# Assessment of intra-coronary pressure and flow velocity relations distal to coronary stenoses to derive a novel index of stenosis severity

Sayan Sen

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International Centre for Circulatory Health

National Heart & Lung Institute

Imperial College of Science, Technology and Medicine

Paddington

W2 1LA

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# Abstract

The optimal treatment for patients with stable angina remains controversial. Coronary angioplasty is increasingly performed in stable patients to reduce symptoms. Over the last 20 years there has been an accumulation of data demonstrating that an objective physiological approach to revasularisation is superior to the tradional angiographic approach.

Several intra-coronary indices of stenosis severity have been proposed using pressure alone, flow velocity alone or a combination of both pressure and flow velocity. The most clinically used index, Fractional Flow Reserve (FFR) uses pressure alone to estimate the effect of a stenosis on blood flow within the coronary artery. Potent vasodilators are administered during its measurement to ensure the intra-coronary conditions are suitable for pressure to be used as a surrogate for flow. Despite the wealth of evidence supporting its use to guide coronary resvascularisation its adoption is poor. One reason is the need for the potent vasodilators that add time and cost to the procedure, cannot be given to every patient, are associated with side effects and in some regions of the world are simply unavailable.

In this series of studies I will use combined pressure and flow velocity measurements to analyse the phasic relations of pressure and flow velocity distal to coronary stenoses. I aim to identify a period in the cardiac cycle that naturally provides the requisite intra-coronary condition for a pressure only index of stenosis severity - stable intra-coronary microvascular resistance. I will then compare the index derived over this period to existing pressure only and flow based indices of stenosis severity. Finally I will perform a detailed analysis of diastole to detemonstrate why this period is suitable by relating wave-mechanics to traditional pressure and flow mechanics.

# Dedication

I dedicate this thesis to my wife Rupalee, for her love, support, encouragement and understanding. To my daughters Eeva and Aarya: this is what Papa was doing on the computer! To my daughters and the boy on the way – this is what can be achieved with hard work, dedication and a wonderful family. I will be forever indebted to my parents for their eternal support, love and guidance.

**Statement of Originality**

The work in this thesis represents my own work and all else is referenced appropriately.

# Acknowledgements

I am very grateful to 4 positive people who have provided enormous support over the past years. They have been generous with their time and ideas in the performance of this research project.

My mentor has been my supervisor Dr Justin Davies. Justin has been a great inspiration to work with, his scientific and strategic vision is incomparable, and his friendship treasured. His support is never lacking and the amount he has taught me cannot be quantified. The last 4 years have been a lesson in how to succeed in clinical research and I feel privileged and honoured to have witnessed it. I look forward to continuing this journey.

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I thank Professor Darrel Francis for continuing to demonstrate that anything is possible. To witness him solve a problem or design a trial to answer a question should be compulsory for any aspiring investigator. I will be forever grateful for his infective enthusiasm for research and keen eye for detail. He has encouraged me to develop a healthy scepticism for the published word and demonstrated that science is not black or white – but zebra-striped!

Professor Hughes has been a great source of wisdom throughout my studies. He has been generous with his time and provided instrumental scientific support at key stages of this thesis. His expertise is simply limitless and I am grateful for all his support.

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# 1. Introduction

## 1.1 Ischaemic Heart Disease

Ischaemic heart disease remains the leading cause of mortality and morbidity in the world (1). To combat this several treatment options are available for patients and the physicians treating them. These vary from non-invasive (medication, life style modification) to invasive therapy (coronary angioplasty, coronary artery bypass grafting). Since the first balloon angioplasty in 1977 by Andreas Gruentzig (2), the use of coronary angioplasty has grown rapidly. This has been aided by the introduction of intravascular coronary stents (3).

Often these patients have more than one stenosis in one or more of their coronary arteries and determining which lesion is causing the patient's symptoms is difficult for the physician. As a result a proportion of these patients have non-invasive stress tests to try and guide the interventional cardiologist towards the culprit stenosis. Unfortunately these tests have their limitations (particularly in multi-vessel disease) and can only isolate 'ischemia' to the level of a myocardial territory that may be supplied by several vessels each with a varying degree of disease (4). Furthermore only a small proportion of patients being referred for invasive assessment actually have a non-invasive test prior to arrival in the catheterization laboratory.

This has lead to the development of invasive measures of coronary stenosis severity which use pressure (4), flow or both to determine stenosis severity (6). Intra-coronary pressure was originally described as a possible tool for interventional cardiologists by Andreas Gruentzig himself in 1979. However, the clinical utility of such information has only really been explored over the last 20 years with improvement of intra-coronary wire and pressure transducer technology. The premise of such intracoronary indices is to determine the effect of the stenosis on coronary hemodynamics. An appreciation of the physiological basis of these indices therefore requires an understanding of interplay between the contracting and relaxing myocardium and coronary blood flow.

### 1.2 Interplay between intracoronary blood flow and the dynamic myocardium

In all arteries blood flow occurs in the presence of a pressure gradient. In systemic arteries this pressure gradient is usually generated at the proximal (aortic) end of the vessel, driving blood towards the capillary bed. The coronary circulation however provides an exception, where fluctuations in pressure not only originate at the proximal end of the vessel, but also originate from the distal (microcirculatory) end of the vessel (7-9). These distal-originating pressure changes are actively generated by compression and decompression of the microvasculature, which cause the flow velocity waveform in the coronary artery to be very different from that of a systemic artery such as the aorta (Figure 1.01).

The effect of the contracting myocardium on blood flow was first demonstrated in an instrumented canine model by Spaan et al. (10). In a series of elegant studies it was demonstrated that as perfusion pressure to the coronary artery was reduced, a critical pressure was reached below which blood flow reversed in a pulsating fashion – indicating a dynamic source of pressure generation from the myocardial bed. In practice the influence of the myocardium on coronary hemodynamics is evident by simply inspecting the pressure and flow velocity wave-forms at different times of the cardiac cycle (Figure 1.01). For example during diastole it can be seen that flow velocity increases rapidly whilst intra-coronary pressure falls. Such a combination of falling pressure and increasing blood flow would not fit the haemodynamic model of a systemic vessel that has a single proximal input of pressure. However, it is possible, and indeed normal, in a scenario in which pressure also originates from the distal circulation as occurs in the coronary arteries. The acceleration in blood flow during this period in the face of falling pressure can therefore only be due to a suction effect originating from the distal vessel, which accelerates blood flow into the microcirculation. Wave intensity analysis is an investigational tool, pioneered by Prof Kim Parker, that combines information from dynamic changes in pressure and flow velocity to quantify such effects of the dynamic myocardium on blood flow as ‘waves’.

### 1.3 What is wave intensity analysis?

A wave is defined as a disturbance that propagates from one place to another with time. Wave intensity analysis can be used to identify and quantify these waves and in its simplest form, net wave intensity, it is calculated as the product of the change in pressure (*d*P) and change in flow velocity (*d*U) at a particular point in the cardiac cycle. Its units are of power ($Ws^{-2}m^{-2}$); with a negative value indicating a backward-travelling wave and a positive value a forward-travelling wave. In the context of coronary arteries, backward-travelling waves originate from the microcirculatory or distal end of the vessel, and forward-travelling waves from the proximal end of the vessel (Figure 1.02) (8, 9). Originally used to study gas dynamics, the ability of wave intensity to quantify and separate waves according to their origin and direction of propagation make it an ideal tool to study the coronary circulation; which has pressure perturbations originating from both the proximal and distal ends. By identifying and quantifying the origin of these waves throughout the cardiac cycle the predominant determinant of coronary flow at any given point in the cardiac cycle can be determined (Figure 1.02).

The derivation of waves, estimation of wave speed and techniques for measurements and calculation of net and separated wave-intensity analysis have been extensively described by Prof Kim Parker (7-9, 11). The principle equations for the calculation of coronary artery wave-intensity are highlighted below.

**Proximal originating wave intensity:**

$$WI_{+} = \frac{1}{4\rho c}\left(\frac{dP}{dt} + \rho c\frac{dU}{dt}\right)^2$$

**Distal originating wave-intensity:**

$$WI_{-} = -\frac{1}{4\rho c}\left(\frac{dP}{dt} + \rho c\frac{dU}{dt}\right)^2$$

**Net wave-intensity:**

$$WI_{net} = WI_{+} + WI_{-} = \left(\frac{dP}{dt}\right)\left(\frac{dU}{dt}\right)$$

*Where ρ is the density of blood, c wave-speed, dU change in flow velocity and dP change in pressure.*

### 1.4 Principal assumptions and requirements of wave-intensity analysis

Each wave is a product of changes in pressure and flow velocity at any individual time point in the cardiac cycle. It is therefore important to ensure high quality pressure and flow velocity envelopes are obtained when measurements are taken to ensure the subsequent derivation of wave-intensity is an accurate reflection of underlying phasic coronary hemodynamics. Whilst achieving a high fidelity flow wave envelope can be time consuming it is usually obtainable by operators experienced in flow velocity measurements and is aided by the use of a combined pressure and Doppler tipped wires that enable simultaneous capture of pressure and flow velocity.

The main assumption in the derivation of wave intensity itself lies with the use of the single point measure of local wave-speed (11). An initial pre-requisite for the use of wave-intensity in the coronary circulation was the development of a new means of estimating wave-speed when making measurements of pressure and flow velocity at only a single point in the coronary artery. Using the relationship between simultaneous pressure and velocity and the density of blood as a constant, a new equation was derived to estimate local wave speed (Equation 2). Whilst initial validation work involved assessment of this in the aorta it is applicable in any artery in which simultaneous measure of pressure and velocity can be made, and is correct when taken over at least one complete cardiac cycle.

**Equation for single point estimate for wave-speed (c):** $$c = \frac{1}{\rho}\sqrt{\frac{\Sigma dP^2}{\Sigma dU^2}}$$

### 1.5 Wave-intensity and current clinically used indices

Wave-intensity has been used to delineate coronary hemodynamics in several pathological conditions such as left ventricular hypertrophy, aortic stenosis and congestive cardiac failure. However, it has not been used to assess hemodynamics in coronary stenoses. Current clinically used indices measure pressure, flow or a combination of both to assess stenosis severity. However, pressure distal to a coronary artery stenosis does not simply reflect the severity of the stenosis but is a composite of residual proximal pressure and pressure arising from the contraction and relaxation of the myocardium distally. This relative contribution of proximal and distal influences on intra-coronary pressure and flow cannot be appreciated by simply measuring either pressure or flow alone. As a result intra-coronary pressure, trans-stenotic pressure gradients and flow velocity at specific periods of the cardiac cycle can poorly reflect the hemodynamic significance of a stenosis.

This was first highlighted by a series of experiments by Gould (12) in the canine model in which varying degrees of coronary stenosis were assessed using pressure and flow velocity both at rest and during adenosine administration. He demonstrated that intra-coronary pressure distal to a stenosis was indeed confounded by the effect of contraction and relaxation of the myocardium. This resulted in stenosis severity being under estimated (during systole) or over estimated (during early diastole) depending on the point in the cardiac cycle during which assessment was made. In this study he concluded that there was a period in the cardiac cycle 'free of accelerative and decelerative forces' during which intra-coronary pressure and flow velocity were most reflective of the up stream stenosis. During this period he demonstrated that the transtenotic pressure gradient had a quadratic relationship with flow velocity, $\Delta P=Fv+SV^2$; with frictional (F) and separation (S) co-efficients. Identification of this period required measurement of pressure and flow using two separate wires consecutively and then post hoc analysis of the data to accurately identify the most appropriate period of the cardiac cycle. This limited the clinical use of such a window for stenosis assessment. Furthermore, whilst the findings of Gould are widely accepted, until recently phasic real time analysis of the cardiac cycle has not been possible. As a result

despite being derived after the findings of Gould the main clinically used coronary physiologic indices of stenosis severity have traditionally used whole cycle measurements. By using modern pressure sensor technology and using wires that can enable combined pressure and flow velocity measurements wave intensity provides a unique tool to assess the phasic behaviour of pressure and flow and how this varies according to stenosis severity in real time; providing the possibility of new insights into the hemodynamics of diseased coronary arteries.

### 1.6 Fractional Flow Reserve

Fractional flow reserve is calculated as a ratio of distal to proximal pressure across a stenosis. This ratio has been demonstrated to correlate with the ratio of flow in a stenosed artery to flow in the same unobstructed artery. It relies on the principle of Ohm's Law which states that the trans-stenotic pressure ratio is proportional to flow velocity when microvascular resistance is constant. During the derivation of this index the investigators demonstrated that when microvascular resistance is constant the reduction in pressure distal to a stenosis is strongly correlated to the reduction in flow (5, 13).

Whilst it is commonly assumed that microvascular resistance must be minimal to ensure a proportional relationship between pressure and flow, Ohm law demonstrates that this is not true – for pressure to be used as a surrogate for flow, microvascular resistance simply needs to be constant. In order to obtain 'constant' microvascular resistance fractional flow reserve is required to be calculated under conditions of hyperaemia. Originally this involved the administration of papaverine using the rationale that if microvascular resistance can be kept minimal it is also constant. The minimisation of microvascular resistance was therefore used to limit variability.

Due to a risk of prolonged QT interval induced by papavarine the vasodilator of choice was switched to adenosine. Over subsequent years the use of fractional flow reserve has been

systematically evaluated as a tool for the guidance of revascularisation in clinical practice. Having demonstrated it was safe to defer therapy on the basis of a FFR>0.75, the investigators then went on to demonstrate that it was safe to guide revascularisation according to a FFR treatment threshold. The FAME and FAME II studies demonstrated that treatment of lesions with a FFR value less than 0.8 and deferral of treatment of stenosis greater than this value is associated with improved clinical outcomes and reduced healthcare costs (14-17).

Based on the wealth of clinical data the use of FFR to guide revascularisation has a 1A recommendation in clinical guidelines.

### 1.7 Flow velocity, Volumetric flow and Flow based indices

Flow velocity is used as an estimate of volumetric flow in intra-coronary physiological studies. One of the limitations of this is that for a given rate of flow along a vessel, velocities can vary both along the direction of flow, for example due to changes of diameter or other irregularities of contour, and across the direction of flow as a result of different spatial 'profiles' of velocities across the lumen. It is therefore necessary that such mesurements are meticulously made to ensure that the optimal flow velocity envelope is obtained. This has limited the use of flow velocity indicies in general clinical practice.

There are several flow velocity based measurements of coronary hemodynamics. They vary according to their use of simultaneous pressure measurements and epicardial to microvascular specificity. The indices referred to in this thesis are described below.

#### 1.7.1 Coronary Flow Reserve

One of the first measures of stenosis severity, coronary flow reserve is defined as the ratio of basal to hyperaemic flow in a coronary artery. The ratio is a reflection of the ability of the coronary artery to increase flow – termed the vessel's vasodilator reserve. Uren et al. (18)

demonstrated that the ability of a vessel to increase flow is reliant on basal vasomotor tone. A greater basal tone reflected a more constricted the microvasculature and resulted in a greater the vasodilator reserve. This was most elegantly demonstrated in diseased coronary arteries where vasodilator reserve was shown to have an inverse relationship to epicardial stenosis severity.

A key limitation of CFR is its inability to differentiate epicardial and microvascular resistance and its relatively greater sensitivity to variations in perfusion pressure. As a result its use as a means of assessing epicardial severity has been superseded by more epicardial specific indices.

### 1.7.2 Hyperaemic stenosis resistance index (HSR)

Derived and validated around the same time as fractional flow reserve (FFR) this index is based on simultaneous measurement of trans-stenotic pressure gradient and distal flow velocity. HSR has the advantage of indexing the change in pressure across a stenosis with the change in coronary flow (19-22). It is therefore able to give a more specific measure of stenosis resistance rather than simply measuring flow or pressure alone. HSR has consistently been demonstrated to be more specific for the detection of stenosis induced ischemia when compared to CFR and FFR. However its adoption into clinical practice has been limited due to the challenges of measuring flow velocity.

### 1.7.3 Hyperaemic microvascular resistance

This index provides a measure of microvascular resistance and is calculated as the ratio of distal pressure to distal flow velocity (23-24). The ratio of basal microvascular resistance to hyperaemic microvascular resistance therefore represents a measure of the ability of the microvasculature to vasodilate and lower resistance. In effect it is another means of determining vasodilator reserve. The measurement of pressure ensures that the increase in flow is indexed per mmHg of pressure. Therefore values can be more readily compared

between individual with different perfusion pressures. As a result it is a more favoured means of determining flow reserve than CFR.

### 1. 8 Aims of this thesis

Despite a variety of intra-coronary indices their clinical adoption to guide revascularisation is low. One of the reasons for this is the need to administer adenosine. This adds cost and time to the procedure, whilst in some countries its cost is prohibitive or it is simply not available; furthermore patients often suffer discomfort during adenosine administration. The use of adenosine has a dual purpose in physiologic assessment. In pressure derived indices it is required to induce stable microvascular resistance whilst also unmasking trans-stenotic pressure gradients that were difficult to detect with the poor fidelity pressure wires available during its derivation, which only permitted cycle averaged measurements. In the pressure and flow derived index of HSR adenosine is simply used to increase flow velocity to unmask pressure gradients. However, pressure wire fidelity has improved significantly since the derivation of FFR and HSR. The overall aim of this thesis, therefore, is to determine if adenosine is still required for stenosis assessment using current high fidelity pressure and flow wires that permit real-time phasic analysis of the cardiac cycle.

Wave-intensity analysis has demonstrated that hemodynamics vary considerably within each cardiac cycle. How such variations effect stenosis assessment has not previously been explored. In the following series of studies I first use wave intensity analysis to characterise the effect of the dynamic myocardium on blood flow distal to coronary stenoses to determine if there is a period in the cardiac cycle most suitable for stenosis assessment. I subsequently aim to derive a new index of stenosis severity that can be calculated under basal conditions. Finally, I use pressure and flow velocity to ascertain why a basal index could provide similar physiologic information as adenosine based indices.

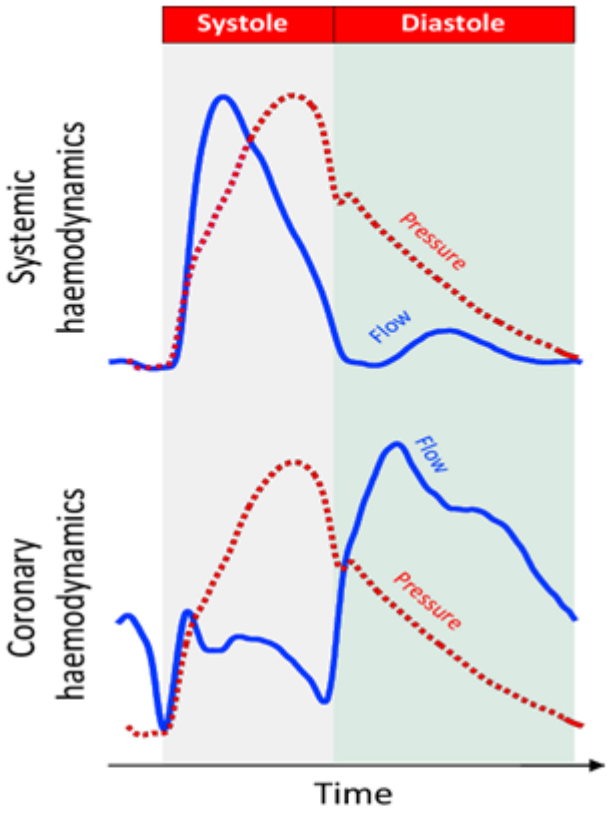



**Figure 1.01: Difference between the pressure-flow relationship in systemic and coronary arteries**
It can be seen that in a systemic artery changes in pressure and flow closely follow each other. In systole they both increase whilst in diastole they both decrease (upper panel). In the coronary circulation (lower panel) this is not the case. After an initial period in systole when pressure and flow increase together, flow velocity plateaus whilst pressure continues to increase. In early diastole it can be seen that pressure falls rapidly whilst flow velocity increases. Such a paradoxical relationship in early diastole cannot be explained by the traditional haemodynamic model of the systemic vessel.

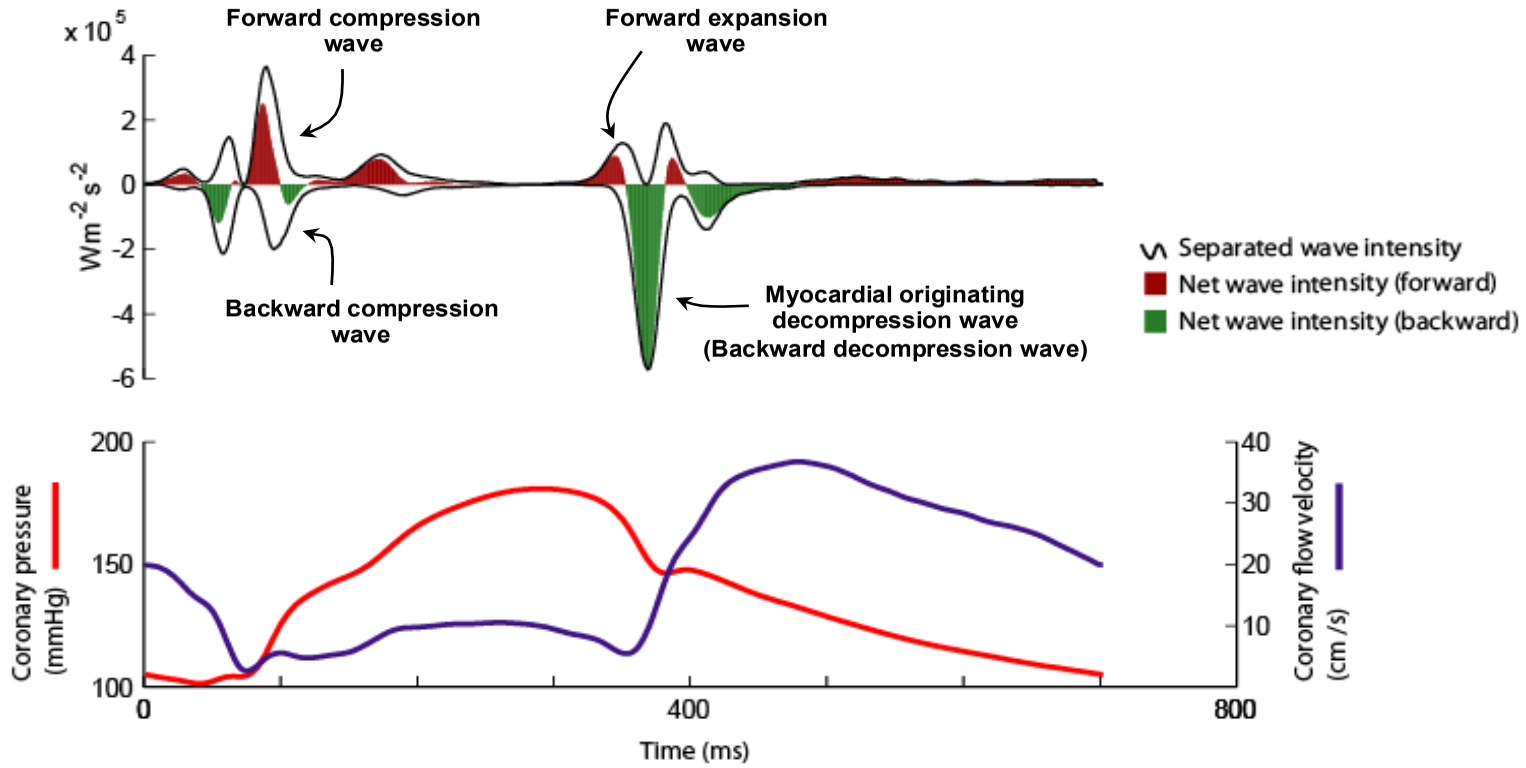



**Figure 1.02: Coronary wave intensity analysis and intra-coronary pressure and flow velocity relationship**

Upper panel: Waves originate from both the proximal (positive values) and distal circulation (negative values). Waves from both ends of the arteries are present in both systole and diastole. The 4 predominant waves of the cardiac cycle are highlighted. The predominant determinant of coronary flow is the myocardial originating decompression wave, which has a suction-like effect.

Lower Panel: Wave intensity can be used to explain the pressure-flow relationship in the coronary artery. For example it can be seen that the paradoxical fall in pressure and yet increase in flow velocity during early diastole is actually due to the myocardial originating decompression wave allowing blood to re-fill the microcirculation. This wave originates in the distal circulation due to relaxation of the myocardium and decompression of the microvasculature (7).

# 2. Materials and Methods

### 2.1 Pre-assessment

Participants were identified from the Imperial College NHS Trust angiography and angioplasty waiting list. These were patients that were listed for angiography and percutaneous coronary intervention for clinical reasons and at no point inclusion to the research study influenced decision-making. Patients eligible for a particular study were offered a pre-assessment appointment one week prior to their scheduled procedure.

At pre-assessment, patients were informed about the procedure they were scheduled to have and also invited to participate in the research study. Information was given with regard to the research study (Appendix I). On the day of their procedure if the patient was willing to participate in the study, a study consent form was completed (Appendix I). All studies were approved by the local research committee (NRES ref: 09/H0712/102; NCT01118481).

## 2.2 Investigations

### 2.2.1 Electrocardiogram

An electrocardiogram (ECG) was recorded for each subject throughout each study, using a LifePulse MMC (model number LP10). The position of each electrode was adjusted to ensure that the R wave was positive and was the dominant deflection. The ECG console outputted a continuous ECG wave signal from which was fed to the analogue input port, as discussed later.

### 2.2.3 ComboMap system (model 6800)

The ComboMap system (Figure 2.01) processes the information it receives from the guide wire (ComboWire), pressure transducer (from the catheter table) and other external inputs. Intravascular blood pressure and/or blood flow velocity measured in the coronary and/or peripheral arteries during diagnostic and/or interventional procedures are displayed on the console screen in real time (Figure 2.02).

### 2.2.4 The ComboWire XT

The ComboWire is a steerable guide wire which combines two different sensors. The guide wire has a diameter of 0.014" (0.36 mm) and a length of 185 cm (Figure 2.03). The CombTip type (model reference 9500) that was used in this study contains a pressure transducer and an ultrasound transducer, both mounted in a single housing at the tip of the guide wire. The ComboWire was connected to the ComboMap system via the patient interface module which conveyed the signals of Doppler flow velocity and pressure from the wire to the console.

### 2.2.5 Same point measurements

Wave intensity analysis requires that the point of acquisition of both pressure and flow is the same and, ideally synchronous. Whilst both the pressure and Doppler sensors are close to the tip in the ComboWire, there remains a difference of 5mm in distance between the two sensors because it is not possible to place the sensors in exactly the same position. It is extremely unlikely that there would be a significant degree of impedance mismatching over such as short distance so a spatial displacement of this magnitude can be regarded as effectively the ‘same point’. In theory this displacement will also introduce a time delay between the pressure and velocity signals. The degree of this delay depends on the wave speed. For wave speeds between 5 - 60 m/s which correspond to the range in arteries at rest and during hyperaemia the delay can be calculated to be between 0.25 – 1 ms (delay = distance / wave speed). Given that the sampling rate of the Doppler signal is 100Hz this delay was considered negligible and was not corrected for.

### 2.2.6 Pressure sensor

The pressure sensor uses the MEMS (MicroElectroMechanicalSystems) technology to form a thin silicon diaphragm over a reference pressure chamber. Tiny resistors are embedded in the diaphragm, and their resistances change when the diaphragm flexes in response to the changing blood pressure. The pressure electronics monitors the resistor values, using factory calibration coefficients to convert the resistance into a pressure reading.

### 2.2.7 Doppler sensor

The Doppler sensor uses quartz crystals (piezoelectric crystals). When an electric current is applied to these crystals, they change shape rapidly. The rapid shape changes, or vibrations, of the crystals produce sound waves that travel outward. Conversely, when sound or pressure waves hit the crystals, they emit electrical currents. Therefore, the same crystals can be used to send and receive sound waves. Thus the piezoelectric transducer can be used both to transmit and receive ultrasound signals. The signal processing electronics uses the pulsed-wave Doppler method, generating the transmit burst waveforms and processing the frequency-shifted echo signals to extract the blood flow velocity information from the received signal (Figure 2.04).

### 2.2.8 Calculation of pressure-velocity signal delay

For accurate determination of wave intensity analysis it was vital that measurements of pressure and velocity were correctly aligned in time. While sensor displacements introduce only trivial relative delays in signals, there are processing delays in the ComboMap which differ for each of the pressure and Doppler sensors. Previous bench top studies have demonstrated this delay to be 43ms (mean 42.5±3.8ms) (7, 11). This delay was subtracted from the timing of the pressure data in all subsequent analyses, so that both pressure and Doppler signals were synchronous.

### 2.2.9 Combo mode

We used the Combo mode on the console screen (as displayed in Figure 2.02) to display both pressure and Doppler signals. In this mode, both pressure and Doppler scales were adjusted to optimize the display of the signals accordingly.

#### 2.2.9.1 ECG input

Real time signals of pressure and Doppler velocity can also be outputted via the connector panel which is situated at the back of the ComboMap (Figure 2.05). Via this connector, we

connected the patient's ECG signal to display it as a scrolling waveform on the monitor (Figure 2.06).

#### 2.2.9.2 Pressure input

The 'Aortic/Aux 1 in' high level input was used to feed aortic pressure recorded via the guide catheter into the console. This was necessary for the calculation of the various intra-coronary indices which require simultaneous aortic pressure measurements for their calculation (Figure 2.06).

#### 2.2.9.3 Pressure output

The high level output of the ComboMap system (Aortic/Aux 1 out and Distal/Aux 2 out) was used for outputting the pressure signals. Aortic out is the aortic signal recorded by the guide catheter during the procedure (Pa). The distal signal is the distal pressure (Pd) recorded from the ComboWire. This output gave 1volt for every 100mmHg.

#### 2.2.9.4 Doppler flow output

To output the instantaneous peak velocity (IPV) and average peak velocity (APV) signals from the Doppler measurements, the high level APV/Q and IPV/I connections were used respectively (Figure 2.06).

## 2.3 Acquisition system design

### 2.3.1 Hardware

The outputted signals of pressure and velocity taken from the ComboMap connector panel were in analogue form. These signals together with the electrocardiogram signal were fed into a BNC connector box (BNC-2010, National Instruments). A 70 multi-pin output cable was then fed from this connector box into a National Instruments analogue to a digital PCMCIA card (DAQ-Card AI-16E-4) within the PC (Figure 2.07).

### 2.3.2 Software

Customized data acquisition software was developed and written using Labview (National Instruments). The hardware and software was developed to be stable at high sampling frequencies (in excess of 10000Hz). However, as the output frequency from the ComboMap console was substantially lower, the sampling frequency was standardized at 1000Hz. Each of Pa, Pd, IPV, APV and ECG were stored in an .SDY file. This was exported at the end of the procedure and analysed in customised software programme that allowed conversation of the data into text files for analysis in Matlab.

### 2.3.3 Post-acquisition Signal Processing

After acquisition, signal processing and data analysis were performed using customized software written in Matlab. This software was fully-automated to allow 100% reproducibility in the measurement of haemodynamic data and calculation of wave intensity analysis.

### 2.3.4 Filtering

All data was passed through a Savitzky-Golay smoothing filter. This filter is ideal for smoothing haemodynamic signals whose frequency span (without noise) is large. This is typical of haemodynamic data where it is common for peaks and troughs to occur rapidly in succession within a short time period. The Savitzky-Golay filter fits a polynomial to each frame of data to minimize the least of squares error. It is thus more effective at preserving pertinent high frequency components of a signal than standard averaging filters. However, whilst the Savitzky-Golay is very good at preserving high frequency components, it is less good than standard averaging filters at removing noise. Savitzky-Golay polynomial order and frame width constants were set at 3 and 31 respectively in all data analysis.

### 2.3.5 Ensemble averaging

All haemodynamic recordings made were at least 60 seconds in duration. However, to analyze wave intensity a single representative waveform is required. To do that, we

ensemble averaged the recorded data. The advantages of ensembling are that any random noise is removed in the averaging process. The disadvantages are that it relies on precise determination of the fiducial point. If this is not correct, ensembled pressures and velocity traces become distorted with a loss of fine detail and a blunting of the peaks and troughs.

### 2.3.6 The fiducial point for the data ensemble

A series of post-processing tests were undertaken to identify the best fiducial (reference) point for data ensembling. Fiducial points were identified using fully-automated custom written algorithms in Matlab. After selection of the fiducial points, data was ensembled and the accuracy of these automated algorithms assessed by inspection of the ensemble traces. The best and most reliable fiducial point was found to be the R wave of the ECG. This was used in all data analysis.

### 2.3.7 Recording of the study

The 'real time' traces of pressure, Doppler and ECG displayed on the ComboMap screen were saved onto the ComboMap hard drive and backed up with a CD (Figure 2.07). This enabled us to play the whole study again at a later stage for further analysis of the signals if needed.

## 2.4 Set-up in the catheterization laboratory

### 2.4.1 Catheters

To standardize the procedure, all recordings were made via a 6 French guiding catheter. It is standard clinical practice to use guide catheters during the physiologic assessment of stenoses because they offer better inner coating, have a larger lumen and allow better torque control of the wire by the operator.

### 2.4.2 Medication

Since most patients studied were being investigated for possible coronary artery disease, it was deemed unethical to stop any of the medications they were taking prior to the procedure. Before the insertion of any intracoronary wire, 5000IU of heparin was given intravenously to reduce the risk of thrombosis. Furthermore, the activated clotting time (ACT) was measured at regular intervals and maintained above 250 seconds. Intracoronary GTN (300mcg) was administered to each artery before physiological assessment was performed to ensure no epicardial artery spasm.

### 2.4.3 Induction of hyperaemia

Current clinically used indices of coronary stenosis and microvascular resistance are measured during the administration of adenosine. The clinically recommended dose varies according to its route of administration. Intravenously a dose of 140mcg/Kg/min of adenosine via femoral venous line is recommended; intra-coronary a dose of up to 120mcg of adenosine by rapid bolus injection directly into the target vessel. Only an intravenous route of adenosine administration was used when simultaneous pressure and flow velocity measurements were made. This was done to ensure adequate time was available to achieve the best possible flow velocity envelope which is especially challenging in vessels with severe stenoses.

### 2.4.4 Pressure measurement

#### 2.4.4.1 Aortic pressure measurement

We used fluid-filled hollow guide catheters to measure aortic pressure (Pa) throughout the procedure. Pressure is transmitted through a tiny fluid column to an external pressure transducer, to which the fluid-filled system is connected. In order to maintain the highest level of quality of the pressure trace, the distance between the coronary artery to the pressure transducer was kept to the minimum and the catheter was kept free of bubbles. The pressure transducer was fixed to the catheter table to avoid erroneous readings of pressure due to height changes of the transducer. Before use, each of the fluid-filled catheters was zeroed at the right atrial level with the patient supine.

The pressure waveform was displayed continuously on a screen to be viewed by the operator together with minimum, maximum and mean values of aortic pressure. The standard procedure in the catheterization laboratory is to mount the pressure transducer of the guiding catheter at a height of 5 cm below the sternum, which is estimated to be the location of the aortic root. As this is merely estimation and can be incorrect, pressure readings may be also be incorrect. Therefore, by adjusting the height of the pressure transducer small errors in pressure can be corrected; decreasing the level of the transducer increases aortic pressure, increasing the height of the transducer will decrease aortic pressure. This manoeuvre was only carried out if during the verification process of comparing the fluid-filled pressure reading with that of the guide wire (at the time when the guide wire is positioned at the tip of the guide catheter while sitting at the coronary ostium) there was a pressure difference between the two readings. This step is explained on the section on equalizing pressure.

#### 2.4.4.2 Pressure-monitoring guide wire

The ComboWire XT 0.0 guide wire (Volcano therapeutics) was used to measure coronary pressure (Pd) and a new sterile wire was used for each patient. Calibration of the pressure wire was carried out outside the body, with the wire positioned and rested on the table, through an automated process by the ComboMap. Once this was done, the 'ready' signal displayed on the touch screen enabled use of the wire. At baseline and with the wire outside the body, a check was carried out to ensure that Pd was reading zero pressure. If not, the wire was zeroed. Only then, was the wire removed from the spiral. Furthermore, to help with rotational movements and manipulation in the coronary arteries, the shapeable guide wire tip was carefully shaped using standard tip shaping practices. With experience, we found that for best results, the shaping of the tip had to be done in the direction of the sensor housing opening. Under fluoroscopic imaging, the wire was positioned in the coronary artery at the site of interest and on occasions torque was applied to facilitate this.

#### 2.4.4.3 Equalising pressure in the ascending aorta

At the coronary ostium, the pressure displayed by both the fluid-filled system and the pressure wire were compared. At this point to ensure wire pressure was equal to aortic pressure the wire pressure was equalised to aortic pressure. The next step of the protocol was only followed once it was confirmed that there was no difference in the two pressures. A guide wire introducer was placed in the Y-connector to facilitate wire manipulations in the coronary artery. The space around the wire within the introducer may leak and lead to aortic pressure measurements which are below the actual pressure. Although in every case we checked that the introducer was not leaking, we took the extra precaution of making all measurements with the introducer out and the Y-connector always locked in the closed position so that there was no leakage around the wire.

It should be noted that equalisation of pressure occurred in the aorta and therefore in the presence of a clear dicrotic notch on the pressure wave form. The presence of this notch

was ensured throughout the measurement process to ensure no damping of aortic pressure was present which has been shown to result in inaccurate intra-coronary measurements. Such a damped trace provides a lower aortic pressure than is actually present. This can lead to artificially high pressure ratios.

#### 2.4.4.4 Signal drifting

One problem encountered during some of the procedures was signal drifting. This is a phenomenon which is frequently encountered during pressure wire measurements and a drift of <5mmHg per hour has been previously regarded as acceptable (25). However, due to the magnitude of the measurements we were making we refused to accept any drift in the measurements. As a result after each of the measurements the pressure sensor was returned to its original position in the aorta (where equalisation was performed) to ensure there was no drift. If any drift was detected the measurements were repeated. If the wire continued to drift it was replaced. No post hoc correction of drift was therefore necessary.

#### 2.4.4.5 Flow velocity measurement

The ComboWire XT 0.0 guide wire (Volcano therapeutics) was used to measure instantaneous peak velocity of blood (IPV) simultaneously with Pd. A new sterile wire was used for each patient. Doppler velocity is measured approximately 5 mm from the tip of the wire. The pulsed Doppler beam angle is 45 degrees and insonates a sample volume of approximately 4 mm downstream of the Doppler probe. Fine rotational movements were carried out so that the Doppler beam captured the highest velocity. The intensity of the Doppler envelope was taken as indicative of this (Figure 2.08). Acquisition of the Doppler signal proved the most demanding aspect of the study acquisition process. With experience we were able to get a strong, dense and steady signal even in the most challenging cases.

## 2.5 Calibration before each study

### 2.5.1 Pressure calibration

### 2.5.2 Input calibration

The two sources of pressure in the ComboMap were the guide catheter and the ComboWire. When exposed to ambient pressure, small differences in the zero line for each of these pressure transducers may be present. For this reason, both pressure signals were compared at the zero mmHg signal. If there was a difference, it was corrected by pressing the zero button.

### 2.5.3 Output calibration

To test the output of each of the pressure signals, a calibration signal was sent to the acquisition computer screen via the output reference buttons.

### 2.5.4 Doppler calibration - Doppler spectrum input

#### 2.5.4.1 Wall filter

At each location, the wall filter function was used to reduce or eliminate low frequency noise returning in the Doppler spectrum when the transducer was near an artery wall. Available settings are 200, 400, 800 and 1600Hz, the optimum was found to be at 400Hz and this setting was used in the majority of the cases.

#### 2.5.4.2 IPV threshold

The IPV threshold is a signal to noise ratio, and establishes the signal threshold: signals below this level are considered noise and not displayed or used for flow measurements. The IPV threshold was set by optimizing the IPV envelope which is displayed as a blue envelope around the flow spectrum. This was adjusted manually in all patients and all vessels studied to ensure that the blue tracking envelope matched the outer edge of the velocity spectrum. A range of 0-3 was used for the majority of studies.

#### 2.5.4.3 Doppler spectrum output

To test the output of the Doppler signal, a calibration signal was sent to the acquisition computer screen via the output reference buttons. Output reference was available at selections of 0, 100, 250 and 500cm/s. The output voltage was in the range 0-5 volts which implied that the output reference was scaled accordingly. For example, if a scale factor of 100cm/s is selected, the 5-volt output covers the range of 0-100cm/sec. In this example, an IPV reference of 100cm/s is equivalent to 5 volts. If, however, 500cm/s is selected, the 5-volt range covers 0-500cm/s. In this case, an IPV reference of 100cm/s is equivalent to 1 volt. We have previously demonstrated that the 250cm/s scale factor maximized the amplitude of the Doppler signals in the majority of the cases; we therefore set this value in all of our studies to avoid any scaling confusion in our acquisition process. This scaling factor outputs 1 volt for every 50cm/s measured.

### 2.6 Reproducibility

Reproducibility of hemodynamic measurements has been demonstrated previously (7). The mean and standard deviation of the difference between the separate 30-second recordings of blood pressure was 12.0±269 Pascal (7,11). The mean and standard deviation of the difference between the separate 30-second recordings of flow velocity was 0.007± 0.022 m/s (7,11).

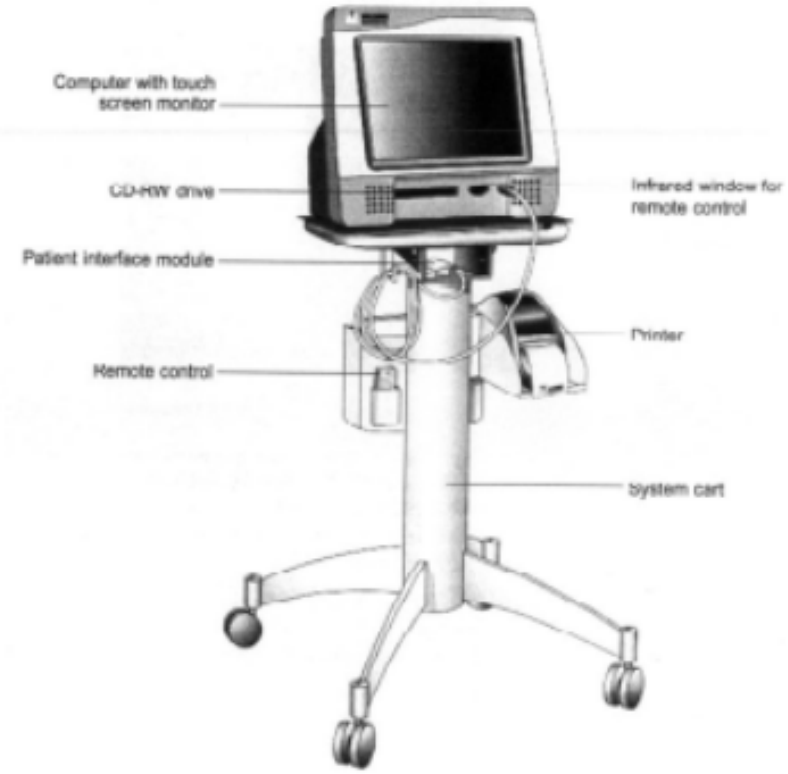



**Figure 2.01: The ComboMap system**

A schematic illustration of the ComboMap system showing the touch screen monitor and all connections and parts (taken from the ComboMap manual).

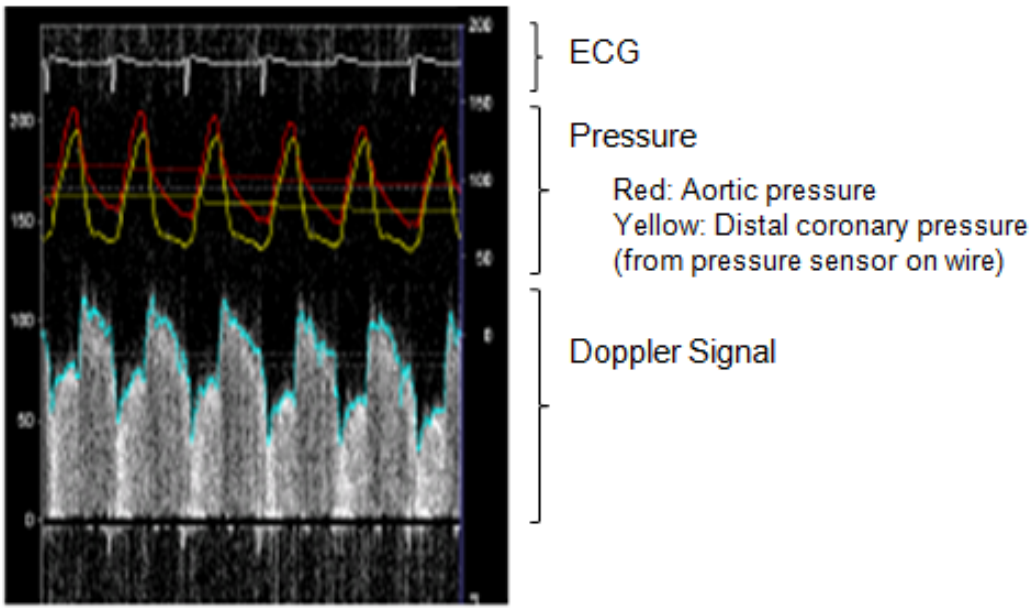



**Figure 2.02: ComboMap console touch screen**

All ECG, pressure and Doppler signals are displayed in real time

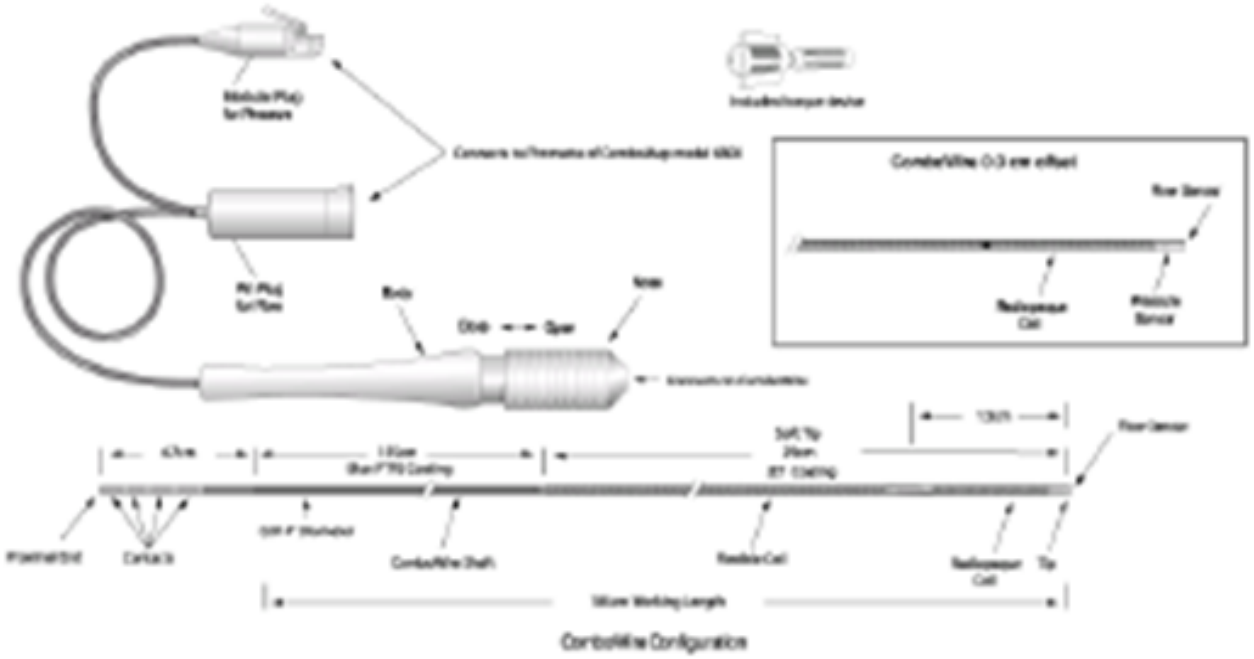
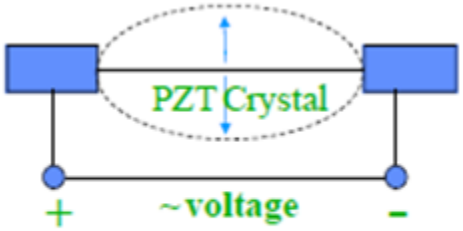


**Figure 2.03: The ComboWire XT**

Schematic representation of the ComboWire XT, 9500 series used in this study. All sections of the wire and connection points are shown.



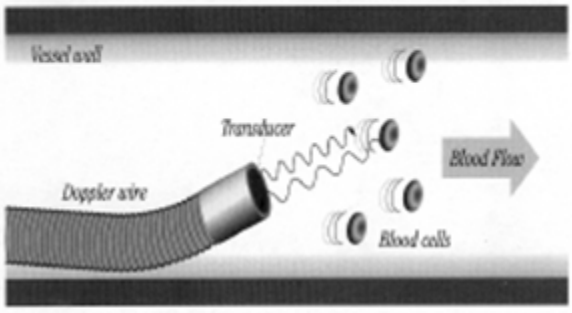




**Figure 2.04: The Doppler sensor**

Voltage generation from the piezoelectric (PZT) crystal in the guide wire used to measure velocity of blood as shown in the bottom panel

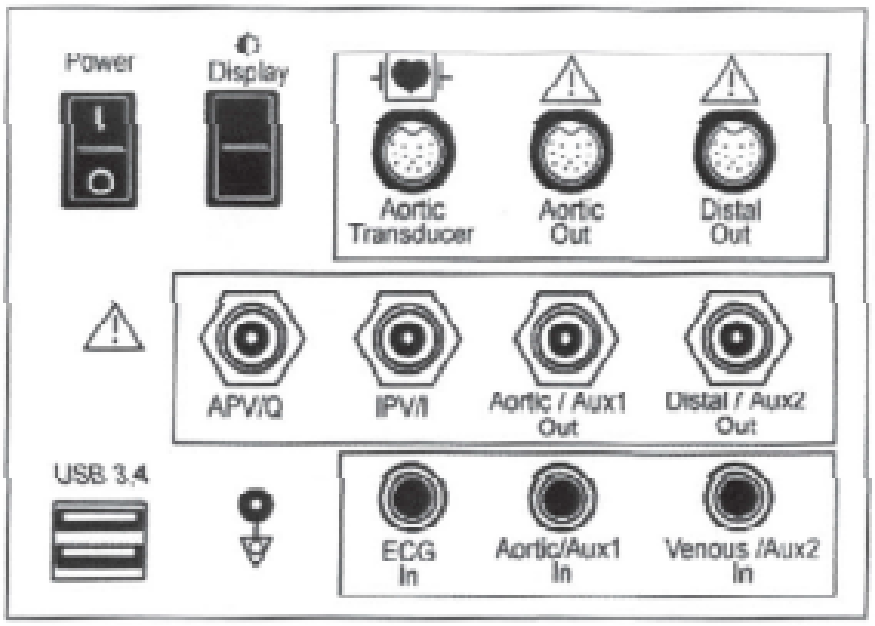



**Figure 2.05: Connector panel of the ComboMap**
Situated at the rear of the console the connector panel has low and high output and input connections. These enable ECG (ECG in), aortic pressure through the guide catheter (aortic in) to be inputted into the console system. In addition, the signals of all of the Doppler (IPV/I and APV/Q), aortic pressure (aortic in/aux1 in) and distal pressure through the ComboWire (Distal/Aux 2 Out) can be outputted for further offline analysis

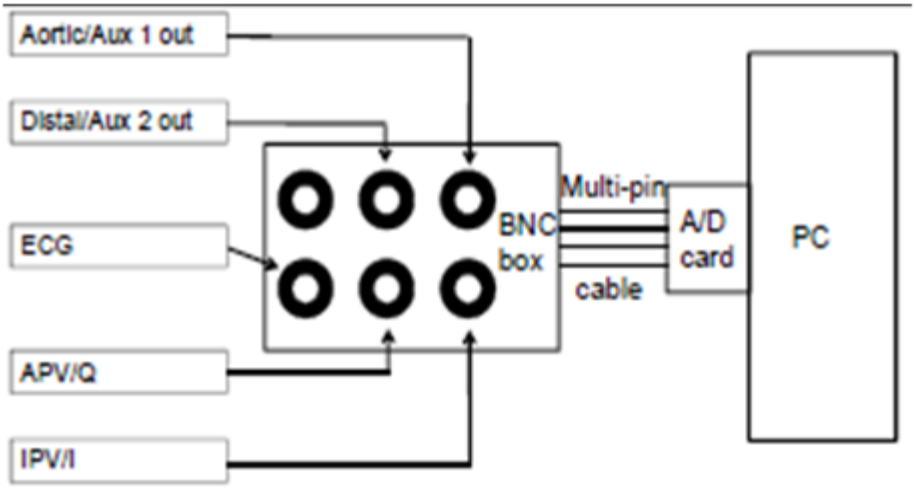



**Figure 2.06: Schematic illustration of the layout of the input data into the acquisition system**

Analogue output signals were taken from the ComboMap and ECG consoles into a BNC connector box. A multi-pin cable was then taken from the BNC connector box into the analogue to digital card within the PC.

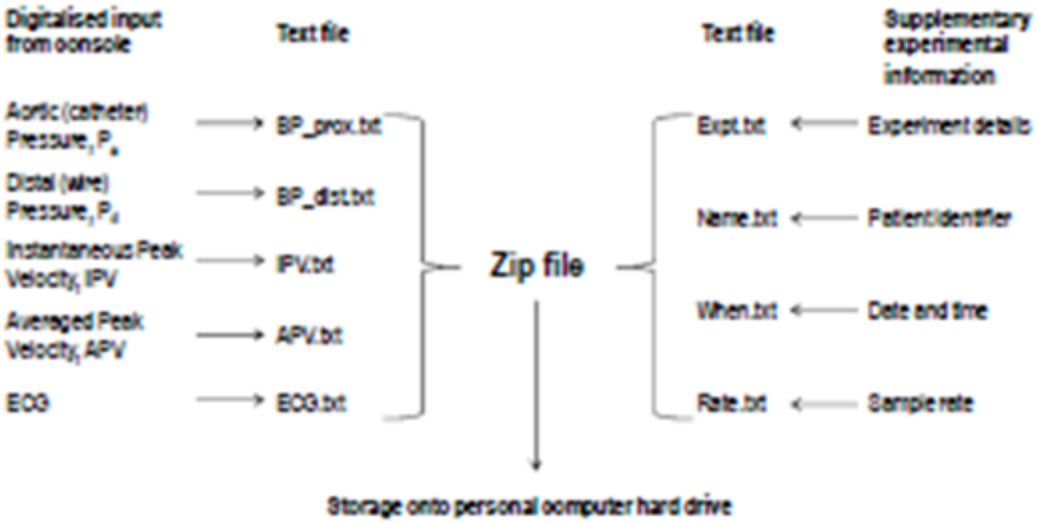



**Figure 2.07: Schematic illustration of the data conversion storage process**

Each variable is given a channel name and then converted into a text file. Each of the text files is then added to a ZIP file together with experimental details, anonymised patient identifier, date, time and sample rate. This ZIP file is then saved to the hard disc.

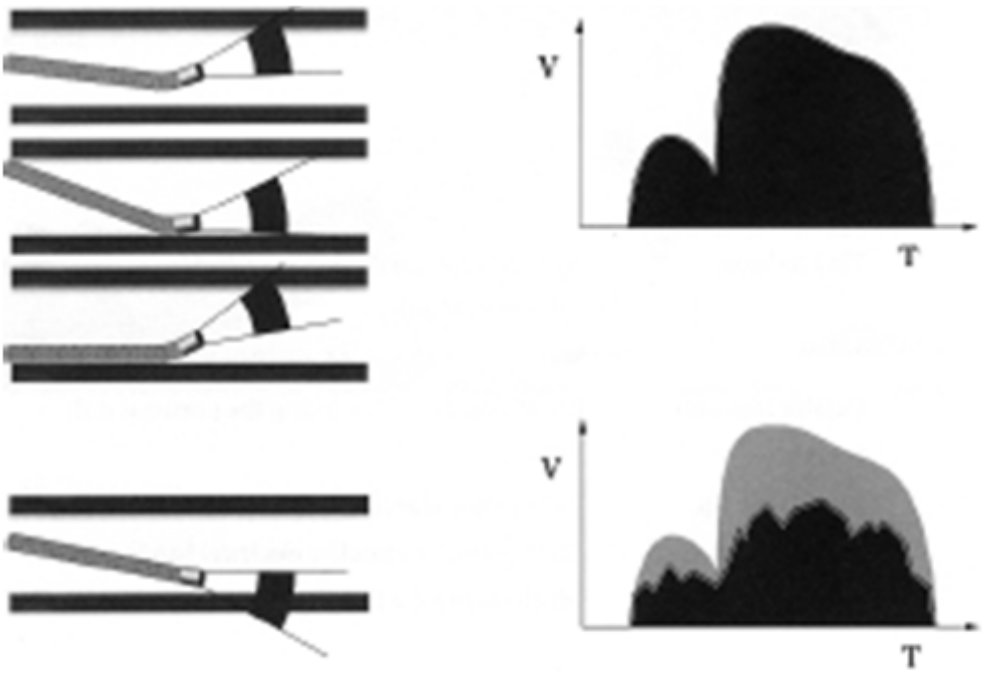



**Figure 2.08 Rotational movements to optimise Doppler signal**

Small rotational movements of the guide wire were made to capture the best flow velocity trace (right panel, upper trace) and avoid sub optimal traces (right panel, lower trace)

# 3.0 The optimal period in the cardiac cycle for the assessment of a coronary stenosis

## 3. 1 Abstract


### 3 1.1 Background

For pressure to be a physiologically and clinically valid surrogate for flow, trans-stenotic pressure must be proportional to flow. In this study we examine phases of the cardiac cycle to identify the most suitable phase for stenosis discrimination.

### 3.1.2 Methods

Pressure and flow velocity was measured in 56 vessels distal to a coronary stenosis at rest. Mean flow velocity, microvascular resistance, trans-stenotic pressure difference, distal to proximal pressure ratio and micro-vascular resistance were calculated over the complete cardiac cycle, and over 50 intervals within diastole. Instantaneous pressure gradient-flow velocity curves were constructed.

### 3.1.4 Results

Pressure gradient flow-velocity curves demonstrated two phases within diastole, which differed with regard to their ability to determine stenosis severity. During the first phase the trans-stenotic pressure gradient lead to an over-estimate of stenosis severity. In contrast, there was a wave-free period occupying 75.8±8.6% of the period between the dicrotic notch and the end of diastole during which pressure loss due to the stenosis had a proportional relationship with flow velocity. The mean pressure difference during the wave-free period varied according to stenosis severity (4.4±4.2mmHg mild vs 13.3±12.2mmHg moderate and 55.7±11.1mmHg severe stenoses, $p<0.001$).

### 3.1.5 Conclusions

A wave-free period can be defined in diastole during which the trans-stenotic pressure gradient is proportional to flow velocity: the necessary condition for pressure-only

assessment of a coronary stenosis. These findings suggest that the requisite intra-coronary conditions for pressure-only stenosis assessment can be achieved without the need for potent vasodilators.

## 3.2 Introduction

Purely pressure-derived indices of coronary stenosis severity, such as fractional flow reserve (FFR) have been reported to improve clinical outcomes when used to guide coronary revascularisation (14-17). Such pressure-only indices infer the effect of the stenosis on coronary blood flow by considering it equivalent to a resistor obeying Ohm's law: pressure drop ($\Delta \boldsymbol{P}$) across a stenosis is proportional to flow ($Q$) if microvascular resistance ($\boldsymbol{R}$) is constant (Equation 1). Using this perhaps overly simplistic analogy (see below) under conditions of relatively constant micro-vascular resistance pressure can be used as a surrogate for flow[4].

*Equation 1*: Ohm's Law: $\Delta \boldsymbol{P} = \boldsymbol{v}\boldsymbol{R}$

When resistance is constant ($\boldsymbol{R}$): $\Delta \boldsymbol{P} \propto \boldsymbol{v}$

### 3.2.1 The capacitive effect of the coronary circulation: implications for the application of Ohm's law to stenosis assessment

If we assume that the flow in the stenosed coronary artery can be described as flow through two resisters in series; the resistance due to the stenosis Rs and the resistance due to the microcirculation Rc. We assume that Rs is constant but that Rc is a function of time because of the constriction of the microcirculatory vessels during systole. Assuming a simple Ohms law relationship between resistance and flow through the two resistances, $\Delta$P=QR, where $\Delta$P is the difference between the upstream and downstream pressure. For simplicity we further assume that the pressure in the venous system is negligible. With these assumptions, the instantaneous flow rate through the coronary artery Q(t) = Pa(t)/(Rs + Rc(t)) where Pa(t) is the time-varying pressure in the aorta. The pressure downstream of the stenosis but upstream of the microcirculation can then be written Pd(t) = Pa(t) - Q(t)Rs.

Substituting for Q(t) from the previous equation we can write (after a little algebraic manipulation) $Pd(t)/Pa(t) = Rc(t)/(Rc(t)+Rs)$.

This shows that the instantaneous ratio of downstream to upstream pressure will vary in time when Rc varies with time. If Rc is constant in time, this expression is simply $Pd(t)/Pa(t) = Rc/(Rc+Rs)$ which indicates that the instantaneous ratio of pressures is constant. Further, if the $Rs << Rc$ the pressure ratio can be approximated as $Pd(t)/Pa(t) = 1 – Rs/Rc$ where the error of the approximation is of order $(Rs/Rc)^2$.

In the FFR method, a vasodilator is injected into the coronary artery to minimise the variation of Rc during the entire cardiac cycle. In the IFR method, a period during diastole is identified when Rc is minimal and effectively constant.

The above analysis is predicated on the assumption that P and Q are related solely through an Ohms law resistance. In general the relationship is more complex because of the distensibility of the artery which introduces a capacitive effect that can be important in the non-steady conditions during the cardiac cycle. A simple way to test for the influence of capacitive effects is to plot $\Delta P$ vs Q or, because we measure velocity, v, which is related to Q through the cross-sectional area of the artery, $\Delta P$ vs v (the $\Delta P$v-loop). At times when the capacitive effects are negligible the $\Delta P$v-loop should have a linear relationship with slope Rs. When capacitive effects are important, the $\Delta P$v-loop will not be linear, depending on the unsteady nature of the flow. Similarly, more detailed fluid dynamic analysis of steady flow through stenosis suggests that the pressure drop across the stenosis can be written in the approximate form $\Delta P = Fv + Sv^2$, where v is the mean velocity, F is a coefficient related to the viscous drag of the fluid and S is a coefficient related to the losses associated with the separation of flow in the stenosis. This behaviour will be seen in the $\Delta P$v-loop as curvilinear

segment of the loop where F and S can be determined by fitting the above quadratic to the data (12).

In order to fulfil the above conditions, FFR uses potent vasodilators to induce the requisite intra-coronary condition of stable microvascular resistance. Instantaneous wave-free ratio (iFR) is a vasodilator-free pressure-only measure of stenosis severity which takes an alternate approach to stabilising microvascular resistance (25). Instead of using the complete cardiac cycle, it is calculated during a specific period in diastole – the wave-free period. During this period intra-coronary flow velocity is significantly higher and microvascular resistance significantly lower than that during the remaining phases of the complete cardiac cycle; this is because the large fluctuation in resistance occurs during systole, and not in diastole (25). iFR has been demonstrated to have a high classification agreement with established pressure derived (FFR), and pressure and flow derived indices (hyperaemic stenosis resistance index) (25, 26) . However, the utility of using the wave-free period over any other period in diastole has not been fully explored. In this study we explore how the hemodynamics of the wave-free period differ from that of the entire cardiac cycle and of the whole of diastole. We determine the hemodynamic characteristics of the wave-free period and their suitability for the pressure-only assessment of coronary stenoses.

## 3.3 Method

### 3.3.1 Study population

This study included 56 vessels (42 patients, 82% male) scheduled for coronary angiography or PCI at Imperial College London NHS Trust, UK and The Royal Brompton and Harefield NHS Trust, UK. In addition to new data, patients were included from part 1 of the ADVISE study (6). The patient demographics are consistent with the broad entry criteria used in recruitment (Table 1). Exclusion criteria were limited to significant valvular pathology, previous coronary artery bypass surgery and weight>200kg. All subjects gave written informed consent in accordance with the protocol approved by the local ethics committee (NRES 09/H0712/102; NCT01118481).

### 3.3.2 Study Protocol

#### 3.3.2.1 Cardiac Catheterization

Cardiac catheterization was undertaken through the femoral approach. After diagnostic angiography, a 0.014inch pressure and Doppler sensor-tipped wire (ComboWire® XT, Volcano Corporation, San Diego, CA) was passed into the target vessel via a guiding catheter. Pressure equalisation was performed at the tip of the catheter prior to its advancement into the distal vessel. 5000iu intravenous heparin was given at the start of the procedure. All patients received 300μg intracoronary GTN.

Pressure and flow velocity recordings were made distal to the target vessel coronary stenosis at rest. Mean flow velocity, resistance and trans-stenotic pressure gradient (aortic pressure (Pa) - distal intra-coronary pressure (Pd)) was calculated over the complete cardiac cycle, the complete diastolic period and over 50 different sampling periods within diastole (from the onset of the backward expansion wave (onset of mechanical diastole) to 5ms from

the end of diastole) to identify the optimal window for the pressure only assessment of a stenosis. Throughout the manuscript we will refer to these different sampling periods, which vary at their onset but all have the same end point (5ms from the end of diastole). These sampling periods are numbered 1-50, with consecutive sampling periods being 2% shorter than the preceding sampling period as shown (Figure 3.01). The instantaneous pressure gradient to flow velocity relationship over diastole was also plotted. FFR was calculated as previously described during stable hyperaemia with 140mcg/kg/min adenosine infused via a large central vein (13).

#### 3.3.2.2 Hemodynamic Recordings

The ECG, pressures and flow velocity signals were directly extracted from the digital archive of the device console (ComboMap, Volcano Corporation, San Diego, USA). At the end of each recording the pressure sensor was withdrawn to the catheter tip to ensure there was no pressure drift. Where drift was identified the measurements were repeated. Data were analyzed off-line, using a custom software package designed with Matlab (Mathworks, Inc, Natick, Mass).

#### 3.3.2.3 Identification of the wave-free period

Wave intensity analysis was performed according to the methodology described previously (Davies et al. Circulation 2006) to identify the wave-free period during each cardiac cycle (7).

The onset and end of the wave-free period was measured for each vessel from both the dicrotic notch as described previously and from the onset of mechanical diastole. Mechanical diastole (defined by the onset of the backward explansion wave) was selected as the start of mechanical diastole. The proportion of the cardiac cycle between the dicrotic notch and the end of diastole free of wave activity was termed the wave-free period (as previously described) (25).

### 3.3.4 Data Analysis

Processing of digital data (pressure, flow velocity, ECG) for the calculation of the various indices and intervals discussed (WIA, selection of wave-free diastolic interval, fractional flow reserve, hyperaemic stenosis resistance, microvascular resistance and the pressure ratio duing the wave-free period) was performed at a workstation using Matlab (Mathworks, Inc, Natick, Mass). The indices were calculated using fully automated algorithms. Statistical analysis was performed using STATA (version 11, StataCorp, Texas, USA). The different sampling periods during diastole were compared with a paired Students t-test. Mean values calculated over at least 5 cardiac cycles are expressed as mean ± standard deviation of the mean unless otherwise stated.

### Definition of microvascular resistance:

Basal microvascular resistance = $\frac{Pd_b}{v_b}$

Trans-stenotic pressure gradient = $Pa_b - Pd_b$

$Pd_b$ = intracoronary pressure distal to stenosis at baseline, $v_b$ = mean flow velocity distal to stenosis at baseline. $Pa_b$ = aortic pressure at baseline.

## 3.4 Results

### 3.4.1 Instantaneous pressure gradient and flow velocity during diastole

The trans-stenotic pressure gradient changed significantly during diastole. Peak trans-stenotic gradient was 11.2±15.2mmHg compared to a minimal value of 2.2±8.6mmHg ($p<0.001$, Figure 3.02 left panel). Flow velocity changed accordingly, peaking at 30.9±14.0cm/s with a minimal value of 12.5±7.0cm/s ($p<0.001$, Figure 3.02, right panel). Highest flow and lowest microvascular resistance values were obtained at the onset of the wave-free period.

Figure 3.03, demonstrates the relationship between the trans-stenotic pressure gradient and flow velocity at rest averaged over the entire patient population. There are two phases to this relationship (Figure 3b). During the initial phase both the pressure gradient and flow velocity increase (black arrow). This corresponds to a period of diastole when there is acceleration of blood flow secondary to active relaxation of the myocardium. During this time wave-intensity analysis demonstrates that acceleration of blood flow is due to decompression arising from the coronary microcirculation. As a result intracoronary pressure during this phase does not simply reflect the hemodynamic effect of the stenosis but reflects the composite influence of the active effect of myocardial relaxation and the fluid dynamics across the stenosis.

The second phase occurs just after flow velocity has peaked. This coincides with the end of the myocardial originating decompression wave, which is coincident with the end of active relaxation of the myocardium. For the remainder of diastole blood flow is seen to be passive and the trans-stenotic pressure gradient and flow velocity fall together (red arrow). In this window of time, there is an almost linear relationship between trans-stenotic pressure gradient and flow velocity. During this period, we demonstrate that both wave-intensity analysis and the pressure-gradient/flow-velocity loops demonstrate the same findings: that

intra-coronary hemodynamics is free of the active accelerative forces of early diastole. Therefore, the confounding effect of myocardial activity on intra-coronary pressure is minimised and intracoronary hemodynamics are most reflective of the severity of the upstream coronary stenosis. When the wave-containing the early phase of diastole is excluded, the relationship between pressure-gradient (ΔP) and flow velocity (v) in the remaining (wave-free) period can be seen to fit the recognised curvilinear relationship, $\Delta P=Fv+Sv^2$, where F is frictional and S is the separation coefficient of the stenosis (12) (Figure 3.03).

### 3.4.2 Duration of the diastolic wave-free period

The diastolic wave-free period commenced at the end of the backward expansion wave in all patients, starting 484.2±61.4 ms after the onset of the cardiac cycle (as defined as the onset of the backward compression wave) and ending at the end of diastole. Its mean duration was 424.6±123.1ms. The duration of the wave-free period was strongly determined by the length of the RR interval ($r^2$=0.845). Expressing the wave-free period as a fraction of diastole (thus accounting for the length of the RR interval), this proportion was more stable, occupying 75.8±8.6% of the period between the dicrotic notch and the end of the wave-free period. The *proportion* of diastole taken by the wave-free period was independent of heart rate ($r^2$=0.03), mean blood pressure ($r^2$=0.04) and stenosis severity ($r^2$=0.01).

### 3.4.3 Intra-coronary resistance during the wave-free period

Across all patients mean micovascular resistance during the wave-free period was 378.4 ± 161.6 mmHg.s/cm which was significantly lower than during the entire diastolic period, 467.1 ± 194.1mmHg.s/cm ($p<0.001$), or the mean microvascuar resistance during the whole cardiac cycle, 509.7 ± 197 mmHg.s/cm ($p<0.001$) (Figure 3.04).

Analysis of the different sampling periods over diastole (Figure 3.04b) demonstrates significant variation during diastole of microvascular resistance. Microvascular resistance during the entire diastolic period had significantly more variability than that during the wave-free period (variance 356.7 $(mmHg.s/m)^2$ diastole vs. 20.7 $(mmHg.s/m)^2$ wave-free period, $p<0.001$). The wave-free period provided the unique combination of low magnitude of microvascular resistance with low variance of microvascular resistance (Figure 3.04B).

### 3.4.4 Identification of the optimal sampling window

Even within the diastolic wave-free period there was some variation in microvascular resistance. For example the last 15% of diastole had significantly higher microvascular resistance than the first 15% of the diastolic wave-free period. Indeed, instantaneous analysis of microvascular resistance over the cardiac cycle demonstrates that there is an increase in microvascular resistance towards the end of diastole as left ventricular end diastolic pressure increases (Figure 3.05). When the last 15% of diastole (associated with this increase in microvascular resistance) is excluded microvascular resistance during the wave-free period can be reduced by a further 7.1±6.6% (378.4±161.6mmHg.s/m vs 353±148.0mmHg.s/m, $p<0.001$). Moreover, exclusion of the last 15% of diastole leads to significant reduction in the variance of micro-vascular resistance (20.74mmHg.s/m vs 3.15mmHg.s/m, $p<0.001$) during the wave-free period (Figure 3.06).

### 3.4.5 Haemodynamics of the wave-free period vary with stenosis severity

When the stenoses are divided according to hemodynamic severity by FFR it can be seen that the proportional relationship between pressure gradient and flow velocity during the diastolic wave-free period remains (Figure 3.07). Furthermore, almost all the data points measured fall on the linear aspect of the curvilinear relationship, with a slope that varies in proportion to the severity of the lesion, with mild, moderate and severe lesions producing significantly different slopes. As a result the pressure difference during the wave-free period

of the three categories of mild, moderate and severe lesions is significantly different during baseline conditions (mean pressure difference: 4.4±4.2mmHg mild vs 13.3±12.2mmHg moderate and 55.7±11.1 mmHg severe stenoses, $p<0.001$).

## 3.5 Discussion

This study has found that during the diastolic wave-free period, microvascular resistance has significantly lower variability and reduced magnitude than either the complete cardiac cycle or over the entire diastolic period. Second, the duration of the wave-free period as a proportion of diastole is consistent across patients with varying hemodynamics and stenosis severity. Third, during this wave-free period the trans-stenotic pressure difference is proportional to underlying flow velocity.

### 3.5.1 Myocardial contraction and relaxation confounds the assessment of coronary stenoses

Coronary blood flow is unique. Unlike other systemic arteries, blood flow in a coronary artery is caused by changes in pressure at both the proximal and distal ends of the vessel (7, 10). This means that the pressure distal to a coronary artery stenosis does not simply reflect the severity of the stenosis but is a composite of residual proximal pressure and pressure arising from the contraction and relaxation of the myocardium surrounding the distal blood vessels (7,10). Trans-stenotic pressure gradients at certain times in the cardiac cycle can therefore reflect the hemodynamic significance of the stenosis itself less well (12). During systole myocardial distal contribution to intra-coronary pressure is known to be important, but our findings suggest that distal contributions also remain significant in early diastole. In early diastole, wave-intensity analysis demonstrates that intra-coronary blood flow is accelerated by a distal-originating decompression wave arising from relaxation of the myocardium (7). The confounding effect of this wave on the accurate assessment of a coronary stenosis is evident on the loop of pressure gradient against flow velocity. Perhaps because of the inherent inertia of blood, during the backward-expansion wave the trans-stenotic pressure gradient rises more quickly than flow. During these periods, the overly simplistic Ohms law relating pressure gradient and flow over-estimates the resistance of the stenosis. Therefore, in order to isolate the hemodynamics of the stenosis from distal myocardial pressure,

assessment should ideally therefore occur in the absence of any accelerative or decelerative forces (12).

These findings are consistent with the findings of Gould in the canine model over 30 years ago in which the pressure gradient flow relationship of coronary stenoses were studied at rest (12). Using pressure-gradient/flow-velocity loops Gould demonstrated the importance of assessing coronary stenosis severity in a period of the cardiac cycle 'free of accelerative and decelerative forces'. We have previously used wave-intensity analysis to also identify a period of passive blood flow within the cardiac cycle, free of accelerative and decelerative forces (7, 25, 26). In our data, applying the traditional pressure-gradient /flow-velocity loops, shows that the period identified by wave- intensity analysis is somewhat similar to the period of passive blood flow identified by Gould (12). Regardless of this similarity, the proportionality of trans-stenotic pressure and flow velocity during the wave-free period confirms the physiological basis of determining stenosis severity during the wave-free period.

These findings have several implications for pressure-only assessment of coronary stenoses and specifically the instantaneous wave-free ratio. First, the relative independence of intra-coronary pressure from the confounding effect of myocardial activity during the wave-free period confirms the diastolic wave-free period as the most suitable window within the cardiac cycle and more specifically within diastole for a pressure-only assessment of the physiological significance of a stenosis. This is because by excluding the period of the cardiac cycle when intra-coronary pressure is influenced by contraction and relaxation of the myocardium, intra-coronary pressure most accurately reflects the effect of the upstream stenosis on coronary blood flow – the Gould principle (12). Second, the proportional relationship of pressure gradient and flow velocity during the wave-free period permits pressure alone to be used to make inferences about underlying flow-velocity and this varies according to stenosis severity. This proportional relationship is not present throughout the complete diastolic period. On this physiological basis, pressure alone cannot be used as a

surrogate for flow during the whole diastolic period under baseline conditions. Third, the stability of the wave-free period demonstrates why isolation of this period can be reliably performed using the pressure waveform alone. Pioneers in this field that have previously isolated this period have required manual post-hoc analysis of the pressure and flow data for its accurate isolation (12, 27, 28). This can be challenging outside expert hands and has therefore limited the clinical adoption of indices using this period (28). Automated isolation of the wave-free period, using pressure alone, circumvents many of these limitations because it can be done without manual selection in real time during cardiac catheterisation.

### 3.5.2 Optimising the signal-to-noise ratio when assessing coronary stenoses

Evaluating biological signals involves preferentially emphasising signal and de-emphasising noise. For pressure-only physiological assessment of coronary stenosis, the signal is the drop in pressure across the lesion caused by flow across it. The noise is the disturbances in pressure arising distally because the myocardium compresses and decompresses the microcirculation.

If measurements are to be made throughout the cardiac cycle, then noise will always be included, but the *signal can be increased* by pharmacologically increasing flow, as has been well documented with FFR.

If precise automated selection is available, however, a segment of the cardiac cycle can be secured in which *noise is naturally minimised* and simultaneously *signal naturally enhanced*. Indeed we demonstrate that completely automated real-time phasic analysis of the cardiac cycle can isolate the most informative data regarding the stenosis (during the diastolic wave-free period when intra-coronary flow is intrinsically at its highest) and set aside the least informative (systole and early diastole) (12, 25, 26). As a result the period of the cardiac cycle most relevant to the hemodynamics of the coronary stenosis can be isolated – easily, in real time and without the need to administer pharmacological agents to increase flow. This elimination of waves and natural increase in flow velocity is the physiological basis of iFR in

signal-to-noise terms. The computational effort of automatically calculating this time window, in effect, replaces the clinical effort of applying adenosine. However, by obviating the need for vasodilators this approach circumvents a key limitation of pharmacological approaches to signal optimisation – a variable response to the drug between patients. Indeed, by drawing on intrinsic physiology, the wave-free period provides a more consistent reduction in microvascular resistance and increase in flow velocity than that possible during adenosine mediated FFR (26).

### 3.5.3 Clinical Implications

The instantaneous wave-free ratio can classify patients similarly to FFR, as seen in the ADVISE study and ADVISE registry (25, 29). However, there has been some speculation regarding the physiological basis of the index and the significance of isolating the wave-free period (30, 31, 32). The detailed analysis of diastole in this study differentiates the wave free period from the rest of diastole and from systole. It delineates why the wave-free period is physiologically the most suitable period within diastole for the assessment of a coronary stenosis. Indeed, incorrect selection of the time, can provide unsatisfactory results as has been highlighted (30, 32) and subsequently corrected (33).

While newer indices of the severity of coronary stenosis based on basal measurements such as iFR offer many advantages over indices based on drug-induced hyperaemic conditions such as FFR, they have not been tested as extensively clinically. Until the clinical tests are completed, it could be argued that similar methods could be applied to hyperaemia-based measurement, i.e. identifying periods during the cardiac cycle when the microvascular resistance is naturally minimised, could result in improved measurements of FFR that are less sensitive to variations in the patient response to vasodilatory drugs.

## 3.6 Study limitations

The number of patients is not large compared to studies that have only addressed pressure or have not addressed timing within the cardiac cycle. The proportion of diastole of the wave-free period may vary slightly. However, this study recruited a wide range of cardiac patients and the low standard deviation of the diastolic proportion suggests that the diastolic window identified should be applicable to the general patient population. Additionally, this is the largest study to date exploring pressure gradient – flow velocity curves and their relation to wave-intensity in humans.

**Conclusion**

The diastolic wave-free period is a distinct period in diastole that uniquely provides the requisite intra-coronary conditions for the pressure only assessment of a coronary stenosis. Its automated detection isolates the fluid dynamics of the stenosis in real time providing a physiological alternative to the traditional pharmacological approach to lesion assessment.

Table 3.1:

| | | Stenoses, %(n) |
|---|---|---|
| **Male** | | 83.9(47) |
| **Age** | | 66.2±9.2 |
| **Risk Factors** | | |
| | Smoker | 32.1(18) |
| | Diabetic | 26.8(15) |
| | Hypertension | 39.3(22) |
| | Family History | 25(14) |
| **Territory** | | |
| | LAD | 55.4(31) |
| | Cx | 25(14) |
| | RCA | 19.6(11) |

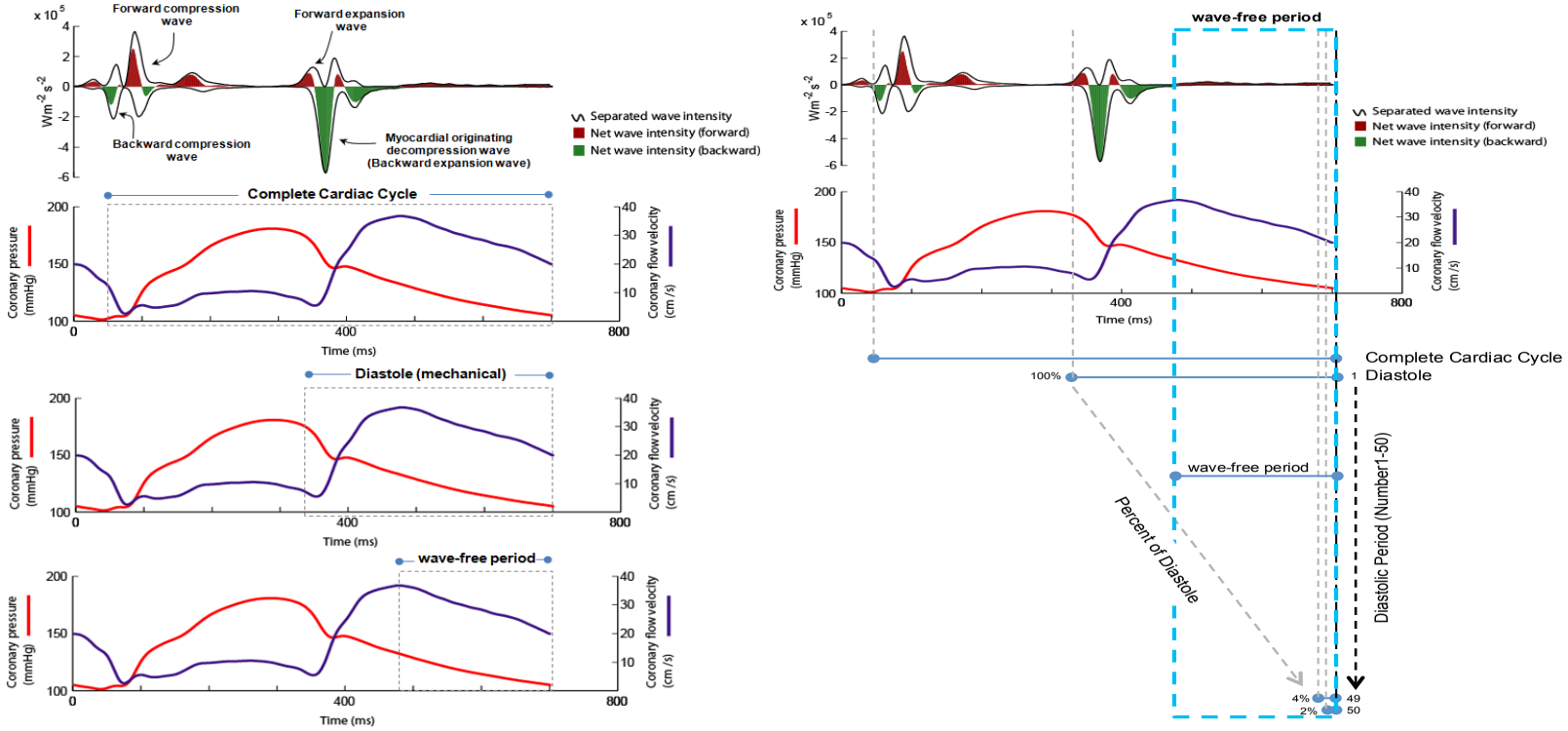



**Figure 3.01: The wave-free period as identified by wave-intensity analysis and its corresponding period on the pressure waveform.**

It can be seen that wave intensity analysis demonstrates two phases within diastole. The first includes the microcirculatory originating decompression wave (or backward expansion wave, BEW) which causes acceleration of blood into the coronary. At the end of this wave, there is a period free of wave activity – the diastolic wave-free period. Throughout the manuscript we compare different sample periods, which vary at their onset but all have the same end point. These sample periods are number 1-50, with consecutive periods being 2% shorter than the preceding period as shown (right panel). (red lines = distal vessel pressure, blue lines = distal vessel flow velocity)

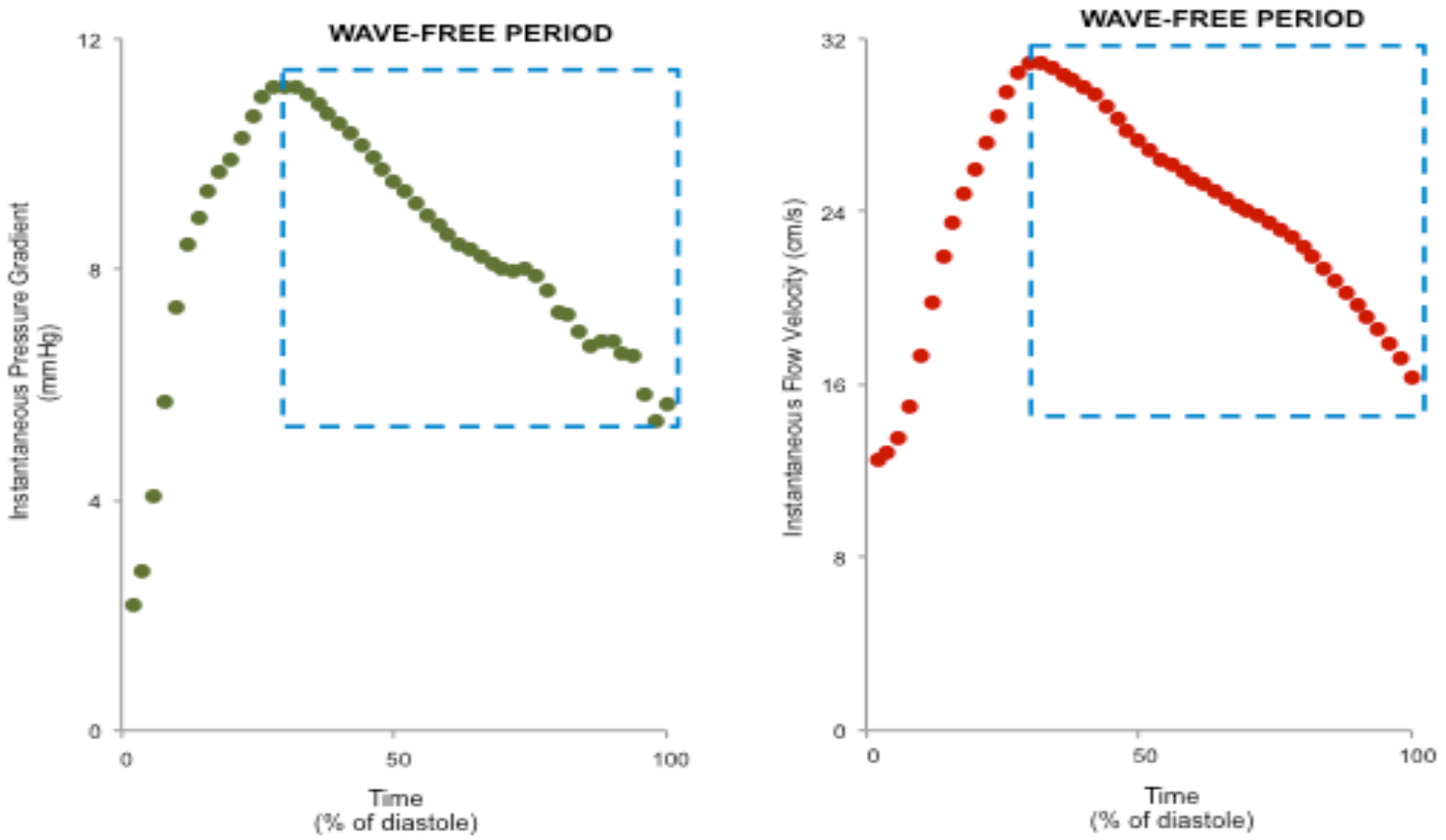



**Figure 3.02: Instantaneous trans-stenotic pressure gradient and flow velocity during diastole**

Both trans-stenotic pressure gradient and flow velocity vary significantly during diastole; the lowest values occurring at the onset of diastole and the largest values at the onset of the wave-free period (data averaged from 56 patients).

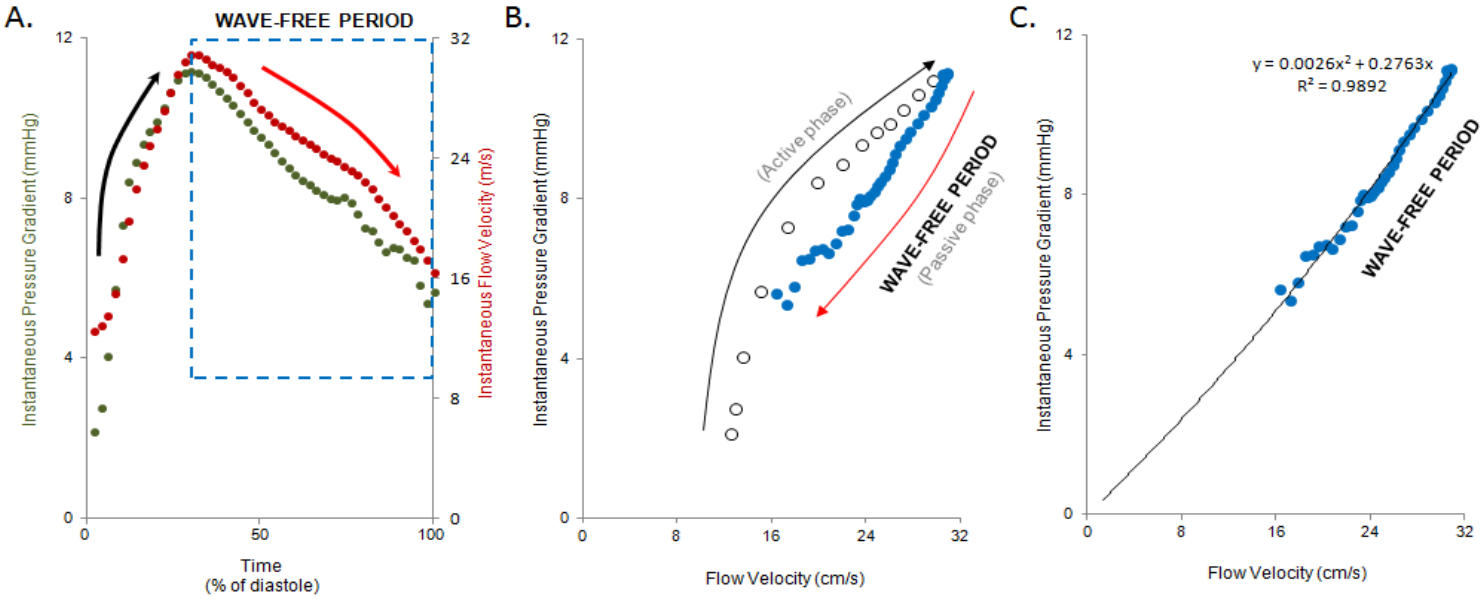



**Figure 3.03: Instantaneous trans-stenotic pressure gradient - flow velocity relationship**

There are two phases of the trans-stenotic pressure gradient flow velocity relationship during diastole. In the first phase (black arrow) trans-stenotic pressure rises faster than flow velocity, as a result it over estimates the underlying flow conditions in the coronary (A&B). The second phase starts as the trans-stenotic gradient and flow velocity peak and at the onset of the wave-free period (B). From this point onwards both trans-stenotic pressure gradient and flow velocity decline in a linear fashion which is consistent with stable microvascular resistance. When the first phase of diastole is excluded (due to the confounding effect of the accelerative forces secondary to the microcirculatory decompression wave) it can be seen that the phase of diastole free of accelerative forces is synonymous with the wave-free period (C). Furthermore the pressure gradient and flow velocity relationship during this period fits the traditional quadratic equation $\Delta P=Fv+Sv^2$ (where F is frictional and S is the separation coefficient of the stenosis) (data averaged from 56 patients).

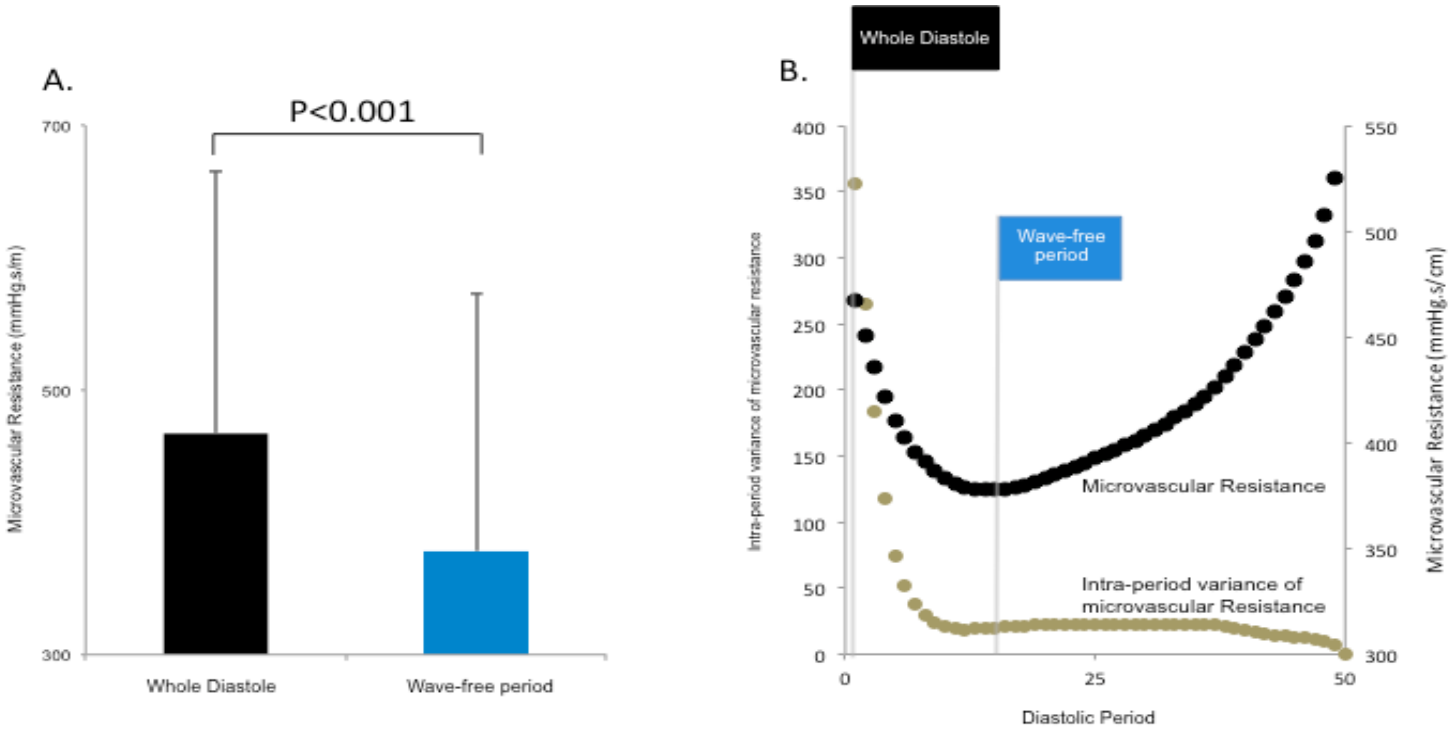



**Figure 3.04: Differentiating the wave-free period from the rest of diastole**

A. Microvascular resistance is significantly lower during the diastole wave-free period when compared with the rest of diastole
B. A plot demonstrating the magnitude of microvascular resistance and intra-beat variance of microvascular resistance for each sample period. The optimal sample period for the calculation of a pressure derived index combines the lowest magnitude of resistance with the lowest intra-beat variability of resistance. This occurred in the sample period including the whole of the last 75% of diastole – the wave-free period. It can be seen that microvascular resistance during the whole of diastole was not only greater in magnitude but also had greater intra-beat variability(data averaged from 56 patients).

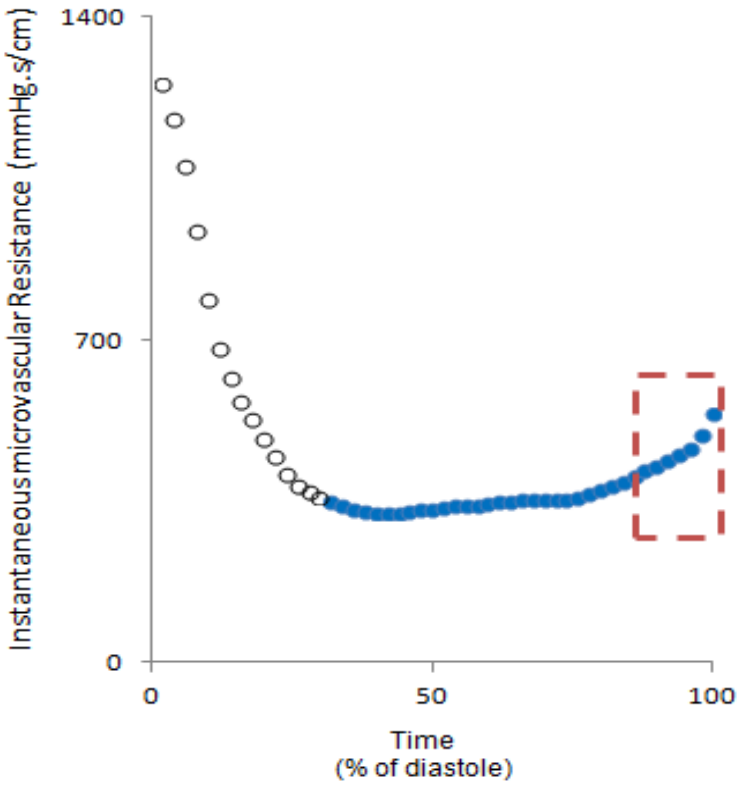



**Figure 3.05: Instantaneous microvascular resistance during diastole and the wave-free period.**

It can be seen that microvascular resistance varies considerably during diastole. It initially falls and then plateaus during the majority of the wave-free period. However, there is a sharp increase in microvascular resistance at the end of diastole, encompassing the last 15% of diastole. Exclusion of this period may make the hemodynamics of the wave-free period more favourable for a pressure derived stenosis assessment (data averaged from 56 patients).

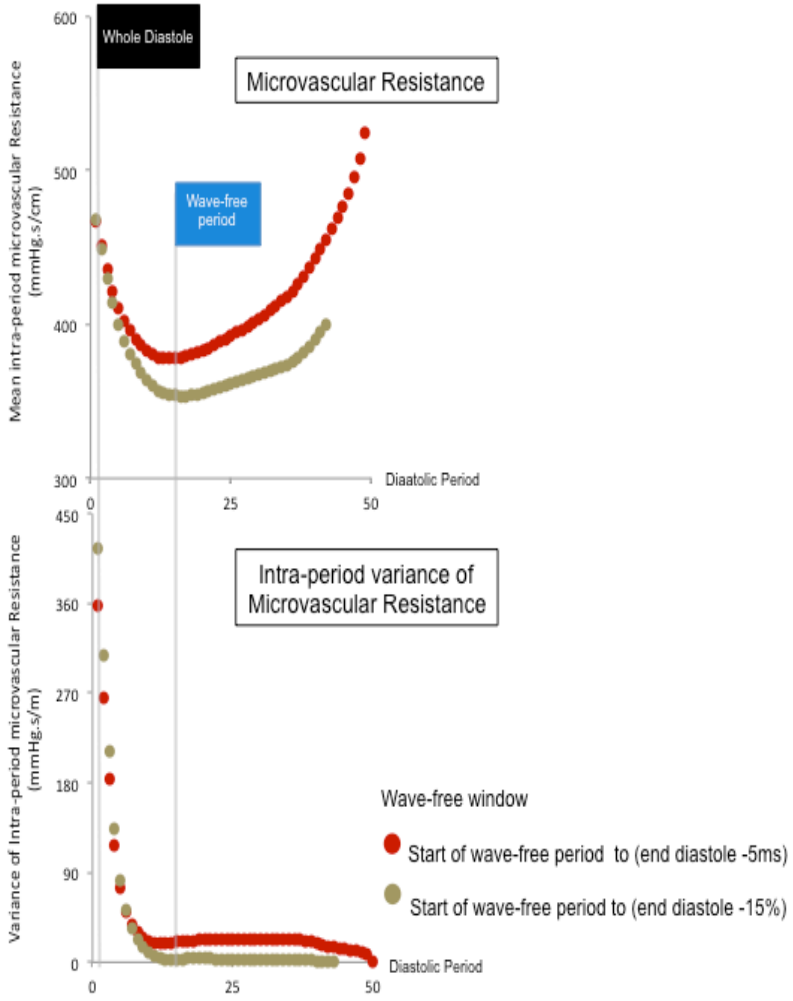



**Figure 3.06: Exclusion of the last 15% of diastole provides lower microvascular resistance and lower variation of resistance**

Upper panel, a plot of microvascular resistance for each sample period using the original end point for the sample periods, 5ms from the end of diastole (red dots) compared to that using an end point that is 15% from the end of diastole (gold dots). It can be seen that the latter provides lower microvascular resistance through exclusion of the increase in microvascular resistance that occurs at the end of diastole as the myocardium prepares for the next cardiac cycle. Lower panel, a plot of the variance of microvascular resistance within each sample period, using the original (minus 5ms end point) and new (minus 15%) end point; it can be seen that the 'minus 15%' end point significantly reduces the variation of resistance within each sample period (data averaged from 56 patients).

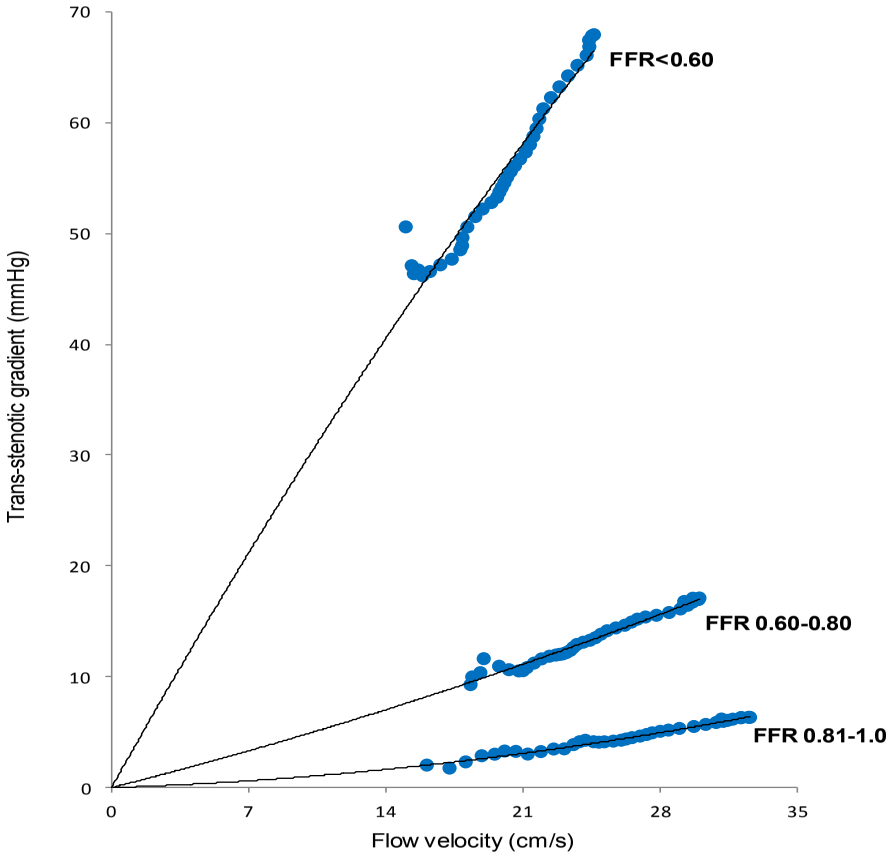



**Figure 3.07: The pressure gradient-flow velocity relationship during the wave-free period according to stenosis severity**

It can be seen that the pressure gradient-flow velocity relationship during the wave-free window (blue dots) consistently occur on the linear aspect of the curvilinear relationship between these two variables and this occurs regardless of stenosis severity. It can be seen that the gradient of this relationship during the wave-free period varies according to the degree of stenosis severity, a feature that permits differentiation of stenosis according to stenosis severity even in the basal state (data from 56 patients).

## 4.0 Development and validation of a new adenosine-independent index of stenosis severity from coronary wave intensity analysis

## Results of the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study

## 4.1 Abstract


### 4.1.2 Background

Assessment of stenosis severity with fractional flow reserve (FFR) requires that coronary microvascular resistance is stable and minimised. This is usually achieved by administration of pharmacological agents such as adenosine. In this 2 part study we determine if there is a time when microvascular resistance is naturally minimised at rest and (2) assess the diagnostic efficiency, compared to FFR, of a new pressure–derived adenosine-free index of stenosis severity over that time.

### 4.1.3 Method

157 stenoses were assessed. In part 1; 39 stenoses, intracoronary pressure and flow-velocity were measured distal to the stenosis; in part 2, 118 stenoses, intracoronary pressure alone was measured. Measurements were made at baseline and under pharmacological vasodilatation with adenosine.

### 4.1.4 Results

Wave intensity analysis identified a wave-free period where microvascular resistance at rest is similar in variability and magnitude (CV:0.08±0.06 and 284±147mmHg.s/m) to those during FFR (CV:0.08±0.06 and 302±315mmHg.s/m, p=NS for both). The resting distal to proximal pressure ratio during this period, the instantaneous wave-Free Ratio (iFR), correlated closely with FFR ($r=0.9$, $p<0.001$) with excellent diagnostic efficiency (receiver operating characteristic area under curve of 93%, at FFR<0.8), specificity, sensitivity, negative and positive predictive values of 91%, 85%, 85% and 91%, respectively.

### 4.1.5 Conclusion

microvascular resistance is naturally constant and minimised during the wave-free period. The instantaneous wave-Free Ratio (iFR) calculated over this period produces a drug-free index of stenosis severity comparable to FFR.

## 4.2 Introduction

Intracoronary physiological indices enable cardiologists to circumvent the limitations of angiography when assessing the hemodynamic impact of stenoses(16, 17). Functional assessment of stenoses in the catheterisation laboratory can be performed by measuring intracoronary flow velocity (coronary flow velocity reserve), pressure (fractional flow reserve, FFR), or both (hyperaemic stenotic resistance)(5, 21). FFR is the most widely used index in clinical practice, being supported by a large body of evidence demonstrating its value in clinical decision-making. When used to guide percutaneous interventions, FFR has been shown to improve clinical outcomes and procedural cost-efficiency (14-17).

The cornerstone of FFR is the linear relationship between pressure and flow under conditions of constant (and minimised) microcirculatory resistance (5). Under such conditions pressure and flow are assumed to be directly proportional, and a fall in pressure across a stenosis reflects a reduction in blood flow to the dependent myocardium. However even after administration of potent pharmacological agents such as adenosine, microvascular resistance is not static, but instead, fluctuates in a phasic pattern (akin to impedance in an alternating current electrical circuit) throughout the cardiac cycle (Figure 4.01). These fluctuations reflect the interaction between the myocardium and microvasculature during systole (high microvascular resistance, compression of microvasculature) and diastole (lower microvascular resistance, decompression of the microvasculature)(8). Accordingly to minimise these effects, FFR is calculated during hyperaemia (maximal flow to the vascular bed) and time-averaged over several cardiac cycles to ensure constant and minimal microvascular resistance.

Whilst time-averaging and the administration of pharmacological vasodilators was a pragmatic solution to achieving appropriate conditions to calculate FFR when computational power was limited, it may now be unnecessary if a time period could be identified from the

resting pressure waveform when microvascular resistance is naturally constant and minimised. Theoretically during such a period in the cardiac cycle intra-coronary pressure and flow would be proportional. Consequently a ratio of trans-stenotic pressures would provide a measure of the severity of a coronary stenosis. Identification of such a period would negate the need for administration of pharmacological agents such as adenosine, saving time, reducing costs and side-effects, and leading to improved adoption in the cardiac catheter laboratory.

In the first part of this study, we identified the existence of a diastolic interval in which microvascular resistance at rest is equivalent to time-averaged microvascular resistance during FFR measurements. We hypothesise that pressure measurements obtained selectively at this specific interval of the cardiac cycle would allow a new pressure derived index of stenosis severity that does not require pharmacological vasodilatation, we term this the instantaneous wave-free ratio (iFR). In the second part of the study, this hypothesis was tested in a larger population by comparing iFR and FFR measurements.

## 4.3 Methods

### 4.3.1 Patients

This multi-centre international, non-randomised study recruited 131 patients (63±10 year, 85% male) scheduled for coronary angiography or PCI at three sites (Imperial College Healthcare NHS trust, London, UK, Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain, and Royal Brompton & Harefield NHS trust, London, UK). The patient demographics are consistent with the broad entry criteria used in recruitment (Table 4.1). Exclusion criteria were limited to significant valvular pathology, previous coronary artery bypass surgery, contra-indication to adenosine administration (e.g. asthma, chronic obstructive pulmonary disease (COPD), heart rate<50 beats per minute and systolic blood pressure <90mmHg), elevated troponin and weight>200kg. All subjects gave written informed consent in accordance with the protocol approved by the local ethics committee (NRES ref: 09/H0712/102; NCT01118481).

### 4.3.2 Study Protocol

#### 4.3.2.1 Cardiac Catheterization

In this 2 part study the patients were divided into two groups providing a total of 157 stenoses (Group 1 39 stenoses and Group 2 118 stenoses) (Figure 4.02).

Part 1 (39 stenoses): Cardiac catheterization was undertaken through the femoral approach. After diagnostic angiography, a 0.014inch pressure and Doppler sensor-tipped wire (ComboWire® XT, Volcano Corporation, San Diego, CA) was passed into the target vessel via a guiding catheter. Pressure equalisation was performed at the tip of the catheter prior to its advancement distal to the stenosis. Pressure and flow velocity recordings were then made at baseline. Adenosine was then infused (140 micrograms/kg/min) via a femoral venous sheath and pressure and flow velocity measurements repeated under conditions of maximal pharmacological vasodilatation.

Part 2 (118 stenoses): Cardiac catheterisation was undertaken via either femoral or radial approach. Adenosine doses of 140 micrograms/mg/min (via femoral vein) or up to 120 micrograms (intracoronary) were used to induce vasodilatation. After diagnostic angiography, a 0.014inch pressure sensor-tipped wire (PrimeWire, Volcano Corp, or Radi PressureWire, St Jude Medical, Minnesota, USA) was equalised and then advanced distal. Pressure measurements were made at baseline and under maximal pharmacological vasodilatation.

In both groups 5000iu intravenous heparin was given at the start of the procedure and 300 micrograms of intracoronary nitrates were routinely given prior to haemodynamic measurements.

#### 4.3.2.2 Haemodynamic Recordings

When the ComboWire or PrimeWire pressure wire was used, the ECG, pressures and flow velocity signals were directly extracted from the digital archive of the device console (ComboMap®). When the Radi PressureWire system was used, continuous digital acquisition and storage of the ECG, aortic, and intracoronary pressures were performed using a 12-bit resolution analog-to-digital converter (DI-200 PGL, DataQ Instruments, Akron, Ohio) controlled by dedicated software (WinDaq 200, DataQ Instruments) in a personal computer. The sampling rate was 114 Hz per channel.

At the end of each recording the pressure sensor was returned to the catheter tip to ensure there was no pressure drift. Where drift was identified the measurements were repeated. Data were analyzed off-line, using a custom software package designed with Matlab (Mathworks, Inc, Natick, Mass).

#### 4.3.2.3 Identification of period of constant and minimal microvascular resistance

Changes in coronary haemodynamics over the cardiac cycle were assessed by calculating instantaneous resistance and by applying wave intensity analysis. An index of resistance was calculated as the ratio between pressure and flow velocity. Wave intensity analysis was performed according to the methodology described previously (7) to identify wave-free periods (Figure 4.01, upper panel). During this wave-free period the onset of minimal microvascular resistance was identified, and its value calculated for each patient. It was not possible to calculate microvascular resistance in 2 cases due to poor tracking of the velocity envelope during diastole. Mean microvascular resistance and its coefficient of variation were then calculated over a minimum of three beats.

In order to minimize any selection bias and truly assess the diagnostic efficiency of our index, we designed this study to include all the cardiac patients that FFR is used in routinely in clinical practice (including single vessel, multi vessel, and diabetic patients). We used both intra-coronary and intra-venous adenosine and pressure wires from RADI and Volcano. FFR was measured in the standard way (5, 15-17), and used to guide the clinical case. However, the invasive measurement team was blind to the iFR value, which was calculated offline using a fully automated Matlab algorithm (Mathworks, Inc, Natick, Mass).

### 4.3.4 Calculation of the instantaneous wave-free ratio (iFR)

Wave intensity analysis was used to identify the backward-travelling waves (Equation 3.1). The onset of diastole was identified from the dicrotic notch, and the *diastolic wave-free window* was calculated from wave-intenisty analysis (7).

Instantaneous wave-free ratio (iFR) was calculated as the mean pressure distal to the stenosis during the diastolic wave-free period ($\overline{Pd}_{wave-free\ period}$) divided by the mean aortic pressure ($\overline{Pa}_{wave-free\ period}$) during the *diastolic wave-free period* (Equation 3.2). All

analyses were performed in a fully automated manner negating the need for manual selection of data time points.

*Equation 3.1*

Backward-travelling waves = $WI_{-} = -\frac{1}{4\rho c}\left(\frac{dP}{dt} - \rho c\frac{dU}{dt}\right)^2$

Start of wave-free period = time ($WI_{-(\text{diastole})} > 0$)

End of wave-free period = end of diastole-5ms

Wave-free period = start of wave-free period to end of wave-free period

*Equation 3.2*

*instantaneous wave-free ratio(iFR)* $= \frac{\overline{Pd}_{wave-free\ period}}{\overline{Pa}_{wave-free\ period}}$

Where, $\rho$ is the density of blood (taken as 1050kgm$^{-3}$), $c$ is the wave speed calculated using the single-point equation (7,11), $dP$ is the incremental change in coronary artery pressure, and $dU$ the incremental change in blood viscosity.

#### 4.3.5 Data Analysis

Processing of digital data (pressure, flow velocity, EKG) for the calculation of the various indices and intervals discussed (WIA, microvascular resistance, FFR, selection of wave-free diastolic interval, iFR) was performed at a workstation using Matlab (Mathworks, Inc, Natick, Mass), Statistical analysis was performed using STATA (version 11)(StataCorp, Texas, USA). A paired Student's t-test was used to compare within patients. The proportional change in microvascular resistance during the cardiac cycle was referenced to baseline mean microvascular resistance. The relationship between FFR and iFR for the entire patient population and all subsequent sub-group analyses was quantified with a Pearson's product moment correlation coefficient. Receiver operator characteristics curves (ROC) were used

to estimate diagnostic efficiency of iFR and to identify the most appropriate cut off value when compared to the FFR treatment threshold of 0.8. Mean values are expressed as mean±standard deviation of the mean. A repeated measures analysis was performed by comparing the iFR from the first half of the recording with the value from the second half of the recording using a paired Students t-test. The relationship of heart rate and blood pressure to iFR was quantified with a Pearson's product moment correlation coefficient. A p-value of $<0.05$ was deemed significant.

## 4.4 Results

### 4.4.1 Identification of period of stable microvascular resistance in the cardiac cycle

In each of the 39 stenoses included in group 1 intracoronary pressure, flow velocity and microvascular resistance was analysed prior to and during the administration of adenosine. Wave intensity analysis allowed identification of a wave-free period after the backward decompression wave when wave intensity and microcirculatory originating pressure return to zero (Figure 4.01, panel 1&2). The mean duration of this period was 354±78ms (75±6% of diastole), starting 112±26ms after the onset of diastole. Intra-coronary microvascular resistance remained minimised and stable throughout this wave-free period (Figure 4.01, panel 3).

### 4.4.2 Microvascular resistance throughout the cardiac cycle at rest and with pharmacological vasodilatation

Adenosine administration caused the mean intracoronary microvascular resistance over the entire cardiac cycle to fall by 51% (613±310 mmHg s/m vs 302±315 mmHg s/m, $p<0.001$). This was predominantly due to a 75% reduction in the systolic contribution to microvascular resistance (Δ systolic resistance 461mmHg s/m, $p<0.001$, Figure 4.03).

Both magnitude and variability of intracoronary microvascular resistance identified during the wave-free period was similar to that achieved over the entire cardiac cycle during pharmacological vasodilatation. The magnitude of microvascular resistance during the wave-free period was 284±147 mmHg s/m compared with 302±315 mmHg s/m during pharmacological vasodilatation ($p=0.70$, Figure 4.04, left panel (A)). The coefficient of variation of microvascular resistance during the wave-free period was 0.08±0.06 compared with 0.08±0.06 during pharmacological vasodilatation ($p=0.96$, Figure 4.04, right panel (B)).

### 4.4.3 Reproducibility and Diagnostic characteristics of iFR

iFR was calculated for each stenosis using the wave-free time window as defined above and this was compared with FFR. iFR was found to be closely correlated to FFR(r=0.90, y=1.0x+0.03, Figure 4.05). Using the established FFR cut-off threshold of 0.8 to define a positive result, a receiver operator characteristic curve was used to identify the optimal iFR cut-off (0.83) with the greatest diagnostic efficiency. The receiver operating characteristic area under curve was 93% (Figure 4.06, left panel). The false negative and false positive data for iFR is demonstrated in Figure 4.07 (right panel). This demonstrates that the positive predictive value of iFR was 91%; the negative predictive value was 85% with sensitivity, specificity of 85%, and 91% respectively.

This relationship persisted throughout our sub-group analysis, with similar levels of correlation independent of type of pressure wire, route of pharmacological vasodilator administration, single or multi vessel disease (Table 3.2), or heart rate ([range 46-120/min] $r^2$=0.016), systolic ($r^2$=0.001) and diastolic pressure ($r^2$=0.005). Furthermore the close correlation of iFR to FFR remained with left coronary (r=0.90) and right coronary arteries (r=0.89) with a diagnostic accuracy in the right coronary of 91%, consistent with the entire cohort (Figure 4.07).

The Bland Altman analysis also demonstrates good agreement between measures with a mean difference between FFR and iFR of -0.05±0.19. A repeated measures analysis of iFR was made in 149 stenoses, which demonstrated a close relationship between the two successive measurements (r=0.996, p<0.001, Figure 4.07) with a mean difference between iFR measurements of -0.0005±0.002 (p=0.78).

## 4. 5 Discussion

The main conclusions of this study are: 1) when selectively measured within a defined diastolic wave-free period, resting coronary microvascular resistance values are similar to those observed during adenosine mediated FFR; 2) the ratio of distal to proximal pressures during this wave-free period produces an index (instantaneous wave-free ratio, iFR) that correlates closely with FFR.

### 4.5.1 The importance of constant intracoronary microvascular resistance in the functional assessment of stenoses

Coronary blood flow is unique in that it is determined not only by variations in pressure arising proximally (as in the aorta and other systemic arteries) but also concurrent variations arising distally in the microcirculation (Figure 4.08) (7). It is considered inaccurate to assess the severity of a coronary stenosis by simply measuring the fall in mean or peak pressure across a stenosis, under basal conditions over the entire cardiac cycle, because distal coronary pressure is not simply a residuum of the pressure transmitted from the aortic end of the vessel (Figure 4.08. upper panel), but is also due to a pressure component arising from active compression and decompression of the coronary microcirculation (Figure 4.08, lower panel). These distal influences cause dramatic variations in the instantaneous ratio between pressure and flow (a simple index of intracoronary microvascular resistance). Wave intensity analysis can be used to distinguish distal microcirculatory-originating influences from proximally-originating influences transmitted from the aorta (7). The most extreme examples of such variations are the rapid rise of pressure in early systole and the rapid fall in early diastole. In early systole, pressure rises rapidly but flow does not, and so the index of intracoronary microvascular resistance rises rapidly. The rapid rise in pressure without corresponding rise in flow is caused by near perfect matching of compression waves arising from the aorta and coronary microcirculation during most of systole (7) (Figure 4.01, top panel). In early diastole, the converse happens; pressure falls while flow accelerates, and so

the index of intracoronary microvascular resistance falls rapidly. This occurs because the microvasculature is suddenly decompressed, causing blood to be sucked in to the coronary microcirculation (Figure 4.01). After this brief, but rapid, phase of pressure decline, pressure and flow then passively decline together slowly. During this gradual decline phase, which extends for the majority of diastole, the index of coronary microvascular resistance is close to minimal and is stable because there is no further wave activity arising from either end of the coronary artery.

Pressure-derived flow indices of coronary stenosis severity such as FFR depend on the proportional relationship of pressure to flow which occurs when microvascular resistance is stable (5); this is only the case for part of the cardiac cycle. Pioneering scientists seeking clinically-applicable methods developed highly refined approaches to circumvent the computational limitations of the day by administering pharmacological agents such as adenosine (5). As we demonstrate these potent vasodilator agents reduce the dramatic variation in microvascular resistance predominantly by reducing the systolic portion of resistance (Figure 4.03 & 4.05), to obtain a stable and minimised microvascular resistance value.

Recent advances in real-time processing now permit automatic selection of the diastolic wave-free period, using measurements of pressure alone, that provides this stable and minimal resistance value without having to administer vasodilator agents. During this diastolic wave-free period, coronary flow is predominantly determined by the passive pressure gradient between the proximal and distal ends of the vessel, analogous to water flowing down a pipe. This natural state of stable and minimised microvascular resistance occurs spontaneously in every cardiac cycle, creating an opportunity to calculate a pressure-derived index without the need for pharmacological intervention.

### 4.5.2 Identification of the wave-free diastolic window

We identified in all patients a period in diastole when microvascular resistance is stable. Across all individual patients the start of this window was 112±26 ms after the onset of diastole (25±6% into diastole) and the end was the end of diastole. For automatic computation, we consider it practical to use an algorithmic definition of the time window that begins 25% of the way into diastole (after the early unwanted variations) and ends 5 ms before the end of diastole, allowing 75% of diastole during which pressure measurements can be made.

**4.5.3 iFR as a tool for instant diagnosis – the challenge of minor uncertainty of FFR**

Using an all-comers selection criteria similar to the FAME study (16), iFR was found to agree closely with FFR with a diagnostic efficiency (AUC) of 93%. This was seen consistently across all subgroups analysed (multi-vessel, single vessel, right and left coronary arteries) and independent of the method of assessment (intracoronary vs intravenous adenosine or RADI vs Volcano pressure wire) (Table 1).

The variability in FFR is small (34) however, as with any biological measure, it is known to vary slightly from one measurement to the next and therefore no technique can correlate perfectly with it. We demonstrate that the variability in iFR is also small. We speculate that his occurs for 2 main reasons. First, spontaneous beat-to-beat fluctuations are most exaggerated during systole (included in FFR, but excluded by definition in iFR). Second, when ectopic or other unwanted disturbances occur, FFR relies on averaging multiple beats to 'dilute' their effects, while iFR matches proximal and distal pressures beat-by-beat basis by performing a paired comparison between each "mother" aortic diastolic pressure component and its own corresponding "daughter" distal diastolic pressure component, resulting in more stable values even during arrhythmia (Figure 4.10). Categorisation using iFR was found to agree with categorisation using FFR in 88% of cases treating FFR as a perfect gold standard.

### 4.5.4 Clinical Implications of iFR

Fractional flow reserve has been revolutionary in implementing intracoronary physiology in clinical practice. Its success is a reflection of the simplicity of the technique and to accumulation of clinical evidence demonstrating the safety of adopting a FFR guided approach to revascularisation (14-17). FFR is currently recommended as a surrogate of ischemia detection tests in the catheterisation laboratory in clinical practice guidelines(31) and, compared with angiography guidance, improves patient outcomes, including mortality, whilst decreasing procedural time and costs when used in PCI (15,16).

In spite of this, the use of FFR is far from universal, being performed in only 6% of PCI procedures in the USA (36). The need to give adenosine has been highlighted as one of the reasons for this poor adoption rate (36). There are several reasons that may explain the reluctance of physicians to use adenosine. First, in addition to costs, the clinical effort of administering adenosine is not trivial, and so it has to be actively chosen on each occasion. Second, some patients have contraindications such as asthma, severe COPD, hypotension or bradycardia. Third, most patients find it uncomfortable. Fourth, it may require central venous access which might otherwise not be necessary for the procedure (37). Finally, initial adenosine response may be incomplete in some patients and this may be difficult to predict reliably in advance (38-40). Thus, a wider use of intracoronary physiology would be expected if the technique is simplified even further. iFR would circumnavigate these issues permitting the benefits of FFR to be accessible to a wider population, at lower cost, less patient discomfort and shorter procedural times.

This study's cohort of patients reflects a wide demographic spectrum and is similar to that of the FAME study (16). The results of this study could be followed by further validation of iFR, in a larger cohort to better establish the diagnostic efficiency of each technique in the same study population. Although this appears as a pre-requisite before iFR can be proposed as an alternative to FFR in all contexts the excellent reproducibility and agreement in classification

with FFR (within the biological variability of fractional flow reserve) suggest that iFR will expand intracoronary functional assessment to circumstances where administration of adenosine is not desirable.

A final word should be dedicated to previous research on the use of diastolic pressures for FFR calculation, so-called diastolic FFR (41,42). The validation of diastolic FFR demonstrated that diastolic-only pressure measurements can be used to estimate stenosis severity with the same diagnostic efficiency as FFR, which uses cycle-averaged pressure measurements (41). This supports the concept that systolic flow can be neglected in the pressure-derived indices like diastolic FFR and iFR. The optimal cut-off value to identify ischemia generating stenoses in that study was slightly higher for diastolic FFR (0.76) than for FFR (0.75) (41), a fact that is in agreement with the differences found in our study between iFR (0.83) and the currently recommended 0.80 FFR cut-off value. However, major differences between diastolic FFR and iFR should be noted: 1) like FFR, diastolic FFR requires the use of adenosine and 2) measurements were obtained throughout diastole, and not selectively at a specific wave-free interval. As discussed above, the use of this wave-free period by iFR, when coronary microvascular resistance remains unchanged and minimal, provides a measure that closely correlates with FFR.

### 4.6 Study limitations

There is no gold standard ischaemia test. We chose FFR because it is quantitative and specific to a vessel, has been validated against three non invasive tests, has robust long term clinical outcome data and is the investigation recommended by cardiology guidelines for assessment of intermediate stenoses in the cardiac catheter laboratory. However there remains a possibility that any disagreement between the two indices may reflect the diagnostic accuracy of FFR rather than iFR.

This pilot study suggests an iFR value of 0.83 provides optimal agreement with an FFR of 0.8. Several hypothesis can be put forward to explain this difference in optimal cut-off values. First, since the optimal cut-off value for diastolic FFR, a diastolic-only pressure derived method like iFR, is also slightly higher that for FFR (41), it is possible that this difference may be genuine due to differences in how the indices are calculated. Second, it may result from subtle differences between pharmacological stabilisation of microvascular resistance compared to that which occurs naturally in the wave-free period. Finally, the possibility that it may be artefactual, given the relatively small size of our study, cannot be ruled out. With a larger patient population any differences might be further explored, and this cut off may alter in a similar manner to FFR during its development. Therefore, future studies are needed to address the diagnostic accuracy between FFR and iFR and the best cut-off value for iFR.

Intracoronary and intravenous administration of adenosine can have differing effects on peripheral and coronary arterial circulations. To mitigate against potential confounding from one or other of these administration routes we decided to include both intravenous and intracoronary administration in our study. In sub-analyses of our results, we have found no significant differences between either routes of administration (Table 2). Finally, a similar agreement between iFR and FFR values was documented in the right and left coronary artery, in spite of the more predominant systolic component of flow in the right coronary artery.

### 4.7 Conclusions

The existence of a wave-free period in diastole when coronary microvascular resistance is constant and minimal opens the possibility of performing pressure derived stenosis assessment without the need for pharmacological vasodilatation. Instantaneous wave-free ratio (iFR), a new index based on this principle, has an excellent diagnostic efficiency in

identifying stenoses with FFR<0.80, and could be used for intracoronary functional assessment when administration of adenosine is not desirable.

Table 4.1: Patient demographics

| | **Group 1** Pressure-Flow | **Group 2** Pressure only | **Overall** |
|---|---|---|---|
| **Stenoses (n)** | 39 | 118 | 157 |
| **Age (yr±SD)** | 64.6±9.9 | 59.2±16.1 | 62.6±10.2 |
| **Male (%)** | 35 (89.7) | 98(83.1) | 133 (84.7) |
| **Diabetes (%)** | 21 (53.9) | 33 (28) | 54 (34.4) |
| **Smoker (%)** | 6 (15.4) | 28 (23.7) | 34 (21.7) |
| **Hypertension (%)** | 23 (59) | 65 (55) | 88 (56.1) |
| **Impaired LV function (%) (EF<50%)** | 4 (10.3) | 9 (7.6) | 13 (8.3) |
| **Stable Angina (%)** | 35 (89.7) | 116 (98.3) | 151 (96.2) |
| **Unstable Angina (%)** | 4 (10.3) | 2 (1.7) | 6 (3.8) |
| **Single Vessel (%)** | 16 (41) | 92 (78) | 108 (68.8) |
| **Multi Vessel (%)** | 23 (59) | 26 (22) | 49 (31.2) |
| **Coronary Artery (%)** | | | |
| LAD | 21 (54.1) | 48 (40.7) | 69 (44) |
| Cx | 11 (27) | 32 (27.1) | 43 (27.1) |
| RCA | 7 (18.9) | 38 (32.2) | 45 (28.9) |
| **Adenosine (route) (%)** | | | |
| Intra-coronary | 0 (0) | 96 (81.4) | 96 (61.2) |
| Intravenous | 39 (100) | 22 (18.6) | 61 (38.8) |

Table 4.2: Sub-group analysis

Correlation of iFR vs FFR for various sub-groups within the study

| | Stenoses | Male | Age (mean ± SD) | Diabetes | Hypertension | Adenosine IC (%) | Adenosine IV (%) | r |
|---|---|---|---|---|---|---|---|---|
| **Single Vessel (%)** | 108 (68.8) | 88 (81.5) | 57.7±16.3 | 35 (32.4) | 57 (52.8) | 76 (70.4) | 32 (29.6) | 0.89 |
| **Multi Vessel (%)** | 49 (31.2) | 43 (87.8) | 66.7±8.7 | 19 (38.8) | 31 (63.3) | 29 (59.2) | 20 (40.8) | 0.92 |
| **Coronary Artery (%)** | | | | | | | | |
| **LAD** | 70 (44.7) | 59 (83.6) | 62.4±10.3 | 20 (28.4) | 43 (61.2) | 39 (55.2) | 31 (44.8) | 0.89 |
| **Cx** | 43 (27.3) | 40 (92.7) | 63.3±11.3 | 18 (41.5) | 27 (63.4) | 21 (48.8) | 22 (51.2) | 0.91 |
| **RCA** | 44 (28) | 39 (88.1) | 62.2±8.9 | 19 (42.9) | 22 (50) | 34 (76.2) | 11 (23.8) | 0.89 |
| **Adenosine (route)** | | | | | | | | |
| **Intra-coronary (%)** | 96 (61.1) | 77 (80.2) | 60.9±9.7 | 23 (24) | 49 (51) | 100 | - | 0.88 |
| **Intravenous (%)** | 61 (38.9) | 54 (88.5) | 65.0±10.3 | 31 (50.8) | 39 (63.9) | - | 100 | 0.90 |
| **Diabetes (%)** | 54 (34.4) | 45 (83.3) | 63.5±8.0 | 54 (100) | 40 (74.1) | 23 (42.6) | 31 (57.4) | 0.88 |
| **Smoker (%)** | 34 (21.7) | 31 (91.1) | 57.1±10.1 | 6 (17.6) | 19 (55.9) | 8 (23.5) | 26 (76.5) | 0.85 |
| **Hypertension (%)** | 88 (56.1) | 73 (83) | 64.0±9.8 | 40 (45.5) | 88 (100) | 49 (55.7) | 39 (44.3) | 0.92 |

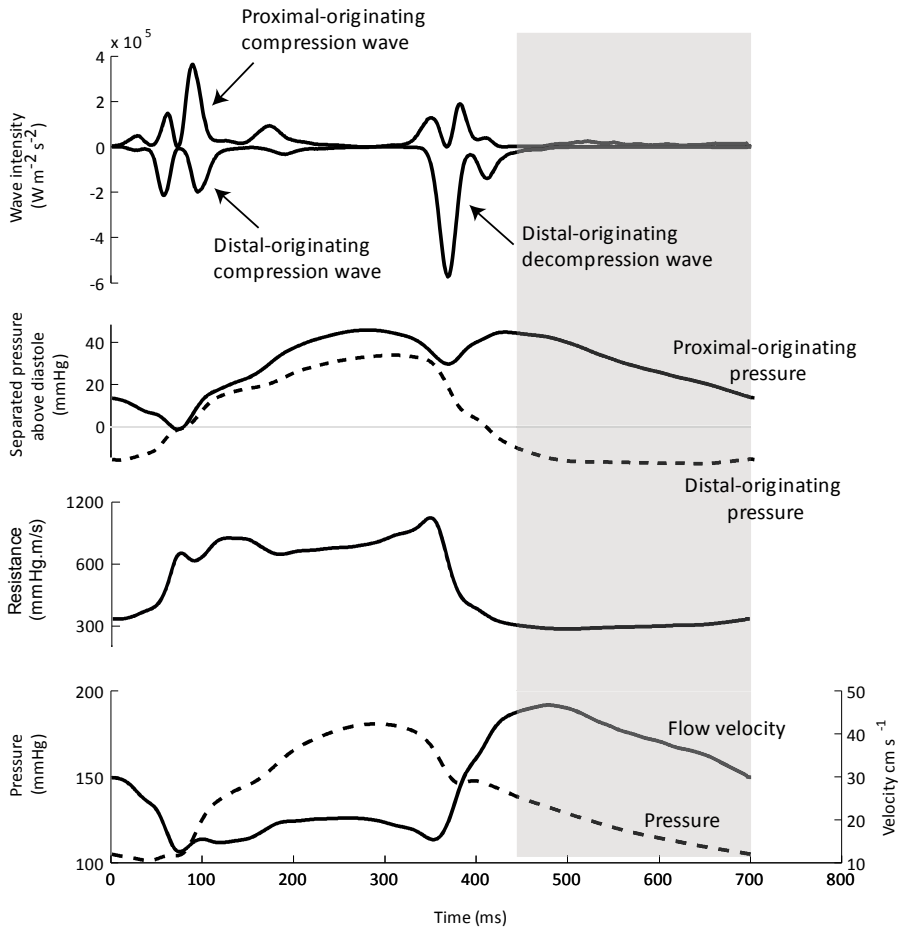



**Figure 4.01: Identification of wave-free period in cardiac cycle**

Wave intensity analysis (upper panel) demonstrates the proximal and distal wave generated during the cardiac cycle. A wave-free period can be seen in diastole when no new waves are generated (shaded). This corresponds to a time period where there is minimal distal originating pressure (second panel), minimal and constant resistance (third panel) and a near constant rate of change of flow velocity (lower panel). Separated pressure above diastole is the residual pulsatile separated pressure component after subtraction of the diastolic pressure.

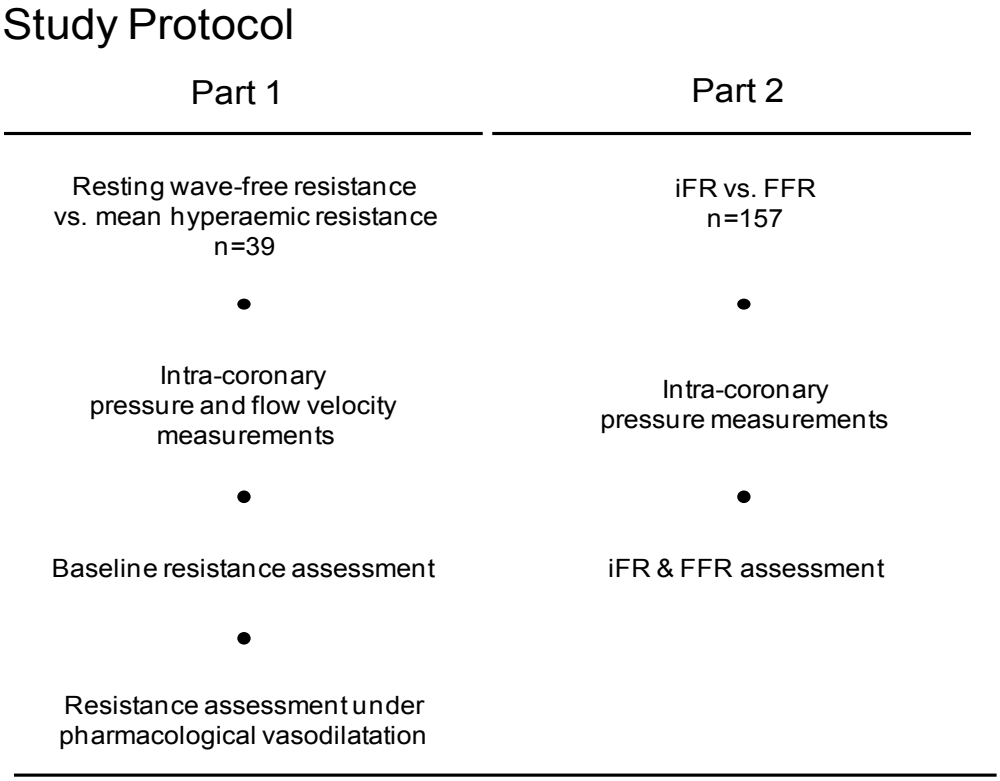



**Figure 4.02: ADVISE study work flow**

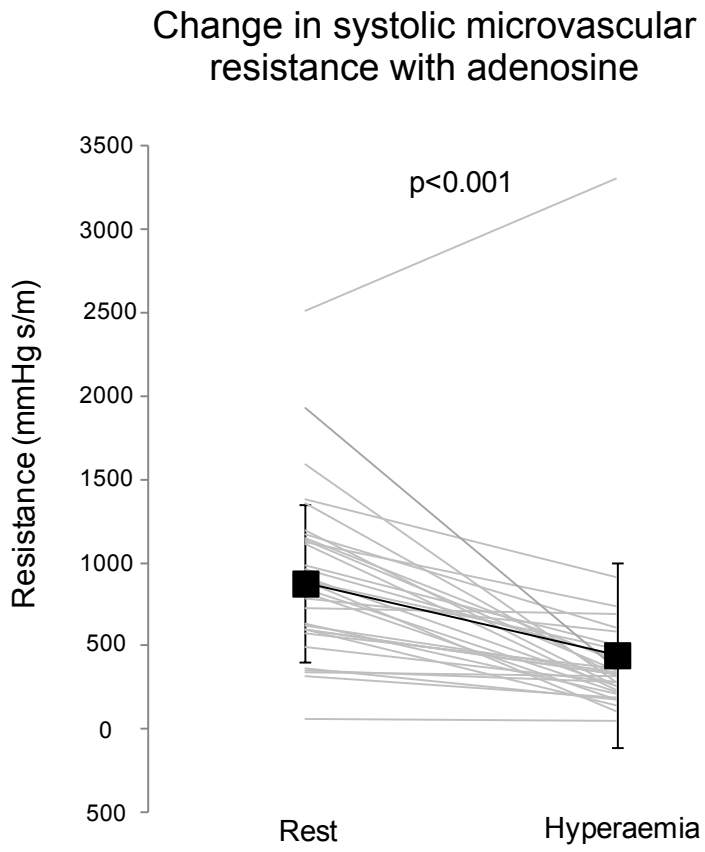



**Figure 4.03: The reduction in systolic microvascular resistance with intravenous adenosine administration**

There was a significant fall in the systolic component of microvascular resistance (Δ systolic resistance: 461mmHg s/m, p<0.001); which was the dominant contributor to the mean fall in resistance over the cardiac cycle.

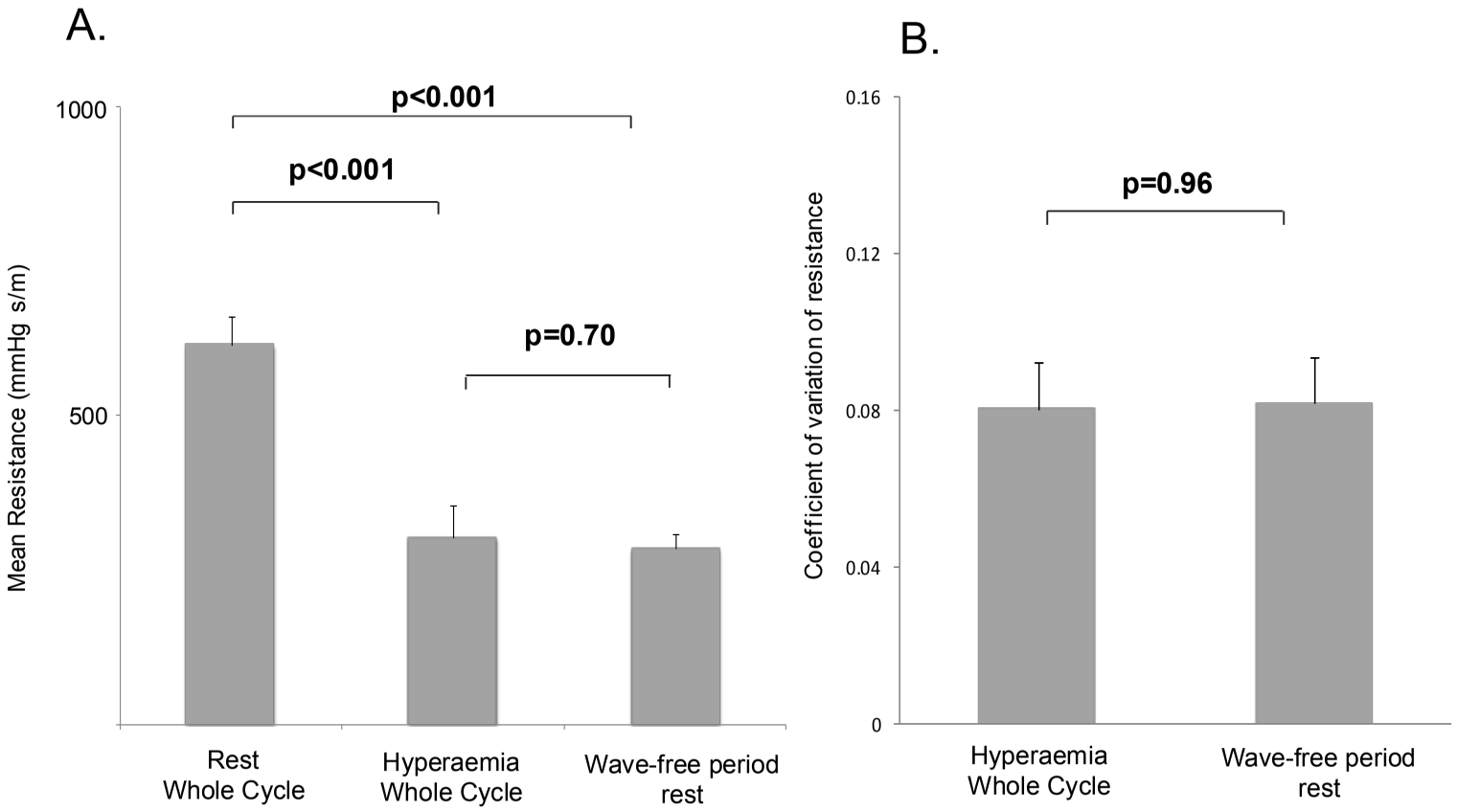



**Figure 4.04: Microvascular resistance during pharmacological vasodilatation compared to microvascular resistance during the wave-free period**

(A) Compared to baseline, there was a significant reduction in microvascular resistance with both pharmacological vasodilatation and during the wave-free period. (A and B) There was no significant difference in the magnitude or variability of resistance with pharmacological vasodilatation (as used for FFR) compared to the wave-free period (as used for iFR). All values are reported as mean ± standard error.

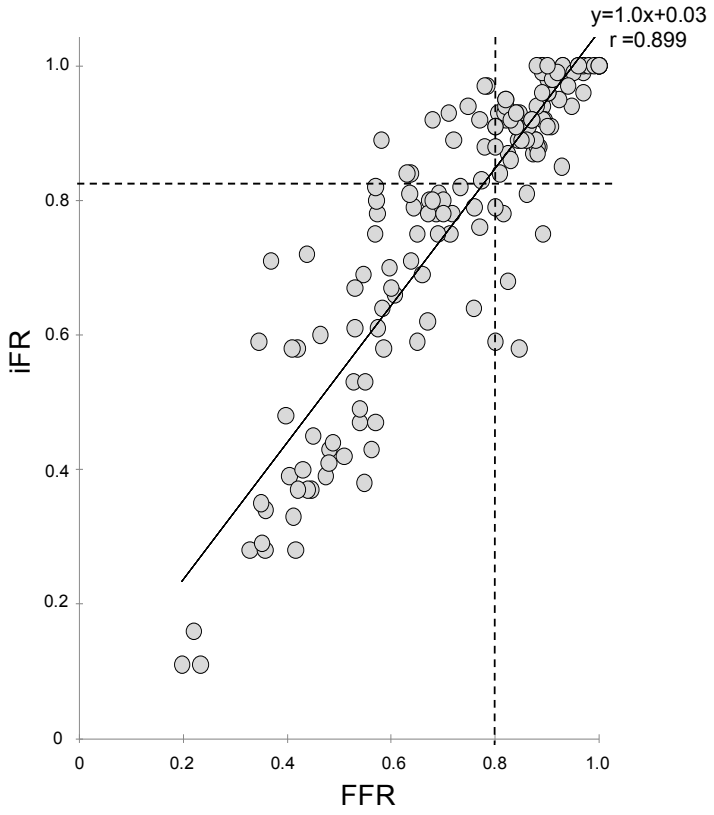



**Figure 4.05: Correlation of instantaneous wave-free ratio with FFR**

The wave-free period was calculated using a fully automated algorithm. iFR was calculated by dividing mean Pd by Pa during the wave-free period under basal conditions. iFR was found to closely agree with FFR (r=0.9, p<0.001). The dotted lines represent the threshold cut-off values for iFR and FFR.

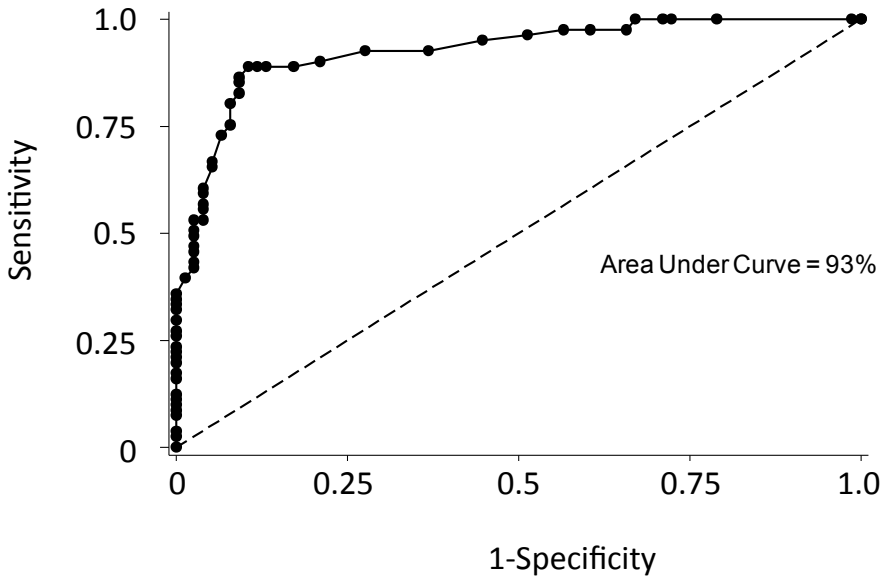



**Figure 4.06: Diagnostic characteristics of iFR**

Receiver Operating Characteristic of iFR. A receiver operation characteristics (ROC) curve was calculated using an iFR and FFR as the reference gold-standard variable. The threshold cut-off for FFR was taken as 0.80. The ROC was found to have an area under the curve of 93%, suggesting high accuracy of iFR as a diagnostic test.

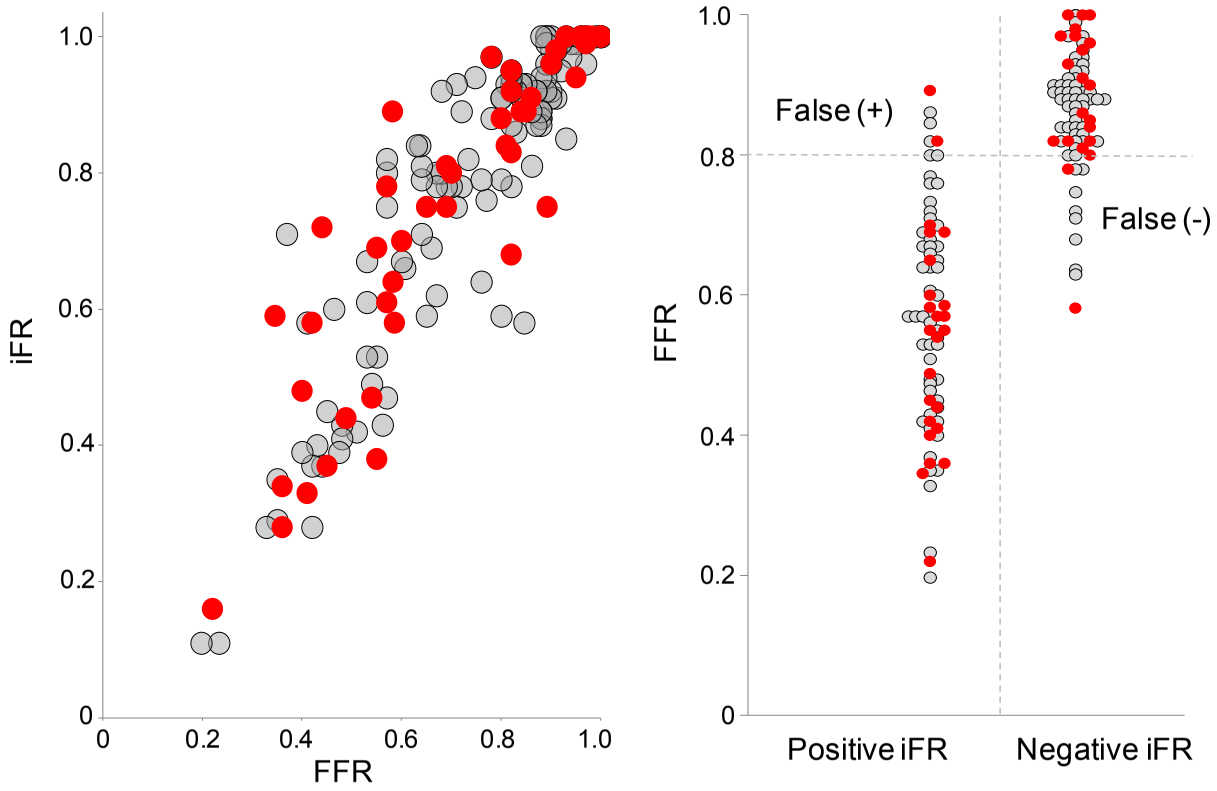



**Figure 4.07: Correlation and diagnostic characteristics of iFR with FFR according to coronary artery.**

Left panel, iFR at a 0.83 treatment threshold compared to FFR at a 0.8 treatment threshold. iFR was found to correlate closely with FFR(r=0.9), this was consistent in both right (r=0.89, red dots) and left coronary arteries (r=0.90, grey dots). Right panel iFR had a diagnostic accuracy, positive predictive value, negative predictive value, sensitivity and specificity of 88%, 91%, 85%, 85% and 91% respectively. This was also independent of the coronary artery studied.

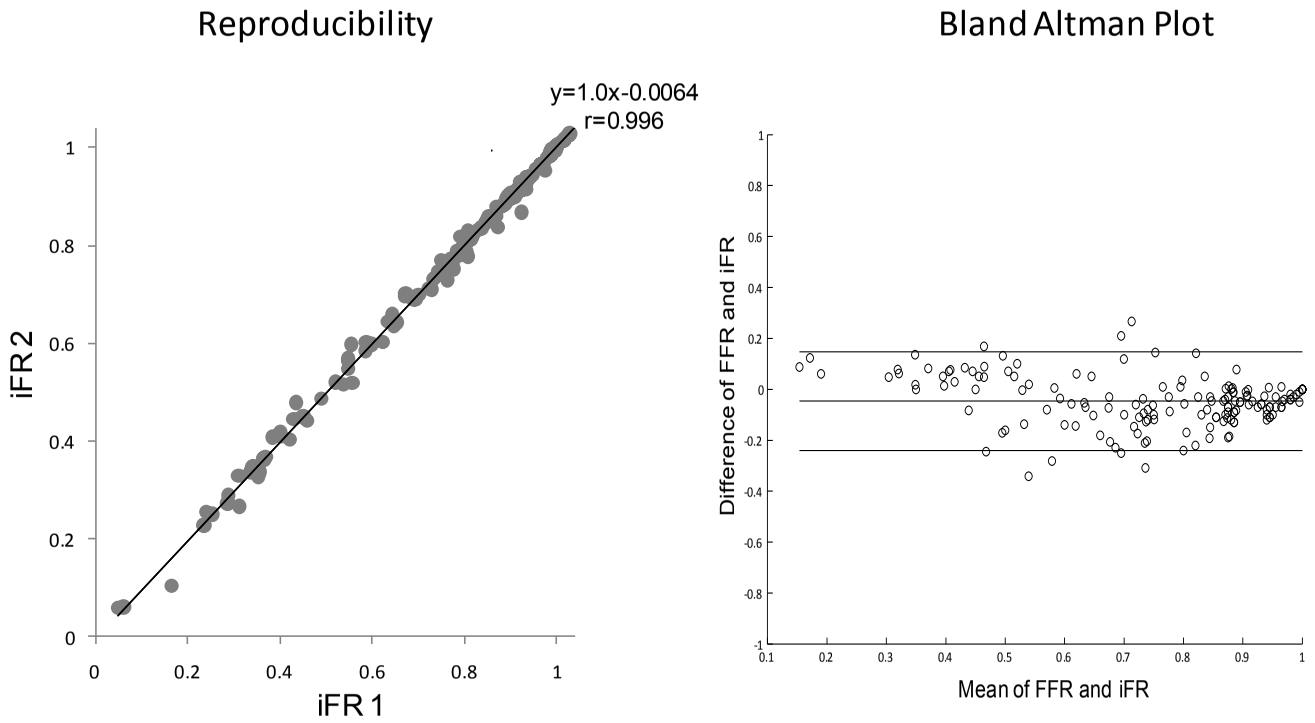



**Figure 4.08: Repeated measures analysis of iFR and Bland Altman plot**

The baseline pressure data was split in half and the iFR for each half was calculated. The correlation of iFR 1 to iFR 2 demonstrates high reproducibility across the entire range of stenosis severity (left panel, mean difference between measures -0.0005±0.002, p=0.78). The Bland Altman plot demonstrates good agreement between iFR and FFR across the entire range of stenosis severity.

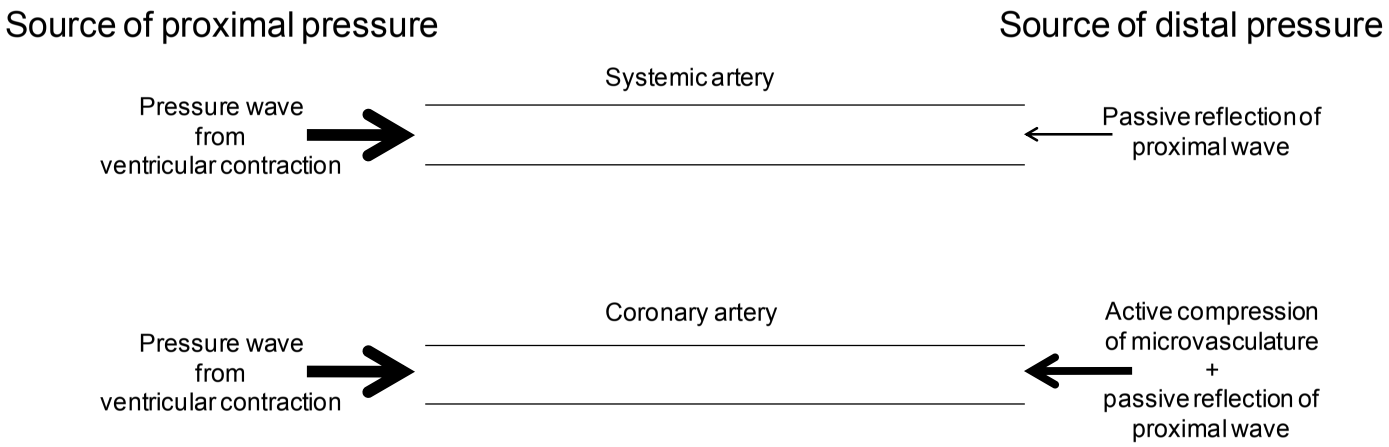





**Figure 4.09: Schematic illustrating the importance of microcirculatory (or distal originating) pressure in the coronary arteries.**

In all blood vessel, blood flows down a pressure gradient. In the systemic circulation a pressure wave is generated following ventricular contraction travelling from the proximal to distal end of the vessel. Whilst most of this wave energy travels in an anterograde direction, a small proportion is reflected back at site of impedance mismatch from the distal circulation (upper panel). This contrasts with the coronary circulation where a pressure wave is generated at both the proximal and distal ends of the vessel, at differing times in the cardiac cycle. Thus intracoronary pressure distal to a stenosis is a composite of residual proximally-originating pressure and the distal originating pressure from compression of the intra-myocardial vessels. iFR is calculated during the wave-free period in diastole, when distal originating pressure in minimised (Figure 3.02). The size of the arrows pointing in the direction of wave travel denote the contribution of proximal or distal pressure to total pressure, with proximal pressure predominant in the systemic artery (upper panel) and equal contribution to total pressure from both proximal and distal ends in the coronary artery (lower panel).

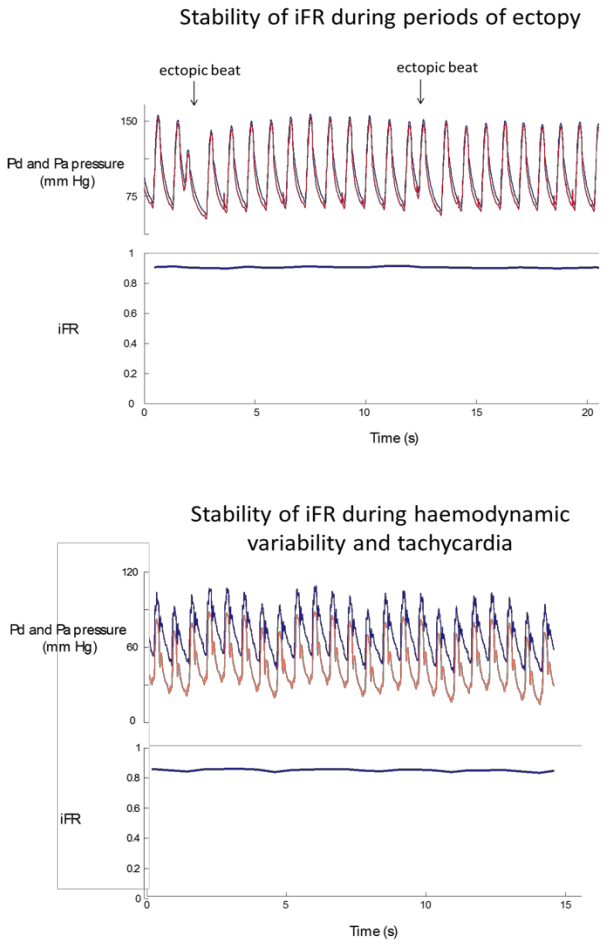



**Figure 4.10: The stability of iFR during haemodynamic perturbation**

iFR provides a beat-to-beat pressure ratio during the wave-free window – comparing each distal pressure with its corresponding aortic pressure. This ensures accuracy regardless of arrhythmia (upper panel, ectopy) or variations in blood pressure and heart rate (lower panel, tachycardia and respiratory variation in blood pressure).

## 5.0 Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration

### Results of CLARIFY

### (the CLassification Accuracy of pressure-only Ratios against Indices using Flow studY)

## 5.1 Abstract


### 5.1.1 Background

The instantaneous wave-free ratio (iFR) is a vasodilator-free pressure-only measure of the hemodynamic severity of a coronary stenosis comparable to fractional flow reserve (FFR) in diagnostic categorisation. In this study we use hyperaemic stenosis resistance (HSR), a combined pressure-and-flow index as an arbiter to determine when iFR and FFR disagree, which index is most representative of the hemodynamic significance of the stenosis. We then test whether administering adenosine significantly improves diagnostic performance of iFR.

### 5.1.2 Method

In 51 vessels intra-coronary pressure and flow velocity was measured distal to the stenosis at rest and during adenosine mediated hyperaemia. iFR (at rest and during adenosine administration, iFRa), FFR, HSR, baseline and hyperaemic microvascular resistance were calculated using automated algorithms.

### 5.1.3 Results

When iFR and FFR disagreed (4 cases, 7.7% of the study population), HSR agreed with iFR in 50% of cases and with FFR in 50% of cases. Differences in magnitude of microvascular resistance did not influence diagnostic categorisation; iFR, iFRa and FFR had equally good diagnostic agreement with HSR (ROC AUC 0.93 iFR vs 0.94 iFRa and 0.96 FFR, p=0.45).

### 5.1.4 Conclusion

iFR and FFR had equivalent agreement with classification of coronary stenosis severity by HSR. Further reduction in resistance by the administration of adenosine did not improve diagnostic categorisation, indicating that iFR can be used as an adenosine-free alternative to FFR.

## 5.2 Introduction

Use of intra-coronary physiological indices to guide revascularisation improves clinical outcomes and reduces procedural costs (14-17). Because of the simplicity of measuring intra-coronary pressure and the wealth of outcome data, fractional flow reserve (FFR) is the most frequently-used measure of stenosis severity. However, intra-coronary pressure distal to a stenosis reflects not only the severity of the stenosis but also pressure generated from the microcirculation (7). FFR is calculated as a ratio of mean distal to aortic coronary pressures over the entire cardiac cycle. In order to separate the hemodynamics of the stenosis from that of the microcirculation, FFR is calculated under conditions of constant (and minimal) microvascular resistance (5). This is achieved with the administration of vasodilators, such as adenosine (5).

The instantaneous wave-free ratio (iFR) is a pressure-only index that takes an alternative approach to the isolation of the hemodynamics of a stenosis from the microcirculation (39). It does not use vasodilators; instead it samples intracoronary pressure during the diastolic 'wave-free' period - a period in the cardiac cycle when intra-beat microvascular resistance is inherently stable and minimized. This wave-free window provides a phase in which microvascular resistance is significantly lower than that over the whole cardiac cycle, and coronary hemodynamics are most suited for assessment of the hemodynamic effects of a stenosis (12, 39). However, it is possible that microvascular resistance during the wave-free period can be lowered even further with the administration of adenosine and it has been suggested that calculating iFR during adenosine administration may improve its ability to accurately discriminate flow-limiting stenoses (30).

In the ADenosine Vasodilator Independent Stenosis Evaluation study (ADVISE) the classification of stenosis severity was good between iFR and FFR, but, in the absence of a

true gold standard, where differences in classification occurred it was difficult to know which index was correct.

The absence of a true ischemic gold standard has hampered the development of new indices in the past. Previously, non-invasive imaging modalities have been used to further evaluate new intra-coronary physiological tools. However, these techniques have limitations in multi-vessel disease and can only isolate ischemia at the level of a territory rather than a specific vessel (44). Therefore, in this study we use the hyperaemic stenosis resistance (HSR) index an invasive pressure and flow based index as the reference standard to determine which of the pressure based indices most accurately represents the hemodynamic severity of the stenosis. HSR falls back to the fundamental importance of simultaneously measuring pressure-flow as first described by Gould and in doing so circumvents many of the limitations of a pressure-only index (12). It is recognised to be more stenosis-specific, and less dependent on adenosine mediated hyperaemia than pressure-only indices (19-22).

In the first part of this study we compared the diagnostic classification of iFR, iFRa and FFR to HSR. We then assessed the changes in microvascular resistance which occur during the three pressure-derived indices to determine how adenosine administration Influences diagnostic categorisation.

## 5.3 Methods

### 5.3.1 Study population

This study included 51 stenoses (66.2±9.2 years, 82.7% male) scheduled for coronary angiography or PCI at Guys and St Thomas' NHS Trust, UK or Imperial College London, UK. In addition to new data, patients were included from part 1 of the ADVISE study (6). Exclusion criteria were limited to significant valvular pathology, previous coronary artery bypass surgery and weight >200kg. All subjects gave written informed consent in accordance with the protocol approved by the local ethics committee (NRES 09/H0712/102; NCT01118481).

### 5.3.2 Study Protocol

Pressure and flow velocity recordings were made distal to the target vessel coronary stenosis in 51 vessels at rest and during adenosine-induced hyperaemia (76.5% intra-venous (140mcg/kg/min) and 23.5% intra-coronary (up to 120mcg).

#### 5.3.2.1 Cardiac Catheterization

Cardiac catheterization was undertaken through the femoral approach. After diagnostic angiography, a 0.014inch pressure and Doppler sensor-tipped wire (ComboWire® XT, Volcano Corporation, San Diego, CA) was passed into the target vessel via a guiding catheter. Pressure equalisation was performed at the tip of the catheter prior to its advancement into the distal vessel.

5000iu unfractionated intravenous heparin was given at the start of the procedure with 300mcg intracoronary GTN.

### 5.3.2.2 Haemodynamic Recordings

The EKG, pressures and flow velocity signals were directly extracted from the digital archive of the device console (ComboMap®). At the end of each recording the pressure sensor was returned to the catheter tip to ensure there was no pressure drift. Where drift was identified the measurements were repeated. An adequate flow envelope was obtained in all patients permitting the calculation of flow based indices. Data were analyzed off-line, using a custom software package designed with Matlab (Mathworks, Inc, Natick, Mass).

### 5.3.3 Data Analysis

Processing of digital data (pressure, flow velocity, EKG) for the calculation of the various indices was performed at a workstation using Matlab (Mathworks, Inc, Natick, Mass). iFR was calculated as the ratio of distal to proximal pressures over the diastolic wave-free period using a fully automated pressure-only algorithm, as previous described (6). This period corresponds to a time in the cardiac cycle when waves are absent from the coronary artery (6)(Figure 5.01). An instantaneous wave-free ratio following adenosine administration (iFRa) was also calculated using the same algorithm. FFR, HSR and basal and hyperaemic microvascular resistance were calculated, in all patients, as previously described (14, 15). Definition of flow based intra-coronary indices:

Hyperaemic Stenosis Resistance (HSR) = $\frac{Pa-Pd}{Q}$

Hyperemic microvascular resistance (HMR) = $\frac{Pd}{Q}$

Basal microvascular resistance (BMR) = $\frac{Pd_b}{Q_b}$

Wave-free microvascular resistance (wfMVR)= $\frac{Pd_{wfp}}{Q_{wfp}}$

$Pa$, mean Aortic Pressure, $Pd$, mean intracoronary pressure distal to stensosis, $Q$, mean flow velocity distal to stenosis during hyperaemia, $Pd_b$ mean intracoronary pressure distal to stenosis at baseline $Q_b$, mean flow velocity distal to stenosis at baseline. $Pd_{wfp}/Q_{wfp}$ distal pressure/ flow velocity over the wave free period

#### 5.3.3.1 Statistical analysis

All data are expressed as mean ± standard deviation or median ($25^{th}$-$75^{th}$ Quartiles), as appropriate. Receiver operator curves (ROC) were constructed for each index and the agreement in diagnostic categorisation was compared between the indices by comparing the areas under the ROC using the *roccomp* command in STATA, version 11, (Statacorp, USA) based on DeLong, E. R., D. M. DeLong, and D. L. Clarke-Pearson 1988 (45). The optimal cut-off for each of the pressure only indices of iFR, iFRa and FFR were selected to be that which maximised the sum of sensitivity and specificity, using HSR as the reference standard. The comparison of FFR to HSR was performed at the 0.75 and 0.8 FFR cut off.

We determined the sample variance (probability distribution) of the observed microvascular resistance values, of each index, as an estimate of true variance of the entire patient population (STATA). The variance of the reduction in resistance for each of the three indices was compared using the F-test. A value of $p<0.05$ was deemed significant. Changes in microvascular resistance for each index are compared to cycle averaged resting microvascular resistance

## 5.4 Results

### 5.4.1 Patient Distribution

There was a unimodal left skewed distribution of stenosis severity with 84.3% of stenoses in the 0.6-1.0 FFR range, 62.7% of stenoses were in the 0.6-0.9 FFR range (Figure 5.02).

### 5.4.2 iFR and FFR

Using a ROC derived iFR cut-point of 0.86 (equivalent to HSR 0.80) there was agreement in diagnostic classification between iFR and FFR in 47 out of 51 lesions (92.3%). In the 4 lesions in which there was disagreement, in two iFR was negative and FFR positive and in the other two iFR was positive and FFR negative (Figure 5.03). When iFR was negative and FFR positive, HSR agreed with FFR in one case and with iFR in the other. In the two cases in which iFR was positive and FFR negative, again HSR agreed with FFR in one patient and with iFR in the other. In both these cases microvascular resistance during iFR was lower than that during adenosine meditated FFR.

iFRa had significantly lower values than FFR and iFR (median iFRa 0.74(0.58,0.85) vs median FFR 0.84(0.70,0.89) and median iFR 0.93 (0.83, 0.98) $p<0.001$ for both). Furthermore, this was true for both intra-coronary and intra-venous adenosine administration. Despite numerical differences, there was no significance difference in the area under ROC curve for either iFR or iFRa when compared to FFR ($p=0.15$).

Of the adenosine based indices, iFRa provided significantly greater trans-stenotic pressure gradients than FFR (iFRa 19.4 (11.2-39.2) mmHg vs 12.2 (7.2-27.9), $p<0.001$). However, iFR produced statistically equivalent trans-stenotic pressure gradients to FFR (iFR 8.2 (3.1-21.6)mmHg vs 12.2 (7.2-27.9) mmHg, $p=0.48$).

### 5.4.3 FFR, iFR and iFRa compared to HSR

The relationship of iFR, FFR and iFRa to HSR was similar (Figure 5.04). Median HSR was 0.35 (0.19,1.08) mmHg/cm.s. Using the established ischemic cut-off point of greater than 0.8mmHg/cm.s for HSR (9), a 0.75 cut-off point for FFR was found to have the optimal diagnostic efficiency (ROC AUC) of 0.96 (95% CI 0.89-1.0) with a sensitivity of 0.86, a specificity of 0.95 and, in this population, a positive and negative predictive value of 0.86 and 0.95 respectively (Figure 5.05, right panel). This compared to the 0.8 FFR cut-off point which had a sensitivity of 0.87, a specificity of 0.84 and a positive and negative predictive value of 0.68 and 0.94 respectively.

IFRa had an equivalent diagnostic performance to FFR, against HSR as the reference standard (ROC AUC 0.94, 95% CI 0.85-1.0, p=0.45 versus FFR, Figure 5.05). Corresponding to its numerically smaller values, the classification cut point for iFRa was also lower, with a cut point of 0.66 found to have the highest diagnostic efficiency. With this cut point, iFRa had a sensitivity of 0.86, specificity of 0.92 and, in this population, positive and negative predictive values of 0.8 and 0.94 respectively.

iFR without adenosine had a diagnostic performance (ROC AUC) of 0.93 (95% CI 0.85-1.0) against HSR as the reference standard. An iFR cut point of 0.86 was found to be equivalent of HSR 0.8 (FFR 0.75). iFR had a sensitivity of 0.86, specificity of 0.95 and, in this population, positive and negative predictive values of 0.86 and 0.95 respectively (Figure 5.04). The relationship of iFR to FFR and HSR was independent of heart rate (Figure 5.06).

There was no significant difference between iFR, iFRa and FFR in terms of agreement with HSR guided treatment classification (p=0.48, Figure 5.05).

### 5.4.4 Magnitude of microvascular resistance reduction according to epicardial stenosis severity

Intra-coronary microvascular resistance was significantly lower during the diastolic wave-free period than averaged values over the whole cardiac cycle at rest (microvascular resistance: 3.3 (2.07-4.38) mmHg/cm.s vs 5.30 (3.68-7.04) mmHg/cm.s, p<0.001, Figure 5.07).

The relationship between resting diastolic wave-free microvascular resistance and hyperaemic microvascular resistance varied according to stenosis severity. In patients with physiologically unobstructed arteries, defined as HSR<0.8mmHg.cm/s (36 stenoses, 70.6% of the study population) the adenosine based indices of iFRa and FFR demonstrated a greater reduction in intra-coronary microvascular resistance (from baseline whole cycle microvascular resistance) than that achieved during iFR (FFR: 57.0 (39.7-66.4)% and iFRa 76.6 (70.3-80.3)% vs iFR 35.8 (30.3-40.6)%, p<0.001 for both, Figure 5.08). Despite the lower magnitude of microvascular resistance observed during iFRa and FFR, in this group agreement in diagnostic categorisation to HSR was equivalent between the three pressure derived indices (diagnostic accuracy = 86.7%).

In patients with physiologically obstructed arteries (HSR>0.8mmHg.cm/s) the fall in microvascular resistance was similar during FFR and iFR (FFR: 34.6 (21.0-52.7)% and iFR 46.4 (32.6-54.3)%, p=0.16, Figure 5.08 & 5.09 right panel), but larger during iFRa (69.2 (64.5-80.3)%, p<0.001 compared to both FFR and iFR).

### 5.4.5 Microvascular resistance during the resting wave-free period can be lower than microvascular resistance during hyperaemic whole cycle microvascular resistance

In 39% of stenoses (20 stenoses, range 0.35-0.99), over both physiologically unobstructed and obstructed vessels (range 0.35-0.99), microvascular resistance was not lower during adenosine mediated FFR compared to that during the baseline iFR wave-free period (Figure 5.09). In this group median FFR was 0.79 (inter-quartile range=0.28) compared to a median iFR of 0.84 (inter-quartile range=0.35). This phenomenon of lower microvascular resistance during iFR occurred in 34.4% (11 stenoses) in the 0.6-0.9 FFR range.

### 5.4.6 Comparison of iFR and FFR in the 0.6-0.9 FFR range

62.7% of stenoses fell within the 0.6-0.9 FFR range. In this range, both iFR and FFR had identical diagnostic agreement with HSR, 87.5%. Diagnostic agreement of iFRa to HSR was 84.4%. The sensitivity of iFR, FFR and iFRa was 66.7% for all. The specificity of iFR, FFR and iFRa was 92.3%, 92.3% and 88.5% respectively (Figure 5.10).

When microvascular reduction (compared to baseline whole cycle microvascular resistance) is plotted according to stenosis severity (Figure 5.11) it can be seen that the reduction in microvascular resistance during the wave free period increases with increasing epicardial stenosis severity (Figure 5.11, right panel). The opposite was true with FFR where the magnitude of reduction in microvascular resistance was lower in vessels with more severe stenoses (Figure 5.10, left panel).

### 5.4.7 Consistency of microvascular resistance reduction achieved during iFR, FFR and iFRa

Across the entire stenosis range, adenosine mediated FFR had a more heterogeneous effect on microvascular resistance than the wave-free period (37.2% (inter-quartile range 15.8%) reduction in microvascular resistance during iFR vs 53.9% (inter-quartile range 29.0%) during FFR, F-test, $p<0.001$), (Figure 5.10, upper panel). This was particularly true of the 0.6-0.9 range (37.2% (inter-quartile range 12.6%) reduction in microvascular resistance

during iFR vs 55.7% (inter-quartile range 34.9%) reduction in microvascular resistance during FFR, F-test, $p<0.001$))(Figure 5.10, upper panels – red dots).

The reduction in microvascular resistance during iFRa was more consistent than that during FFR (microvascular resistance reduction during iFRa 75.6% (inter-quartile range 12.3%) vs median microvascular resistance reduction during FFR 53.9% (inter-quartile range 29.0%), F-test, $p<0.001$). Despite microvascular resistance reduction during iFRa being numerically greater than that during iFR (microvacular resistance reduction durng iFRa 75.6% (inter-quartile range 12.3%) vs microvascular resistance reduction duing iFR 37.2% (inter-quartile range 15.8%), $p<0.001$), micorvascular resistance reduction during iFR was just as consistent as that during iFRa (F test, $p=0.73$). Furthermore, this was true in the 0.6-0.9 FFR range (iFR inter-quartile range 12.6% vs iFRa inter-quartile range 11.8%, F-test, $p=0.10$).

## 5.5 Discussion

In this study we found that: 1) iFR and FFR have equal diagnostic classification agreement with HSR, 2) reduction in microvascular resistance during iFR is more consistent than that achieved during adenosine mediated FFR 3) microvascular resistance reduction during iFR is higher with increasing stenosis severity whilst the opposite is true for FFR and 4) despite resistance being lower when iFR is measured following administration of adenosine (iFRa) this does not improve classification agreement with HSR.

### 5.5.1 iFR and FFR have equivalent agreement with HSR across the entire stenosis range

The equivalent diagnostic performance of iFR and FFR are consistent with the findings of three other studies, including more than 800 stenoses: ADVISE (25), ADVISE-Registry (46) and the South Korean prospective blinded study (47). Importantly, in all these studies the same automated algorithm for calculation of iFR was used. However, when iFR was calculated using a different investigator-designed algorithm, in the VERIFY study, a weaker correlation between iFR and FFR was reported (43). Furthermore, VERIFY suggested that resistance could made lower over the wave-free period following adenosine administration perhaps leading to improvement in stenosis discrimination.

It has been accepted that iFR and FFR have excellent agreement at the extremes of stenosis severity. However, since the publication of ADVISE there has been much speculation with regard to the scatter in correlation plot between iFR and FFR in the 0.6-0.9 range. Despite the fact that FFR itself has not been validated extensively in this intermediate range (46, 48, 49) this disagreement has been attributed by some as a limitation of iFR (30). Our findings suggest that hyperaemic whole cycle microvascular resistance is far more variable than resting wave-free microvascular resistance and that this variability is maximal in the intermediate range of stenosis severity (Figure 5.10); a finding consistent with those of

others (18). This suggests that this biological intrinsic FFR variability may be the principle driver of differences between iFR and FFR. This variability in microvascular resistance during adenosine administration is likely to occur due to variability in adenosine mediated responses of the myocardium and microvasculature (50, 51). The more consistent reduction in microvascular resistance during iFR and iFRa compared to FFR suggests the predominant cause of the variable effect of adenosine on coronary microvascular resistance occurs during systole and early diastole – active phases of the cardiac cycle that are excluded by the wave-free window (25). This is consistent with the seminal work of Gould which demonstrated that the pressure drop across a stenosis can be assessed most reproducibly during a period in the cardiac cycle free of the confounding effect of active contraction and relaxation of the myocardium on intra-coronary pressure (systole and early diastole) (12, 25).

In terms of FFR this manifests clinically as the cause of disagreement in repeated measures of FFR in the same lesion. Consequently the test re-test agreement of FFR in the 0.6-0.90 range, based on the DEFER reproducibility dataset where FFR was measured twice 10 minutes apart, is not 100% but only 81% (46). Therefore when iFR and FFR disagree in this range it is not certain that a repeated measure of FFR will even agree with itself. Indeed, stenoses in this range were never explored with the same power as those at the extremities of severity in the ischemia validation studies of FFR. As a result, it is possible that this may be an inherent limitation of using FFR as a reference standard in this range (46, 47).

By measuring both pressure and flow HSR is less susceptible to the heterogeneous response to adenosine (37-40). When used as the reference standard in this range, our results demonstrate equivalent diagnostic categorisation of iFR and FFR (Figure 5.09). Given these findings it is reasonable to speculate that FFR, with its significantly more variable microvascular resistance reduction in the 0.6-0.9 range, is the predominant contributor to the scatter in this region (Figure 5.10).

A simple post hoc restricted correlation analysis between iFR and FFR in a limited range of FFR values (such as 0.6 to 0.9) can be misleading, especially when the intrinsic variability of FFR is not taken into account (14, 46). A more robust method of further characterising the diagnostic accuracy of iFR in this range is to prospectively identify a study population rich in lesions around this range. To this end the ADVISE Registry (339 patients) and the South Korean Registry (238 patients) were designed to answer this question (46, 47). To the best of our knowledge, these were the first studies to ever assess FFR in a distribution similar to that seen in routine clinical setting (80% lesions in 0.6-0.9 range). Reassuringly, when accounting for the inherent variability of FFR in this range, these studies also demonstrated close categorisation match between iFR and FFR.

### 5.5.2 How can greater reduction of intracoronary microvascular resistance not give greater diagnostic value?

Pressure derived indices rely on Ohm's law which demonstrates that a pressure gradient ($\Delta P$) is equal to the product of flow ($Q$) and resistance ($R$) ($\Delta P = QR$). Therefore, for a pressure gradient to be used as a surrogate for flow, intracoronary microvascular resistance simply needs to be stable. However, to provide a clinically useful index, microvascular resistance also needs to be low enough, and flow high enough, to discriminate between trans-stenotic pressure gradients and therefore permit the index to differentiate between stenoses of differing severity. This has led to the current dogma which suggests that ever greater reductions in microvascular resistance should lead to an improvement in classification agreement (43). However, our results indicate that iFR, FFR and iFRa had equivalent agreement in diagnostic classification with HSR. This observation is in keeping with other recent independent studies, which have also shown that diagnostic categorisation

agreement is not necessarily improved after the administration of pharmacological vasodilators (52).

From our results, the lack of incremental diagnostic benefit of the hyperaemic indices of iFRa and FFR is because of two principle reasons.

1. Microvascular resistance reduction in FFR varies according to stenosis severity

During FFR, adenosine mediated reduction in microvascular resistance was most marked in patients with physiologically unobstructed arteries (as defined by HSR) (Figure 5.08). In these patients the reduction in microvascular resistance was significantly greater than that during iFR (Figure 5.09, shaded area left panel). This is simply a reflection of the effect of auto-regulation which keeps coronary flow constant (18); as stenoses get progressively more severe the microvasculature dilates to ensure adequate flow to the myocardium. Consequently, the effect of adenosine in arteries with severe lesions is limited as the microcirculation has little scope to dilate further when adenosine is administered - they have limited vasodilator reserve. However, the effect of adenosine in arteries with mild lesions is much greater as the microcirculation is relatively vasoconstricted and as a result the vasodilator reserve of these arteries is much larger. These findings are consistent with previous observations demonstrating an inverse relationship between adenosine mediated vasodilator reserve of a coronary artery and epicardial stenosis severity (18, 53).

Therefore when there is a significantly greater reduction in microvascular resistance during FFR, as compared to iFR, it does not impact on diagnostic accuracy because it occurs in the physiologically least obstructive cases (which are so far from the ischemic cut-off point that they are anyway correctly classified). These cases of physiologically unobstructed arteries contrast markedly with those patients with significant obstructive coronary disease. In cases of physiologically significant coronary disease (HSR>0.8) the magnitude of microvascular

resistance reduction achieved by adenosine during FFR is far lower (Figure 5.08, 'whole cycle adenosine') and microvascular resistance during iFR is equivalent to that during FFR, and in some cases even lower (Figure 5.09, left panel unshaded area).

2. Reduction in microvascular resistance during the wave-free period is sufficient to differentiate between stenosis severities

Microvascular resistance reduction during iFRa was consistently greater than that possible during iFR and FFR. Despite this, diagnostic accuracy of iFRa was not improved even in the clinically relevant 0.6-0.9 FFR range. This suggests that the natural increase in coronary flow velocity and reduction in microvascular resistance during iFR is sufficient in magnitude to assess the fluid dynamics of a stenosis and to accurately differentiate according to severity without the need for adenosine.

These two observations question the need for "maximal flow" in stenosis assessment. Indeed, for any apparent-maximal flow achieved with one dose of one vasodilator, that with another dose or drug might be different (54). Moreover, even setting aside pharmacological considerations, for any maximal flow achieved over the whole cardiac cycle, the flow in diastole may be higher and that during the wave-free period higher still. Since the increases in flow will not be exactly identical between methods, the pressure drops will also not be identical, and the methods will have some degree of numerical disagreement reflected in their different cut points. But, as this study finds, the indices will not necessarily differ in their diagnostic discrimination, provided the increase in flow is sufficient, consistent and microvascular resistance remains *stable*. Thus, instead of chasing the potentially unachievable state of "maximal" hyperaemia, isolating an intrinsically stable resistance phase of the cardiac cycle, the diastolic wave-free period, provides a mechanism to obtain a flow that is consistently high enough, for the accurate assessment of a stenosis.

### 5.5.3 Why microvascular resistance during the wave-free period can be lower than that during FFR

In approximately 40% of stenoses microvascular resistance during the wave-free period was lower than that over the complete cardiac cycle during adenosine mediated FFR. This phenomenon occurred across the entire range of stenosis severities, including approximately one third of stenoses in the 0.6-0.9 FFR range. In practice, this means that in a significant proportion of patients, adenosine mediated FFR fails to increase flow greater than that already present at baseline during the diastolic wave-free period. This has previously only been described in a small minority of cases when comparing resting whole cycle microvascular resistance to hyperaemic whole cycle microvascular resistance (FFR) (55).

There are several potential reasons why the proportion of stenoses in this study demonstrating this phenomenon is larger than that previously described. Firstly, in contrast to previous studies documenting this phenomenon this study used predominantly intravenous adenosine. This enables measurements to be made in more severe lesions, where the operator has more time to attain a good Doppler trace. This is often far harder using intra-coronary adenosine, where the increase in flow velocity following adenosine administration is more transient and therefore the time window to achieve a good Doppler envelope is far shorter. Secondly, the larger proportion of stenoses with this paradoxical response may also reflect the unique hemodynamics of the wave-free period. Phasic analysis of coronary pressure, flow and microvascular resistance demonstrates that microvascular resistance is approximately 30-40% lower during the wave-free period when compared to whole cycle microvascular resistance. Consequently adenosine mediated FFR microvascular resistance is required to be consistently lower to surpass the reduction in microvascular resistance already achieved by simply selecting the wave-free period. Unfortunately, the variable reduction in microvascular resistance during FFR (18) prevents

this from being consistently achieved and it is not possible to predict, in advance, in which patients this will occur. By obviating the need for vasodilator administration iFR is not subject to the natural variability associated with drug administration between patients and therefore provides a more consistent assessment across lesions of similar severity (Figure 5.10).

## 5.6 Study limitations

Whilst we use HSR as the reference standard in this study it should be noted that there is no gold standard ischemia test. Whilst this is an inherent limitation to the establishment of any new ischemic test we chose HSR as the reference standard because it measures both pressure and flow and is therefore less susceptible to the heterogeneous effect of adenosine and because of its high specificity for ischemia (19-22).

The iFR cut point of 0.86 in this study is different to that in the ADVISE study (25). This is because in this study we compare iFR to the ischemic cut-off points of HSR (0.8) and FFR (0.75). It should be noted that this is different to the ADVISE-Registry (46) and the Korean study (47) which were both highly powered to assess the cut-point relating to the clinical (non-ischemic) FFR cut-off of 0.8. Their findings were consistent with 0.89 being equivalent to FFR 0.8. In this study the HSR 0.8 cut off is equivalent to FFR 0.75, and as such, it was necessary to obtain the iFR value (0.86) pertaining to these values.

This is a small study compared to the larger pressure-only studies in this field. As with all mechanistic studies interpretation of our findings should be done in the context of the study size. However, this remains one of the largest pressure and flow studies using intravenous adenosine, and the only study comparing FFR, iFR and HSR in the 0.6-0.9 range. The number of patients in which iFR and FFR disagree with each other is small and their significance should be interpreted with caution. However, it should be noted that the

proportion (7.7%) is consistent with clinical populations, ADVISE Registry (6%) and South Korean Study (6%), suggesting that the study findings are consistent with other, larger datasets (46, 47).

The distribution of stenoses in this study is unimodal with leftward skew, which is more reflective of the distribution seen in routine clinical practice (46, 47). It may be argued that the skew towards normal may have masked any potential differences between iFR and the hyperaemic indices. However, rather than acting in favour of iFR such a skew is more likely to place iFR at a disadvantage, particularly if the magnitude of microvascular resistance is a key discriminator between the diagnostic accuracy of iFR and FFR as is assumed. This is because in a population such as this, the skew towards normal identifies a population with marked differences in microvascular resistance between iFR and FFR. Given that reductions in microvascular resistance with hyperaemia are most marked in patients with less obstructive lesions one would expect the agreement of iFR to FFR and HSR to be weak in such a population and therefore biased against iFR. The fact that the level of agreement between indices is good (including the 0.6-0.9 range) suggests that our conclusions that the flow velocity achieved during the wave-free period is sufficient to assess a stenosis and pharmacologically induced greater flow is surplus to requirement is valid. Therefore, rather than introducing bias, the good level of agreement in this data distribution should reassure clinicians that the principal physiological findings of this study are applicable to the patients that they see in the catheterisation laboratory.

The ability to measure flow velocity accurately is challenging and has the potential to introduce a source of error. However, this was limited as measurements were made with intravenous adenosine to ensure adequate time was available to achieve the best possible flow velocity envelope and performed by experienced operators well practiced at making flow measurements. To this end it is reassuring that our resistance findings are consistent with that reported by others (18).

## 5.7 The next step for iFR

Physiologic guided revascularisation has been demonstrated to improve clinical outcomes and reduce procedural costs (1, 2). However adoption into clinical practice has been limited (56). One of the reasons for this is the requirement of adenosine (56, 57). As a vasodilator independent index iFR has been proposed as a possible solution to this problem. Given the good categorisation match with FFR in over 800 stenoses to date it can be argued that there is little to gain from further comparisons with FFR. Furthermore, by measuring flow we identify a physiological reason that questions the use of FFR as the reference standard particularly in the 0.6-0.9 range – the variable response to adenosine. Whilst we find that iFR is equivalent to FFR at detecting hemodynamic significant stenoses (as defined by HSR) the true measure of the clinical utility of the index will be determined by outcome studies. To this end a systematic appraisal of iFR guided deferral of therapy would allow clinicians to begin to assess its place in the clinical domain.

Table 5.1: Patient Demographics

| | Stenoses, %(n) |
|---|---|
| **Male** | 82.4(42) |
| **Age** | 66.2±9.2 |
| **Risk Factors** | |
| Smoker | 29.4(15) |
| Diabetic | 27.4(14) |
| Hypertension | 35.2(18) |
| Family History | 25.5(13) |
| **Vessel** | |
| LAD | 56.8(29) |
| Cx | 21.6(11) |
| RCA | 21.6(11) |
| **Adenosine Route** | |
| IV | 76.5(39) |
| IC | 23.5(12) |
| **Stenosis Severity** | |
| (-) HSR | 70.6(36) |
| (+) HSR | 29.4(15) |

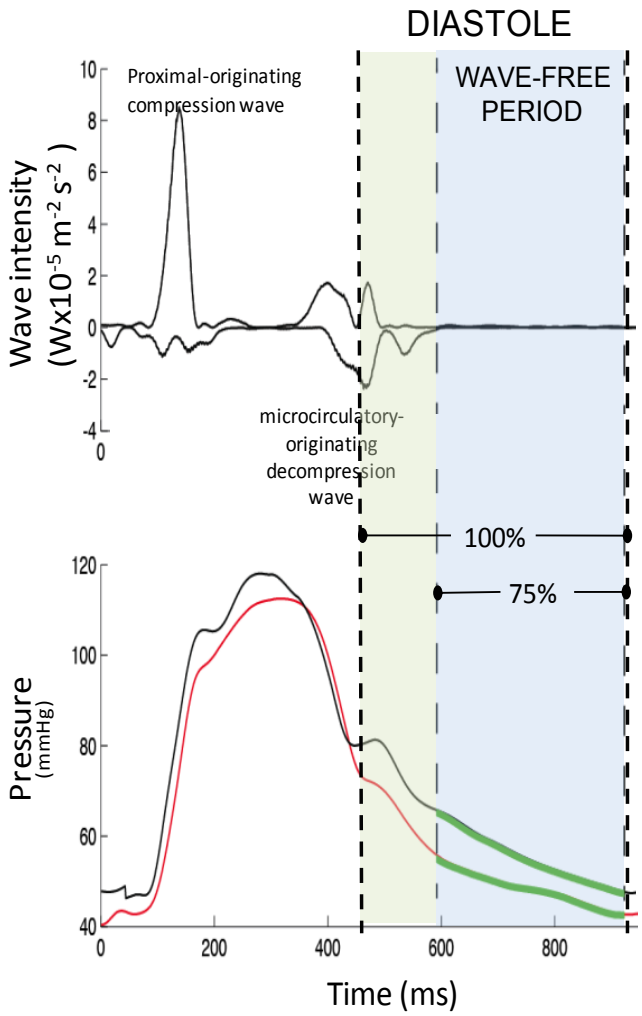



**Figure 5.01: Wave intensity during the diastolic 'wave-free' period.**

Representative traces showing coronary artery wave intensity (upper panel) and corresponding pressure waveform (lower panel). The duration of diastole and the diastolic wave-free period are indicated with dashed vertical lines. The portion of the pressure waveform used to calculate the instantaneous wave-free ratio (iFR) in this study is highlighted in green.

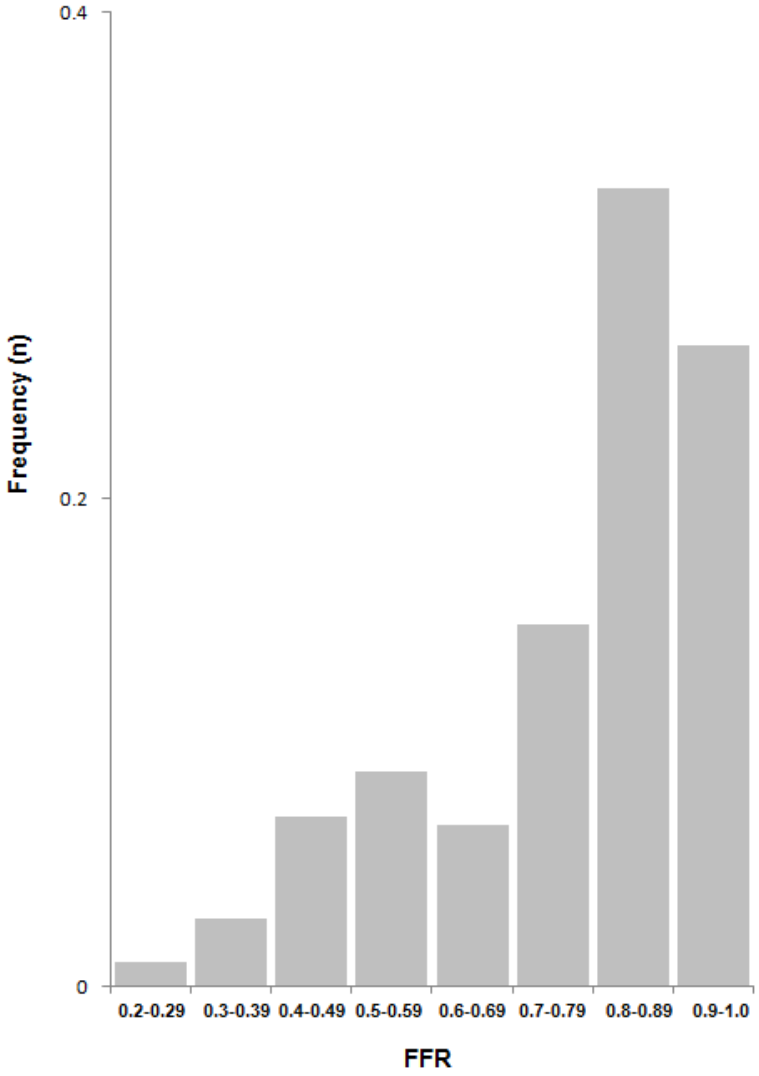



**Figure 5.02: Frequency distribution of Fractional Flow Reserve (FFR) values in study.**

It can be seen that a significant proportion (62.7%) of the stenoses are in the 0.6-0.9 range.

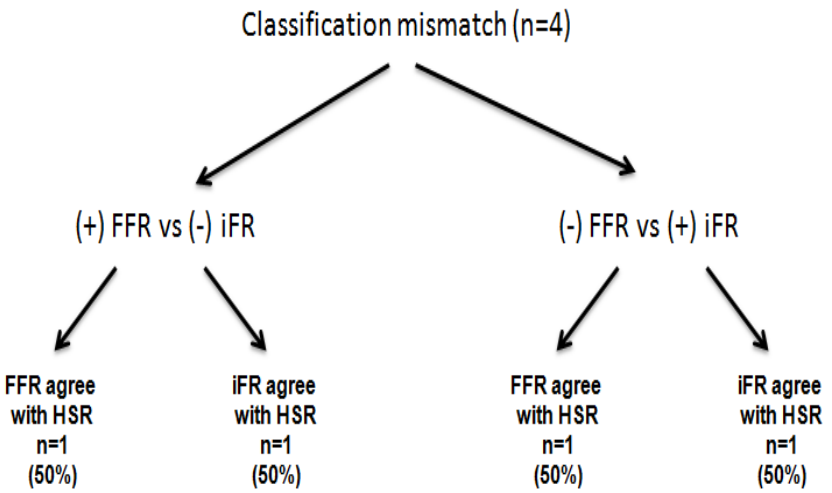



**Figure 5.03: iFR and FFR disagreements**

iFR and FFR disagreed in 4 stenoses in terms of treatment categorisation. When this occurred HSR agreed with iFR in 50% of cases and FFR in 50% of cases.

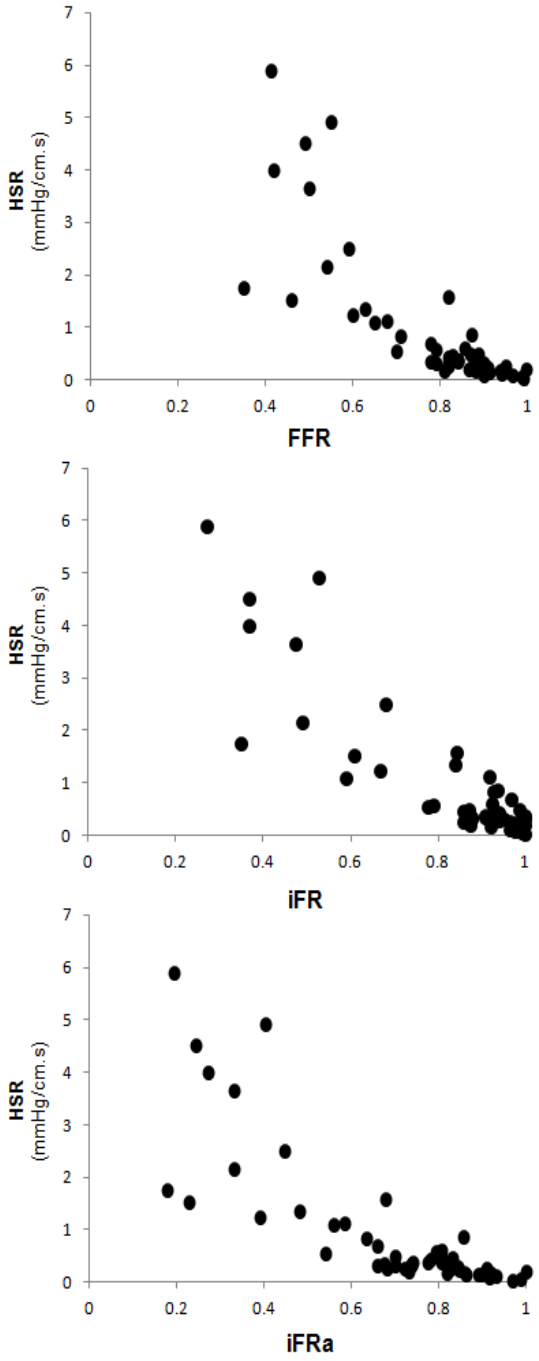



**Figure 5.04: Relationship of iFR, FFR and iFRa to HSR**

All three pressure derived indices have an inverse numerical relationship with HSR. As stenosis resistance increases the pressure derived indices decrease in value.

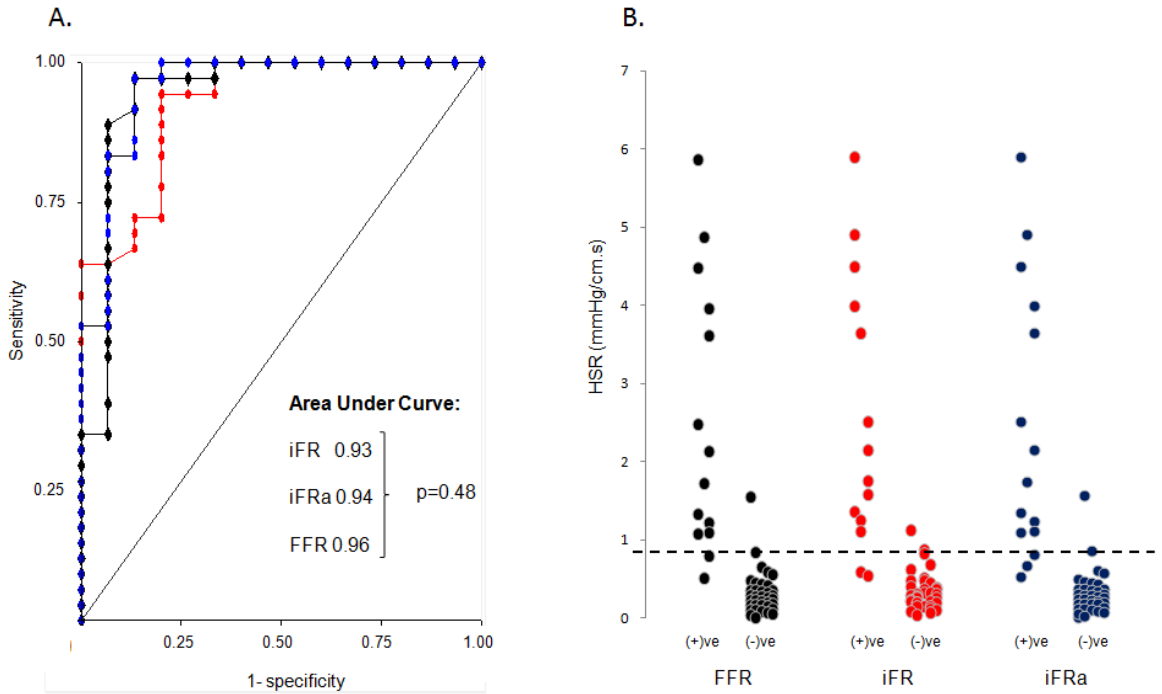



**Figure 5.05: Diagnostic characteristics of iFR, iFRa and FFR using HSR as the reference standard.**

A) Receiver operator curves (ROC) for iFR, iFRa and FFR vs. HSR.
•B) ndividual values of iFR, iFRa and FFR categorized into positive ((+)ve) and negative ((-)ve) according to the parameters own cut-point plotted in relation to HSR. The cut-point for HSR (0.8) is shown as a horizontal dotted line. Areas under the ROC were compared as described by DeLong et al. (42)

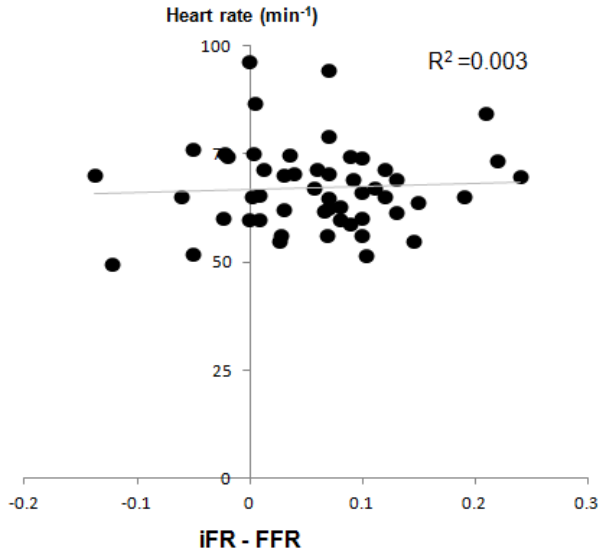



**Figure 5.06: The influence on heart rate on agreement of iFR with FFR**

It can be seen that when the difference between iFR and FFR cannot be explained by patient heart rate.

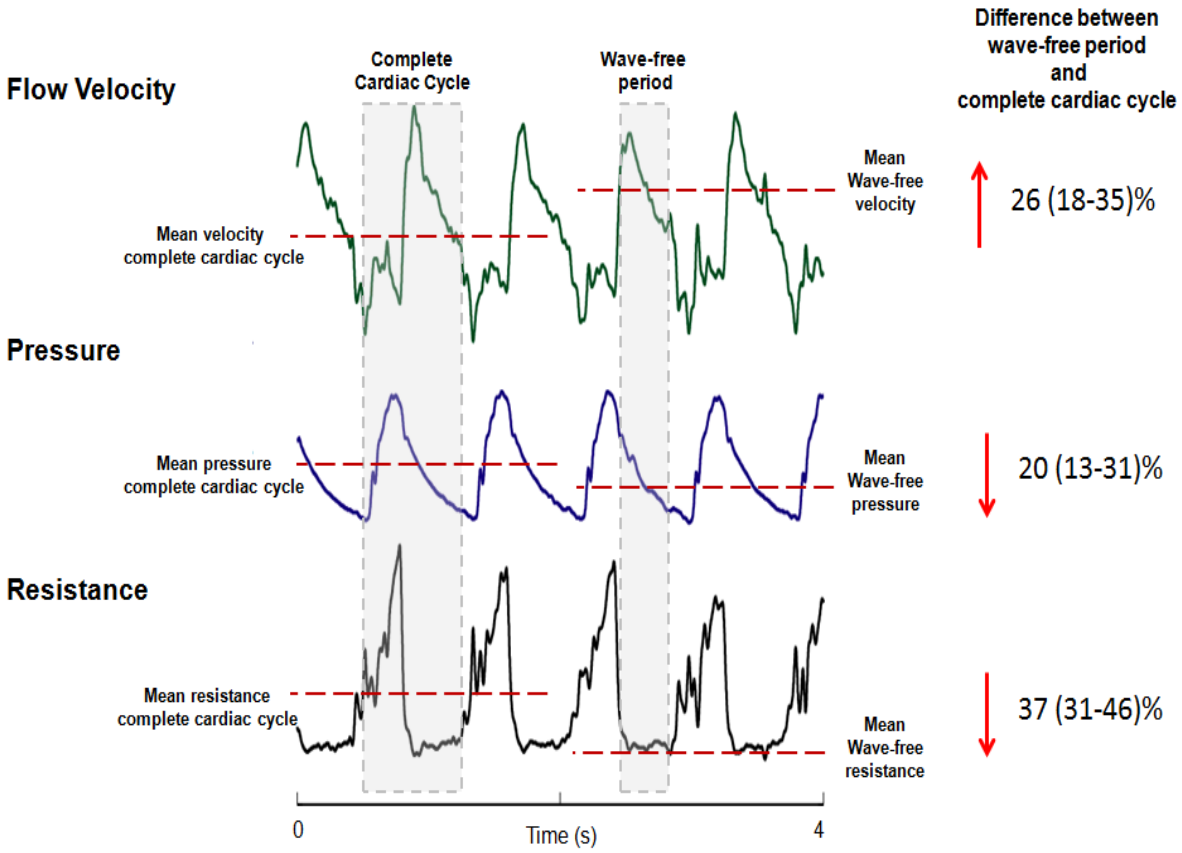



**Figure 5.07: Flow velocity, pressure and instantaneous microvascular resistance during the wave-free period compared to that of the cardiac cycle under resting conditions.**

The percent difference between measures calculated over the wave-free period and the entire cardiac cycle are shown (values are expressed as median±IQR).

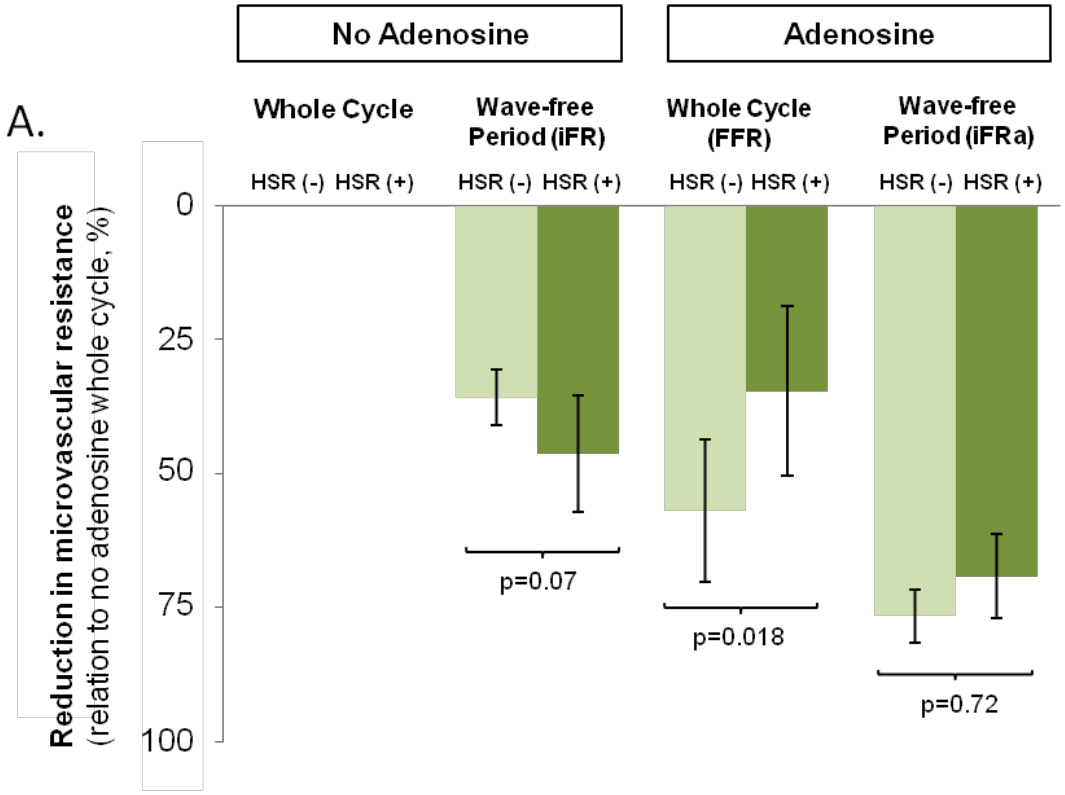



**Figure 5.08: Reduction in microvascular resistance according to epicardial stenosis severity**

A histogram comparing the magnitude of microvascular resistance reduction in each of the three pressure based indices to that of the complete cardiac cycle under resting conditions. Microvascular resistance reduction is consistent with iFR and iFRa in vessels with significant and non significant stenosis. However, with FFR microvascular resistance reduction is significantly lower in vessels with significant stenoses.

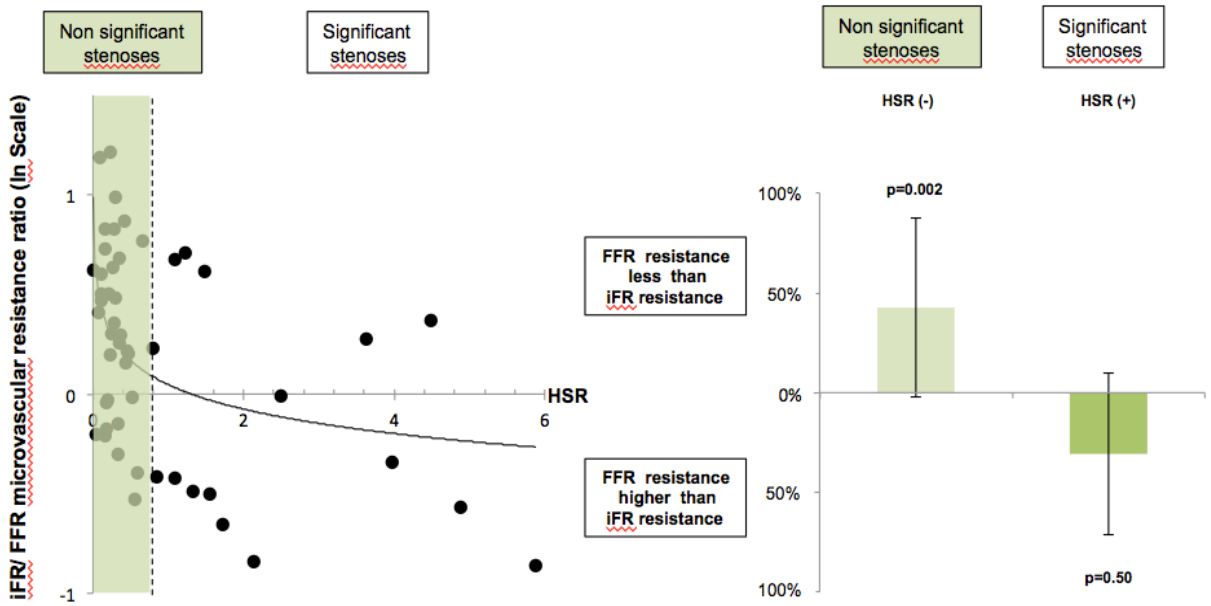



**Figure 5.09: iFR vs FFR Reduction in microvascular resistance according to epicardial stenosis severity**

A plot of difference in microvascular resistance between iFR and FFR against stenosis severity according to HSR. It can be seen that when FFR microvascular resistance is significantly lower than that during iFR it invariably occurs in vessels with non significant stenoses, As stenosis severity increases this difference falls, such that microvascular resistance during iFR and FFR in significant stenoses are equivalent (p=0.50), right panel. In 39% of stenoses iFR microvascular resistance was lower than that during FFR and this was not confined to severe lesions. (Green bar=negative HSR)

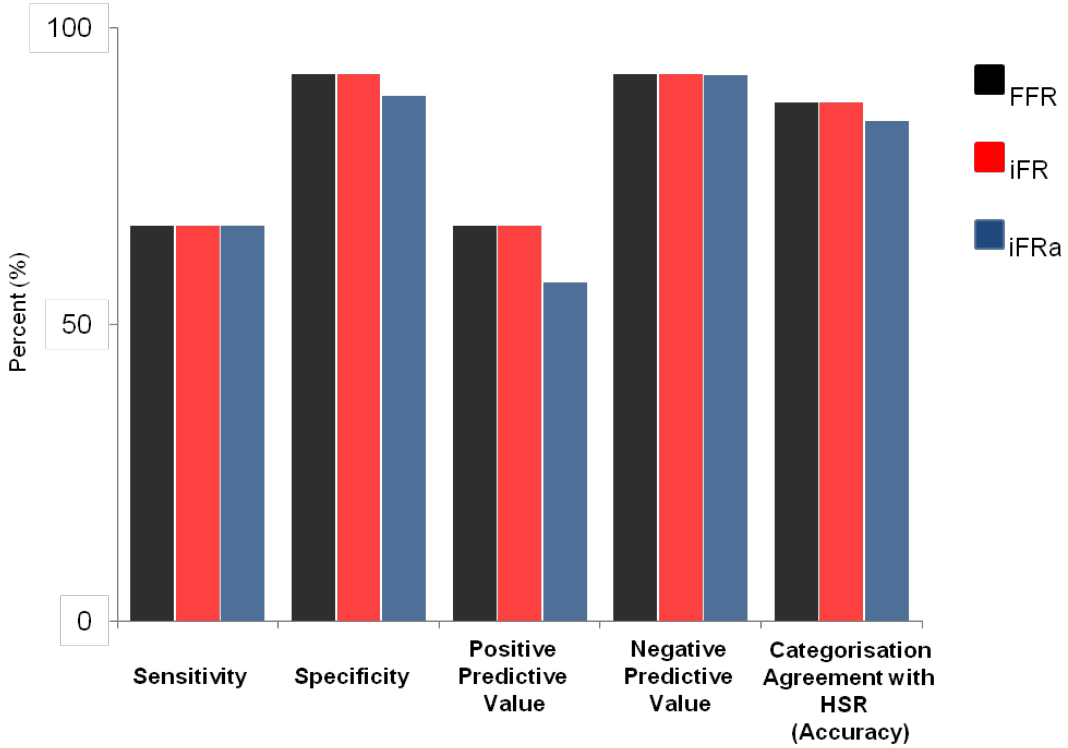



**Figure 5.10: Comparison of diagnostic characteristics of iFR, FFR and iFRa in stenoses in the 0.6-0.9 FFR range**

iFR and FFR have equivalent diagnostic characteristics when compared to HSR diagnostic categorisation in the 0.6-0.9 FFR range

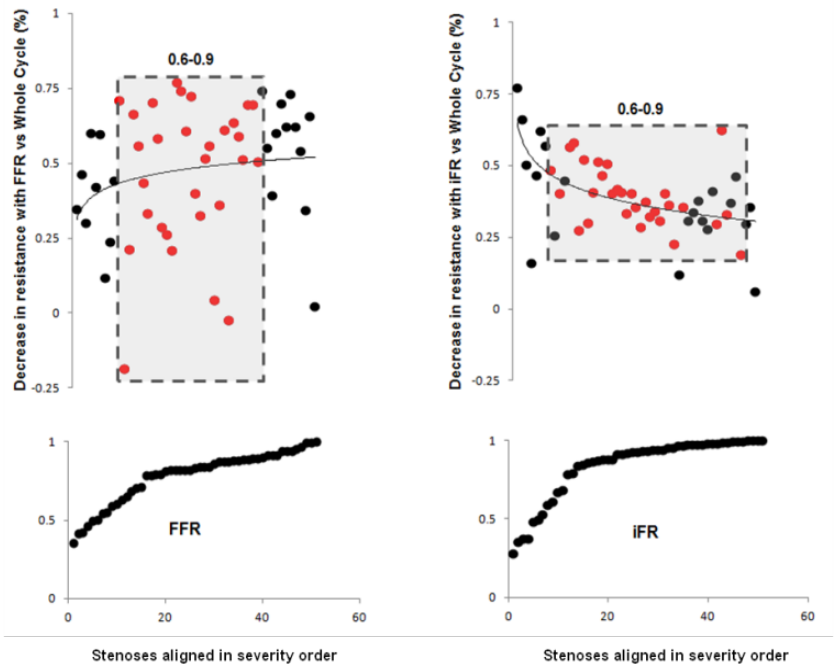



**Figure 5.11: Variability of microvascular resistance reduction according to stenosis severity for both iFR and FFR**

When iFR is close to a value of 1 microvascular resistance over the wave-free period is consistently lower than that during the whole cycle at rest. As stenosis severity increases the reduction in microvascular resistance during the wave-free period increases suggesting that the autonomic system causes microvascular dilatation in order to maintain flow as epicardial stenosis severity increases. In contrast adenosine mediated FFR has a more variable effect on resistance. For a similar grade in stenosis its effects on microvascular resistance are far more varied. Furthermore as stenosis severity increases the ability of adenosine to increase flow is reduced.

# 6.0 Synthesis

In this series of studies I have identified a period in the cardiac cycle that provides the most appropriate widow for the pressure only assessment of a coronary stenosis – the diastolic wave-free period. During this period microvascular resistance is as stable as that induced during adenosine mediated fractional flow reserve and intra-coronary pressure is free of the confounding effect of the contracting and relaxing myocardium distally. The trans-stenotic pressure ratio measured during this window at rest provides similar stenosis classification to fractional flow reserve. Furthermore the ability of iFR to correctly classify stenoses is not improved with the administration of adenosine; suggesting that the flow velocity increase during this window is sufficient for stenosis discrimination.

This series of studies challenge the current dogma that hyperaemia is absolutely necessary for stenosis assessment. As a result several of the findings in these studies deserve closer discussion in the context of pre-existing data in the literature.

**6.1 Whole cycle or phasic analysis?**

*'The purely fluid dynamic character of the stenosis, [that is] the pressure gradient-velocity relationship of the stenosis without the extraneous effects of deceleration and acceleration,..'*

*KL Gould, Circulation Research 1978 (12)*

Separate from the discussion with regard to the need for hyperaemic agents the period of the cardiac cycle most appropriate for the haemodynamic assessment of a coronary stenosis has been investigated by others over the last 30 years. In a seminal study by Gould in 1976, in the canine model (12), he elegantly demonstrated the importance of assessing stenosis severity during a period in the cardiac cycle when intra-coronary pressure and flow velocity are free of the confounding effects of

the contracting and relaxing myocardium. Using separate pressure and Doppler tipped wires and manual post hoc analysis of the data Gould demonstrated that stenoses could be differentiated according to severity at rest. Furthermore, he determined that the trans-stenotic pressure gradient had a curvilinear relationship with flow velocity – fitting the relationship $\Delta P=Fv+Sv^2$. This seminal work was followed several years later by that of Marques et al (56, 57). They derived a new pressure and flow velocity derived index that used the pressure gradient flow velocity at the mid point of diastole using the onset of adenosine mediated hyperaemia to create curves similar to that of Gould. They then extrapolated their curves to a velocity of 50cm/s to derive a pressure gradient. This pressure gradient at fixed velocity (dpv 50) was found to provide a more accurate assessment of ischemia than fractional flow reserve (28). However, there were several limitations to this index. First, it required simultaneous pressure and flow velocity measurements, which was not possible until the introduction of the Combiwire in 2006. Therefore the investigators were forced to make measurement with separate pressure and Doppler tipped wires adding time and complexity to the procedure. Second, interpretation of the data required extensive post hoc manual analysis of the data. Finally, in a significant proportion of patients the traditional curves could not be constructed. As a result despite the clear physiological advantages of this index it was not clinically adopted.

Around about the same time Abe et al. (41) derived the hyperaemic diastolic fractional flow reserve. This isolated diastole according to the LV pressure wave-form and therefore required a catheter in the left ventricle. The resulting index was found to be superior to FFR in determining stenosis severity. However, once again its measurement was more complicated than FFR - limiting its clinical adoption.

Despite the clinical impracticality of the DpV50 and diastolic FFR they both demonstrated that it was possible to use phasic rather than whole cycle averaged haemodynamics to assess stenoses in humans and more important when this is done the resultant index is more accurate than whole cycle indices.

Wave intensity analysis integrates the changes in pressure and flow velocity at each point in the cardiac cycle to determine the predominant determinant of coronary flow. It is therefore the ideal tool to identify a period in the cardiac cycle when the effect of the dynamic myocardium is minimized – the wave-free period. Using traditional pressure and flow velocity analysis I demonstrate that this period is in fact synonymous with the period defined by Gould in 1978 in the canine model. Our approach, derivation of the pressure gradient flow velocity loop and identification of diastole has important distinctions with that of the work of Marques and Abe. First the derivation of these curves did not require the administration of adenosine but simply the natural pressure and flow velocity changes that occur throughout diastole. As a result the curves are independent of the heterogeneous effects of adenosine. Second, the curves were constructed using automated algorithms permitting more rapid construction. Third the onset of diastole was defined by using the aortic pressure trace rather than the LV pressure wave-form obviating the need for a catheter in the left ventricle. Most importantly, whilst the advantages of measuring stenosis severity during a period in the cardiac cycle free of the confounding effect of the myocardium was previously documented, by using modern high fidelity pressure and flow wires and computational power, we are the first to isolate such a period in real time in a fully automated manner. Furthermore, we make an incremental step by using pressure alone over this period to determine stenosis severity. Consequently, contrary to prior investigators, we have derived an index over this window that can be easily adopted into clinical practice.

## 6.2 The effect of adenosine on microvascular resistance according to stenosis severity

ADIVSE demonstrated that microvascular resistance during the diastolic wave-free period was as stable as that provided by adenosine mediated fractional flow reserve. It also demonstrated that the magnitude of resistance was similar to that induced by adenosine during FFR. Whilst the former finding has not been disputed the latter finding has caused much controversy in the field (31, 32). It can be explained, however, by taking into account the differential effect of adenosine on microvascular resistance according to stenosis severity.

Uren and Colleagues in 1994 (18) used PET to demonstrate that the effect of adenosine varied according to stenosis severity. In patients with unobstructed coronaries flow was markedly enhanced by the administration of adenosine. However, as stenosis severity increased the effect of adenosine diminished, such that its effect on flow was minimal in the 50-90% stenosis range (as defined by QCA). Furthermore, they demonstrated the marked heterogeneous effect of adenosine between patients with similar stenosis severities. These finding can be used to explain the discrepancies between the microvascular resistance findings of ADVISE and CLARIFY.

In CLARIFY, in patients with non flow limiting disease (HSR<0.8) I demonstrated that microvascular resistance values were on average significantly lower than that possible over the resting wave-free period. However, in patients with flow limiting disease (HSR>0.8) I demonstrated that microvascular resistance over the wave-free period was similar and in some cases much lower than that possible during adenosine medicated FFR. The resistance comparison between iFR and FFR is therefore acutely sensitive to the composition of stenoses in the patient population. If

there is a predominance of mild stenoses hyperaemic microvascular resistance will be much less than resting wave-free resistance. In contrast a higher proportion of severe lesions may mean that microvascular resistance between the two indices is similar. Whilst it is clear that wave-free resistance is not always similar to that achieved during adenosine mediated FFR the diagnostic implications of this finding appears to be minimal as the cases in which there are large disparities between the two indices are so far away from the treatment cut point that clinical categorization remains unchanged. This is confirmed by the findings of CLARIFY.

## 6.3 Rest flow, 'maximal' flow or will somewhere in between suffice?

*'A direct relation between coronary pressure and flow, however, may only be presumed if the resistances in the coronary circulation are constant (and minimal) as theoretically is the case during maximum arteriolar vasodilation'*

*NH Pijls et al Circulation 1993(5)*

Adenosine administration did not necessarily reduce microvascular resistance. Adenosine had a more consistent effect when systole was excluded. For example, the administration of adenosine in the context of FFR was associated with a highly variable response; with approximately 40% of patients having lower microvascular resistance over the resting diastolic wave-free period. This was not true for iFRa. Adenosine administration during the wave-free period provided a consistently greater reduction in microvascular resistance than that possible during iFR and FFR. Furthermore, this effect did not appear to be as sensitive to stenosis severity as FFR. Traditional teaching would suggest iFRa should therefore provide a more accurate measure of ischemia as microvascular resistance is minimized further. However, despite the significantly lower distal to proximal pressure ratio of iFRa it was not

found to afford better diagnostic accuracy than FFR or even the resting index of iFR. These finding can be explained by using the original Gould pressure gradient flow velocity curves. The higher flow velocity simply pushes the pressure gradient along the same curve therefore whilst the pressure gradient is lower the stenosis does not change treatment classification/ severity as the increased flow velocity is taken into account with a lower treatment threshold 0.66 for iFR vs 0.75 for FFR.

These findings have significant implications for adenosine mediated fractional flow reserve. A stipulation of FFR is the need to assess stenosis severity at maximal flow and therefore minimal (and constant) microvascular resistance in the subtended artery. However, as others have demonstrated with ever increasing doses of adenosine, the addition of alpha blockers, sodium nitroprusside or ACE inhibitors - flow in the coronary can be increased further than that possible with 140mcg/kg/min of adenosine. Furthermore regardless of the drug or combination of drugs flow will be higher during diastole and higher still during the wave-free period –questioning the feasibility of ever obtaining maximal hyperaemia.

However, these findings do not negate the role of FFR; the FAME (16) and FAME II (17) studies used adenosine at a dose of 140mcg/kg/min and demonstrated clear clinical benefits. But they do challenge the stipulation that flow needs to be maximal for the accurate assessment of a coronary stenoses. This suggests that microvascular resistance during pressure only assessment of coronary stenoses needs to satisfy two conditions:

1. Sufficiently stable so trans-stenotic pressure can be used as a surrogate for flow and

2. Low enough to permit accurate discrimination between stenoses of differing severities

The equal diagnostic categorization of iFR, FFR and iFRa suggest that microvascular resistance during the resting diastolic wave-free period satisfies these requirements and further pharmacological reduction is perhaps surplus to requirement.

## 6.4 Estimating true underlying flow – should we use resting pressure or hyperaemic pressure?

It is assumed that hyperaemic pressure provides a more accurate refpection of true underlying flow. However, the literature does not support this view. The effect of vasodilatation on stenosis geometry and the relationship of trans-stenotic pressure gradient, flow velocity and flow volume were described in detail by Gould and Kelly (58). In this study, in the canine model, they demonstrated that the pressure gradient flow velocity relationship and pressure gradient flow volume relationship were identical at rest. They went onto demonstrate that this was not the case during hyperaemia. During hyperaemia there was a clear divergence between the pressure gradient-flow volume curves and pressure gradient flow-velocity curves; with the latter overestimating the true pressure gradient-flow volume curves.

If this over estimation was consistent and predictable then it could be accounted for unfortunately this is not the case and therefore during hyperaemia whilst trans-stenotic pressure may be proportional to flow velocity it may not be proportional to true flow.

These findings suggest that provided flow velocity is high enough to provide adequate sensitivity (as is true of the wave-free period) the resting pressure gradient provides an accurate assessment of true underlying flow within the vessel and the absence of vasodilatation does not under-estimate the true effect of the stenosis on coronary flow volume.

The wave-free period provides flow velocity that is high enough along the resting pressure gradient flow velocity curve to permit accurate discrimination between stenoses but also by remaining on the resting curve may perhaps provide a more accurate assessment of true underlying flow. This hypothesis will be investigated in future studies.

## 6.5 Limitations of no gold standard

The development of any ischemia test is limited by the lack of a gold standard. Whilst fractional flow reserve has been advocated as the gold standard ischemia test it has clear limitation in the context of microvascular function – highlighted by the 30% discordance rate between CFR and FFR.

Furthermore, the ability of FFR to agree with itself is limited.. There has been much speculation about the scatter of patients in the correlation of iFR to FFR in ADVISE (58, 59). We were surprised that the poor correlation in this zone was so readily attributed to iFR given the well documented large variance in flow during hyperaemia. Indeed Gould in 1974 demonstrated that hyperaemic flow is significantly more variable than resting flow (59). This is substantiated by the test-re-test agreement of FFR in this range of only 81% in the DEFER study (14). As a result when iFR and FFR disagree in this range it is not clear if a repeated measure of FFR would in fact agree with its first measurement. Therefore it is difficult to understand why scatter in this range is so readily attributed to iFR as opposed to that of the hyperaemic index (i.e. FFR) with a far larger variance.

This is further confounded by the limited data on FFR in the in the range straddling the 0.75 cut point.  In the two seminal papers comparing FFR to non-invasive tests the proportion of patients in this range was limited. In the New England Journal paper

of 1996 (49) only 53.0% of lesions were between 0.6-0.9 where as in the PET study of 1994 (48) there were only 32.8% of lesions in this range. In this respect CLARIFY, which includes 62.7% of lesions in this range, represents one of the largest flow based studies comparing FFR to ischemia (HSR) to be performed in 0.6-0.9 range. Despite this, the numbers of patients are small so a post hoc restricted analysis of the correlation of iFR to FFR in this range that does not account for the inherent variability of FFR may produce misleading results (60).

A more robust method of further characterising the diagnostic accuracy of iFR in this range is to prospectively identify a study population rich in lesions around this range. To this end the ADVISE-Registry (46) and the South Korean Registry (47) were designed to answer this question. Surprisingly, these were the first studies to ever assess FFR in a distribution similar to that seen in a clinical setting, with 80% of the patients in the 0.6-0.9 range in both registries. Reassuringly these studies demonstrated a close categorisation match between iFR and FFR. However, given the inherent variability of FFR in this range, in the small proportion of patients where there is categorisation mismatch CLARIFY used HSR to determine which index (iFR or FFR) is more indicative of ischemia.

By indexing the trans-stenotic pressure gradient by flow velocity, HSR, similar to the indexes used by *Logan* has been demonstrated to provide a more epicardial specific assessment of coronary stenosis with the ability to differentiate between the 30% of patients where FFR and CFR are discordant. Importantly, it has been demonstrated to be more reflective of ischemia than FFR (20, 22). As an invasive index that circumvents the limitation of pressure only indices it was deemed the most appropriate arbiter to determine, when FFR and iFR disagree, which was most likely to represent the true physiological significance of the stenosis at the level of the specific artery.

## 6.6 What does the community think?

The publication of the findings in this thesis has been met with much debate in the community. Other groups, including that of Gould, have compared iFR to FFR and alternative invasive and non invasive indices. Apart from a notable exception (61) the results have been remarkably consistent. So far iFR and FFR have been compared to an independent arbiter of ischaemia in over 500 lesions. Each study has demonstrated no difference between the two, arguably with a signal suggesting that the resting index may be more accurate.

On the basis of the studies so far iFR has been adopted into clinical practice in over 300 centres worldwide (Figure 6.1). The natural progression from this point is the comparision of iFR guided revascularisation to FFR guided resvascularisation in the context of a large blinded randomised trial; using the hard end points of death, myocardial infarction and revascularisation as end points. Such a trial is currently being performed.

More interestingly and separate to the discussion regarding the accuracy of iFR as an index of ischaemia these series of studies have lead the community to re-evaluate the broader issue of how new indices of ischaemia should be validated and ask the more philosophical question of ‘what is ischaemia?’.

# 7. 0 Conclusion

Combined analysis of pressure and flow velocity using wave-intensity analysis demonstrates a period in the cardiac cycle during which intra-coronary haemodynamics are naturally most reflective of the upstream fluid dynamics of the stenosis. This diastolic wave-free period provides a more consistent reduction in microvascular resistance than that possible with adenosine whilst also lowering microvascular resistance sufficiently to discriminate between stenoses. As a result it satisfies the requisite conditions for a pressure only assessment of stenosis severity without requiring potent vasodilators. The instantaneous wave free ratio is a vasodilator free index of stenosis severity that is calculated during this period. It appears to have equivalent diagnostic agreement to traditional vasodilator based indices and warrants further investigation into its clinical potential with outcome studies.

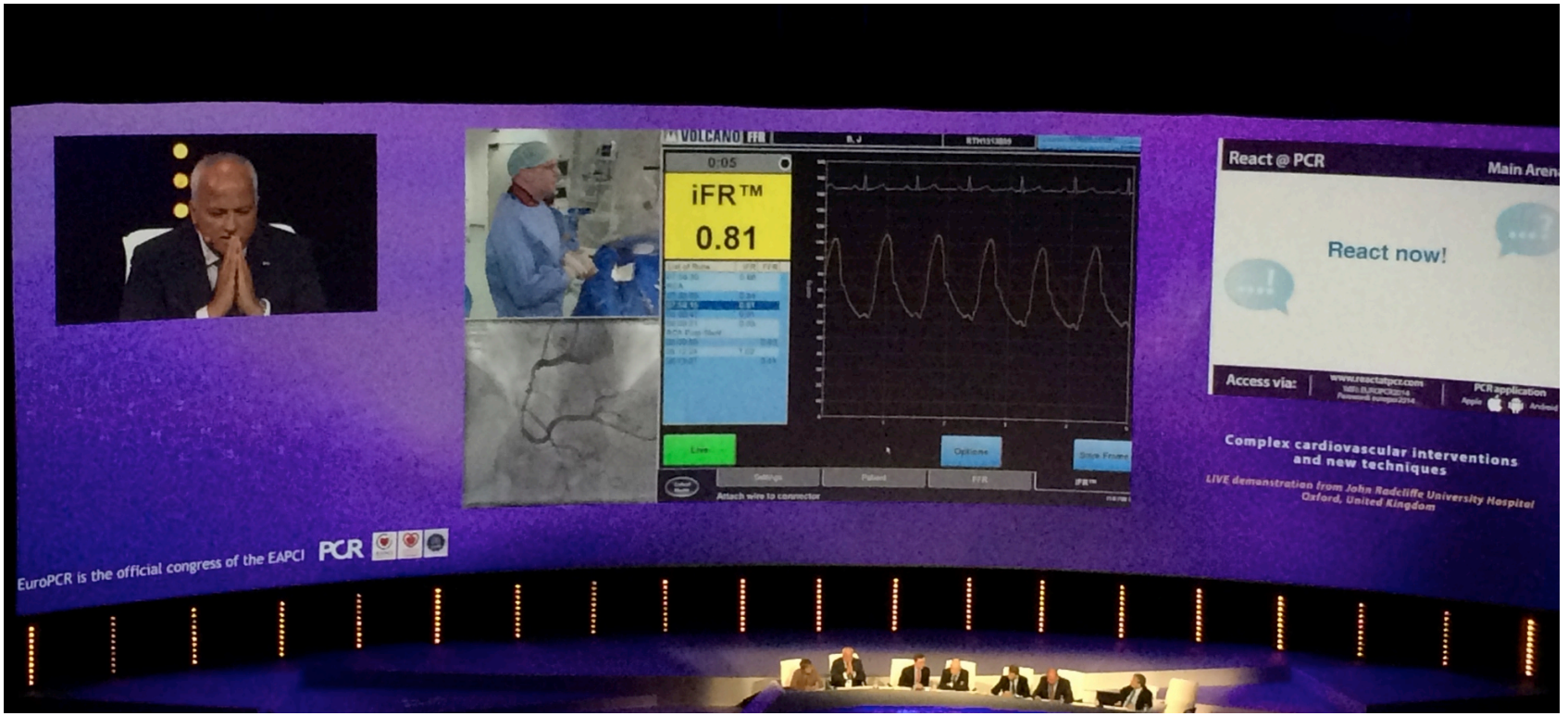



**Figure 6.1 : From bench to bed-side, the use of iFR to guide clinical decision making during a live case at EuroPCR 2014**

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# 9.0 Appendix

# 9.1 Publications arising from this thesis

**IFR, Science, Size and Serendipity – can lightening strike twice?** Sen S. Escaned J, Petraco R et al. In Press Journal of the American College of Cardiology, 2013

**Can anatomy be use as a surrogate for physiology? The IVUS conundrum.** Sen S and Davies JE. In Press, International Journal of Cardiology, 2013

**Instantaneous wave-free ratio (iFR): Numerically different, but diagnostically superior to FFR? Is lower always better?** Sen S, Nijjer S, Petraco R, Malik IS, Francis DP, Davies JE. In Press Journal of the American College of Cardiology, 2013

**Wave Intensity Analysis in the Human Coronary Circulation in Health and Disease**. Sen S, Petraco R, Mayet J and Davies JE. In Press, Current Cardiology Reviews, 2013

**Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration Results of CLARIFY (the CLassification Accuracy of pressure-only Ratios against Indices using Flow studY).** Sen S, Asrress K, Nijjer S et al. J Am Coll Cardiol. 2013;61(13):1409-20.

**Letter by Sen et Al regarding article, "diagnostic accuracy of combined intracoronary pressure and flow velocity information during baseline conditions: adenosine-free assessment of functional coronary lesion severity".** Sen S, Davies JE, Escaned J. Circ Cardiovasc Interv. 2012 Dec 1;5(6):e85.

**Reply.** Sen S, Escaned J, Francis DP, Davies JE J Am Coll of Cardiol.,2012 59 (21),1917-1918.

**Development and validation of a new adenosine-independent index of stenosis severity from coronary wave intensity analysis Results of the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study.** Sen S, Escaned J, Malik IS et al. Journal of the American College of Cardiology 2012;59:1392-402.

**Fractional Flow Reserve–Guided Revascularization: Practical Implications of a Diagnostic Gray Zone and Measurement Variability on Clinical Decisions** Petraco R, Sen S, Nijjer S, Echavarria-Pinto M, Escaned J, Francis DP, Davies JE. J Am Coll Cardiol Intv. 2013;6(3):222-225

**Baseline coronary pressures, instant wave-free ratio (iFR) and Pd/Pa: making the most of available information.** Petraco R, Sen S, Nijjer S et al. Eurointervention, In press.

**Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation**. Petraco R, Park JJ, Sen S, et al. EuroIntervention. 2012 Dec 21. doi:pii: 20121206-02. [Epub ahead of print]

**Classification performance ¬of instantaneous wave-Free Ratio (iFR) and fractional flow reserve in intermediate coronary stenosis: results of the ADVISE registry.** Petraco P, Javier Escaned J, Sen S, et al. EuroIntervention. 2012 Aug 25. doi:pii: 20120413-02. [Epub ahead of print]

## Other publications during PhD studies:

**Why does primary angioplasty not work in registries? Quantifying the susceptibility of real-world comparative effectiveness data to allocation bias.** Sen S, Davies JE, Malik IS, Foale RA, Mikhail GW, Hadjiloizou N, Hughes A, Mayet J, Francis DP. Circ Cardiovasc Qual Outcomes. 2012 Nov;5(6):759-66.

**Maximal expansion capacity with current DES platforms: a critical factor for stent selection in the treatment of left main bifurcations?** Foin N, Sen S, Allegria E, Petraco R, Nijjer S, Francis DP, Di Mario C, Davies JE. EuroIntervention. 2012 Oct 22. doi:pii: 20120509-02. [Epub ahead of print]

**Improvement in Coronary Blood Flow Velocity with Acute Biventricular Pacing is Predominantly Due to an Increase in a Diastolic Backward-Travelling**

**Decompression (Suction) Wave.** Kyriacou A, Whinnett ZI, Sen S, et al. Circulation. 2012;126(11):1334-44

**Arterial pulse wave dynamics after percutaneous aortic valve replacement: fall in coronary diastolic suction with increasing heart rate as a basis for angina symptoms in aortic stenosis**. Davies JE, Sen S, Broyd C, et al. Circulation. 2011;124(14):1565-72.

# 9.2 Awards

| | |
|---|---|
| **Winner, Royal Society of Medicine President's Gold Medal** | **2013** |
| **Winner, Armstrong Medal and Prize, Imperial College London** | **2012** |
| **Winner, Young Investigator of the year**, British Cardiovascular Intervention Society | **2012** |
| **Winner, Best Interventional Cardiology Abstract**, British Cardiac Society | **2012** |
| **ADVISE – Late Breaking Clinical Trial**, TCT, USA | **2011** |
| **Clinical Research Training Fellowship,** Medical Research Council | **2010** |
| **Finalist, Young Investigator of the year**, Artery | **2010** |
| **Finalist, Young Investigator of the year**, British Hypertension Society | **2010** |
| **Winner, Young Investigator Prize**, AMC Microcirculatory Symposium, Holland | **2010** |
| Imperial NHS Trust Director of Medical Education **Travel Scholarship** | **2010** |
| Imperial NHS Trust Director of Medical Education **Travel Scholarship** | **2009** |

St Mary's NHS Trust

Imperial College London

International Centre for Circulatory Health
St Mary's Hospital & Imperial College
59-61 North Wharf Road, Paddington
London W2 1NY

**Patient Information Leaflet**
**For patients undergoing coronary angioplasty**
**Assessment of Coronary Stenosis: development and application of separated pressure Fractional Flow Reserve**
**Chief Investigator Dr Justin Davies**

**Version 5.0 18.12.2009**

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

**What is the purpose of the study**?
You are suffering from chest pain or shortness of breath on exertion. This may be due to a narrowing of one of your heart arteries. In order to determine if this is the case we sometimes use a test to measure the pressure across the narrowing. This is called Fractional Flow Reserve (FFR). In some patients it may not be that accurate. We have developed an alternative way of assessing blood flow in the heart arteries. The results from this study may lead to a new way of assessing how severe the narrowing in your artery is and therefore may affect how we treat patients with your condition in the future.

**Why have I been chosen?**
You have been chosen because you are scheduled to have an angioplasty, are not asthmatic and do not have any metal implants. As a normal part of this procedure, a small tube will be inserted into the main artery in the groin. This means that at the time of your procedure, we can use this tube to pass our wires into your heart arteries and safely take measurements in your heart's blood vessels.

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

**What will happen to me if I take part?**
You will undergo the routine investigations required prior to angiography which includes an ultrasound of the heart (Echocardiogram). After we have performed the procedure and obtained all the necessary information to assess your symptoms we will make our measurements. We will enter the artery at the top of your leg via the same tube that is required for the angiogram. Wires and a balloon will then be passed into the heart arteries and measurements taken with an adenosine infusion. This will require a small tube to be placed at the top of the leg next to the first tube. Local anaesthetic will be used and this should not cause any discomfort. In total the process will add 10 minutes to the procedure. The measurements will not prolong your recovery from the procedure. At the end of the procedure the wires will be removed.

You will then be invited to return to hospital for an MRI scan. This is a non invasive test that lasts for 30 minutes where we take pictures of your heart.

You will then be followed up by the clinical team as normal.

**What are the possible side effects, risks and disadvantages of taking part?**
We do not expect you to experience any significant side effects as a result of participating in this study.

During the measurements we will administer a medication called adenosine. This is routinely used every day in the cardiac catheter laboratory and maybe used in the clinical stages of your procedure. The risk of using adenosine is very low, but, in some patients it may cause a short lived chest discomfort which usually disappears within 3-5 seconds of stopping the drug. In order to administer the adenosine we will place a second tube at the top of the leg using local anaesthetic which should not cause any discomfort. In order to administer the adenosine we will place a second tube at the top of the leg using local anaesthetic which should not cause any discomfort. The measurements extend the length of the procedure by 10 minutes.

There is a very low risk (less than 1 in 1000) that the wire used to make the measurements will cause any damage to your blood vessels. The risk of death, heart attack or stroke is the same as your routine angiogram. This risk is minimised as the measurements are performed by an experienced senior Consultant Cardiologist. We will place the wires under x-ray guidance; the extra dose has not been associated with any side effects. This has been checked by a radiation expert.

As part of the study you will be invited to have a MRI scan of your heart. This involves lying on a table and passing through a tube during which time we take pictures of the heart. There are several reasons why you may not be suitable for a MRI. In particular, patients who have implanted medical devices (e.g. pacemakers or defibrillators, cochlear implants, cerebral aneurysm clips), or who may have iron fragments in their eyes, are not suitable for MRI investigation. Orthopaedic pins, mediastinal clips, coronary stents, and the majority of artificial heart valves are safe to scan. There are no known risks from undergoing MRI during pregnancy. A small number of people suffer from claustrophobia (<5%). We will inject a small amount of contrast during the study into a small arm vein and there is a small risk of an allergic reaction, although this risk is very low.

**What are the possible benefits of taking part?**
You will not directly benefit from this study, but the information we gain will give us a much better understanding of how blood flow to the heart muscle is affected in your condition and may help develop a new way of assessing if the narrowing in your heart artery is causing your chest pain.

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

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

**Will my taking part in this study be kept confidential?**
If you agree to take part, data collected about you will be entered onto a computer. However, all data entered will be in an anonymous format and any information obtained from this investigation that can be identified will remain confidential. Relevant sections of your medical notes & data collected during the study may be looked at by individuals from Imperial College,

from regulatory authorities or from Imperial NHS trust, where it is relevant to you taking part in this research. We will ask for your permission for these individuals to have access to your records. Your GP will be informed that you are participating in this study.

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

**Who has reviewed the study?**
This study has been reviewed and given a favourable ethical opinion by the Outer London Research Ethics Committee.

If you have any further questions please do not hesitate to contact:
Dr Sayan Sen on 0207 594 1264 or Dr Justin Davies on 0207 594 1264

**Thank you for taking the time to consider participating in this study**

Imperial College London

St Mary's NHS
NHS Trust

International Centre for Circulatory Health
59-61 North Wharf Road, Paddington
London W2 1NY

CONSENT FORM

(Patients scheduled for pressure-flow wire measurements during coronary angioplasty)

**Assessment of Coronary Stenosis: development and application of separated pressure Fractional Flow Reserve**

Chief Investigator: Dr Justin Davies, Dept of Cardiology, ICCH St Mary's NHS Trust

| | | Please initial as applicable |
|---|---|---|
| 1. | I have read the Patient Information Sheet (Version 5.0 Date 18/12/2009) for patients scheduled for **Assessment of Coronary Stenosis: development and application of separated pressure Fractional Flow Reserve** | Yes …… No…… |
| 2. | I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions. | Yes …… No…… |
| 3. | I have spoken to Dr.....…… | Yes …… No…… |
| 4. | I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care. | Yes …… No…… |
| 5. | I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the NHS Trust. I give permission for these individuals to access my records. | Yes …… No……<br>Yes …… No……<br>Yes …… No…… |
| 6. | I agree to take part in this research study. | Date..... |
| 7. | I agree to my GP being informed about my participation in this research study. | Date..... |

Signature.....……

Name (block capitals).....……..

Signature of Study Investigator.....……

Name (block capitals).....……