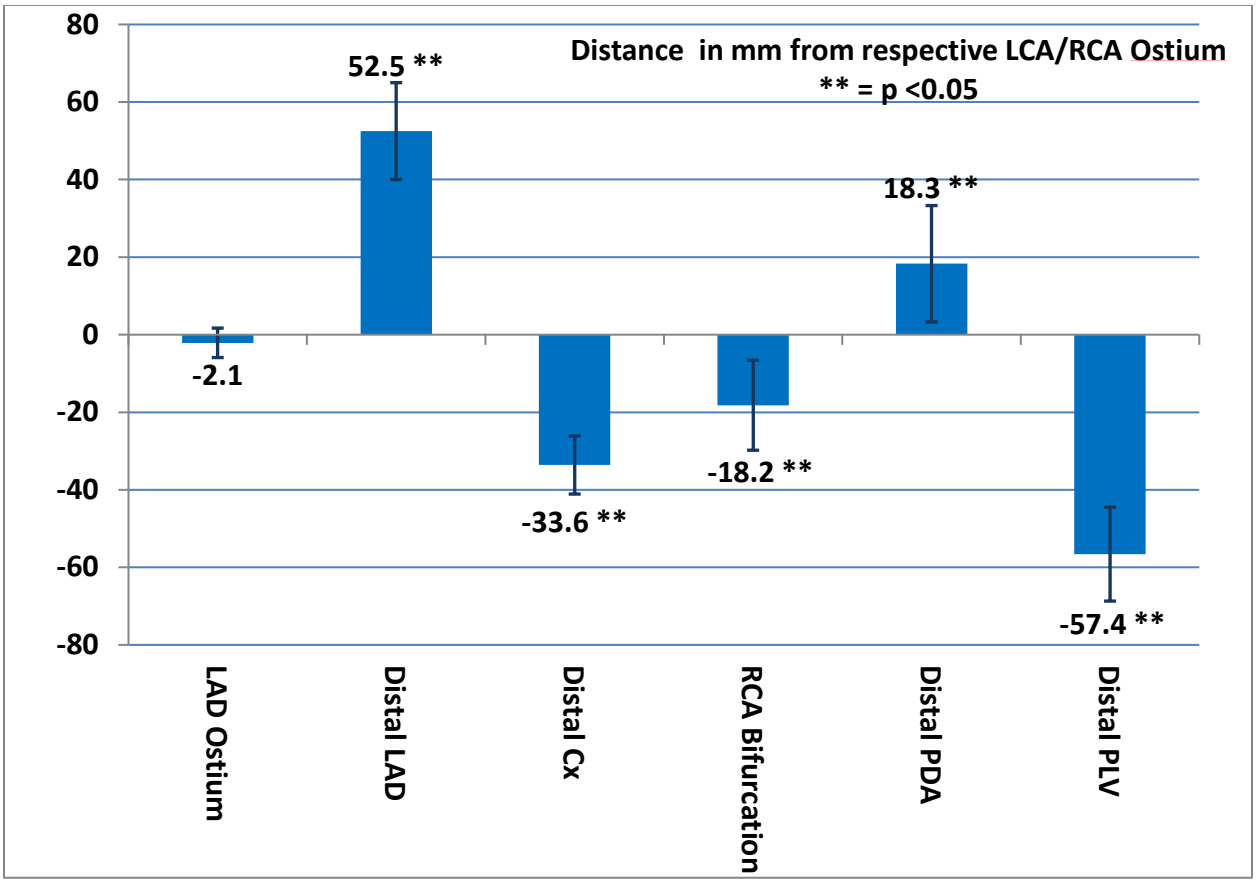
Figure Legend

Figure 1



Vessel height measurement illustration on coronary CT
The image demonstrates the measurement calliper from the left main stem ostium, to the upper rim of the CT table

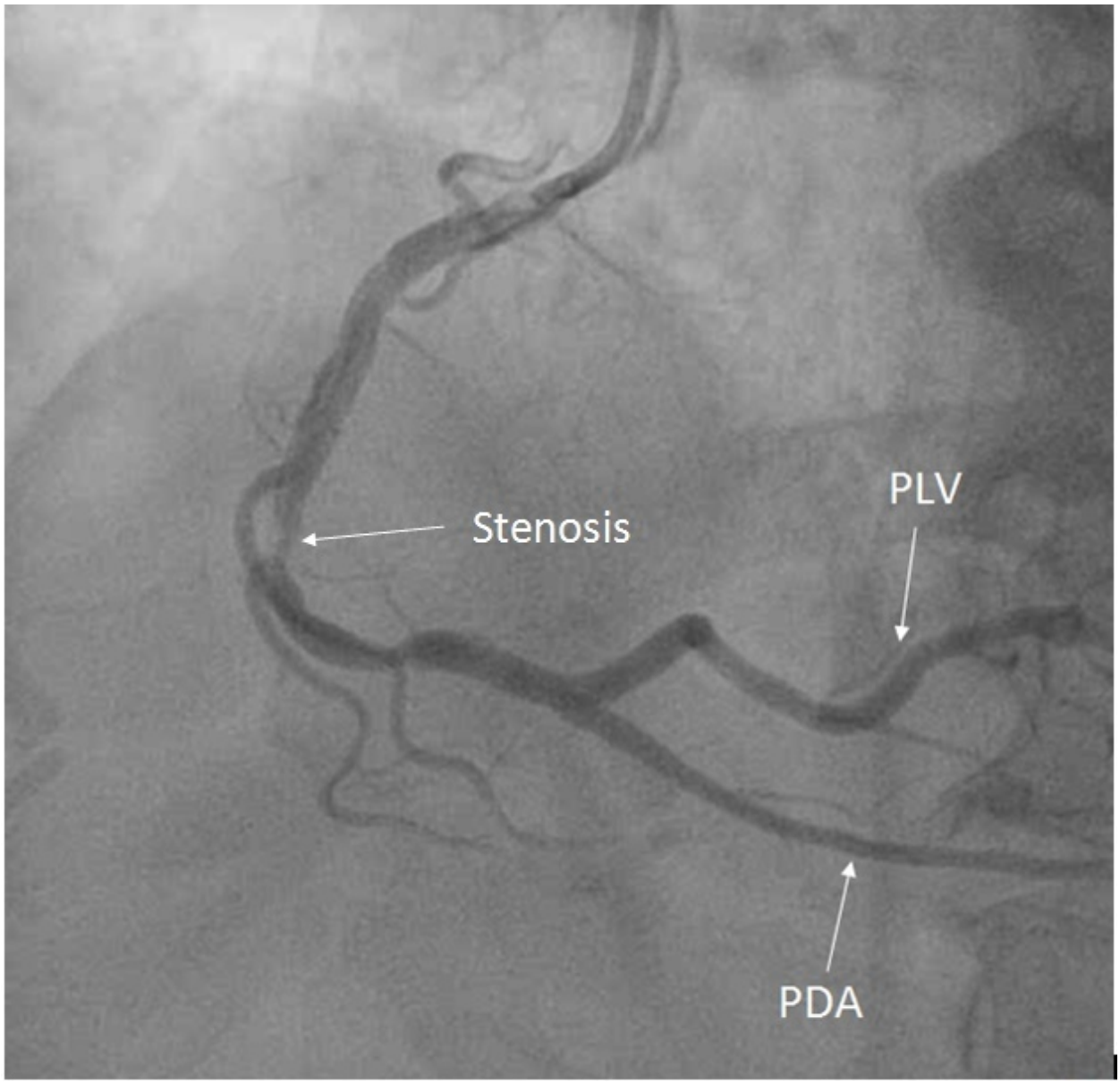
Figure 2



Coronary height variation from their respective ostium

Figure 2 demonstrates the height variation of the distal vessel from its respective ostium. ** These measurements were statistically significant.

Figure 3



Mid right coronary artery stenosis
The stenosis is shown in the mid right coronary artery, with arrows indicating the PLV and PDA.

Table Legend

Table 1

Characteristic	Number (also % as n=100)
Age	55.9
Female	68
Current smoker	12
Ex-smoker	19
Hypertension	33
Hypercholesterolaemia	25
Family History	24
Ejection Fraction	54.8%

Patient Demographics

Demographics of 100 study patients

Table 2

Measurement Point	Mean height from Upper Rim of CT Table (mm) (Standard Deviation in mm)	P Value compared to vessel ostium
Left Coronary Circulation		
LCA Ostium	170.0 (± 19.6)	N/A
LAD Ostium	167.9 (±19.6)	0.06
Distal LAD	222.5 (± 28.3)	<0.0001
Distal Cx	136.4 (± 20.4)	<0.0001
Right Coronary Circulation		
RCA Ostium	193.8 (± 21.1)	N/A
RCA bifurcation	175.6 (± 28.3)	<0.0001
Distal PDA	212.1 (±30.7)	<0.0001
Distal PLV	136.4 (±26.1)	<0.0001

CT Height measurements

The vertical height measurements are shown from the upper rim of the CT table. P values are calculated for each point to the respective vessel ostium.

Table 3

Measurement Point	Height from respective coronary ostium (mm)	Height effect on distal pressure (Pd) - mmHg	FFR Correction factor
Height from Left Coronary Ostium			
LAD Ostium	+2.1	-0.2	**+0.002**
Distal LAD	+52.5	+4.2	**+0.04**
Distal Cx	-33.6	-2.7	**-0.03**
Height from Right Coronary Ostium			
RCA bifurcation	-18.2	-1.5	**-0.02**
Distal PDA	+18.3	+1.5	**+0.02**
Distal PLV	-57.4	-4.6	**-0.05**

FFR effect

The height variations have been converted into pressure effect in mmHg. The impact on FFR with a Pa of 100 is shown in the far right column.

Table 4

Vessel point (+change in Pd pressure)	% FFR below 0.8	% FFR above 0.8	% cFFR below 0.8	% cFFR above 0.8	% Crossing 0.8
Distal LAD (-0.04)	45.5	54.5	6	94	42.5
Distal Cx (+0.03)			72	28	26.5
Distal PLV (+0.05)			92	8	46.5
Distal PDA			30.5	69.5	15

(-0.02)					

Effect on FFR measurements between 0.75 and 0.85
The effect on 200 randomly generated FFR measurements is shown for each vessel point. % values crossing a threshold of 0.8 is shown in the far right column

Table 5

Measurement point	FFR	Flow (cm/s)
PDA	0.75	17.1
PLV	0.8	19.1
3 vessel diameters beyond stenosis (mid RCA)	0.79	18.6

Clinical case data
The data from the clinical case described is shown in table 5. FFR measurement varied by 0.05 between PLV and PDA. Velocity measurements did not vary significantly. This is due to the vertical height differences in both vessels and in turn the hydrostatic effect.